

**Clinical trial results:**

A phase II, multinational, multicentre, double blind, double dummy, randomised, cross-over, active - and placebo-controlled clinical study to compare the bronchodilator effect of single administration of CHF 1535 pMDI (fixed combination of extrafine beclomethasone dipropionate 50 g + formoterol fumarate 6 g/metered dose, total dose 100/12 g) given with spacer vs. free combination of licensed extrafine beclomethasone dipropionate pMDI given with spacer (total dose 100 g) plus formoterol pMDI given with spacer (total dose 12 g) in terms of FEV1 AUC0-12h in asthmatic children

Summary

EudraCT number	2011-002060-24
Trial protocol	PL Outside EU/EEA
Global end of trial date	26 February 2013

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-0903-PR-0060
-----------------------	------------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01584492
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici SpA
Sponsor organisation address	Via Palermo 26/A, Parma, Italy, 43122
Public contact	Clinical Trial Transparency Manager, Chiesi Farmaceutici SpA, clinicalTrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency Manager, 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	26 February 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 February 2013
Global end of trial reached?	Yes
Global end of trial date	26 February 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority in terms of bronchodilator effect of single administration of CHF 1535 50/6 pMDI (fixed combination of extrafine beclomethasone dipropionate 50 µg + formoterol fumarate 6 µg/metered dose, 2 inhalations, total dose 100/12 µg) given with spacer vs. free combination of extrafine beclomethasone dipropionate 50 µg/metered dose pMDI (2 inhalations, total dose 100 µg) given with spacer plus formoterol 6 µg/metered dose pMDI (2 inhalations, total dose 12 µg) given with spacer in terms of FEV1 AUC 0-12 hours corrected by time for the 12 hours study period in asthmatic children

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	27 December 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ukraine: 39
Country: Number of subjects enrolled	Poland: 20
Worldwide total number of subjects	59
EEA total number of subjects	20

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)	59
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 81 patients were screened, of whom 59 patients were randomised from eight sites. Twenty-two patients failed screening because they did not meet the inclusion criteria. 1-week $\pm$ 3 days run-in period was followed by five single-day randomised treatment periods separated by wash-out periods of 14 $\pm$ 7 days.

Period 1

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

Blinding implementation details:

Two matched placebos were provided to achieve a complete double-blind, double-dummy design. The canisters/actuators of CHF 1535 and FF pMDI were identical. The randomisation list was provided to the labelling facility but was not available to patients, investigators, monitors or employees of the centre involved in the management of the trial before unblinding of the data, unless in case of emergency. The Sponsor's clinical team was also blinded during the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence A/B/C/D/E

Arm description:

- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 μ g/FF 6 μ g) + placebo HFA pMDI with spacer, 5 inhalations
- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 μ g/FF 12 μ g) + placebo HFA pMDI with spacer, 4 inhalations
- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 μ g/FF 24 μ g) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 μ g/FF 24 μ g) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 μ g HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 μ g) + extrafine BDP 50 μ g, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 μ g) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic

Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.. Each patient will have 6 inhalations at each

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

Dosage and administration details:

A 1-week $\pm$ 3 days run-in period was followed by five single-day randomized treatment periods separated by wash-out periods of 14 $\pm$ 7 days. A safety follow-up phone contact was made 7 $\pm$ 3 days after the last treatment visit or premature discontinuation, for safety purposes.

During the run-in period and during the wash-out periods, patients were treated with BDP pMDI HFA 50 μ g extrafine (Ventolair®, Teva), 1 inhalation twice daily (daily dose: BDP 100 μ g) administered with AeroChamber Plus™ spacer device.

Arm title	Sequence B/C/D/E/A
-----------	--------------------

Arm description:

- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations

Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

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

Dosage and administration details:

A 1-week ± 3 days run-in period was followed by five single-day randomized treatment periods separated by wash-out periods of 14±7 days. A safety follow-up phone contact was made 7 ±3 days after the last treatment visit or premature discontinuation, for safety purposes.

During the run-in period and during the wash-out periods, patients were treated with BDP pMDI HFA 50 µg extrafine (Ventolair®, Teva), 1 inhalation twice daily (daily dose: BDP 100 µg) administered with AeroChamber Plus™ spacer device.

Arm title	Sequence C/D/E/A/B
------------------	--------------------

Arm description:

- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations
- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations

Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

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

Dosage and administration details:

A 1-week ± 3 days run-in period was followed by five single-day randomized treatment periods separated by wash-out periods of 14±7 days. A safety follow-up phone contact was made 7 ±3 days after the last treatment visit or premature discontinuation, for safety purposes.

During the run-in period and during the wash-out periods, patients were treated with BDP pMDI HFA 50 µg extrafine (Ventolair®, Teva), 1 inhalation twice daily (daily dose: BDP 100 µg) administered with AeroChamber Plus™ spacer device.

Arm title	Sequence D/E/A/B/C
------------------	--------------------

Arm description:

- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations

- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

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

Dosage and administration details:

A 1-week ± 3 days run-in period was followed by five single-day randomized treatment periods separated by wash-out periods of 14±7 days. A safety follow-up phone contact was made 7 ±3 days after the last treatment visit or premature discontinuation, for safety purposes.
During the run-in period and during the wash-out periods, patients were treated with BDP pMDI HFA 50 µg extrafine (Ventolair®, Teva), 1 inhalation twice daily (daily dose: BDP 100 µg) administered with AeroChamber Plus™ spacer device.

Arm title	Sequence E/A/B/C/D
------------------	--------------------

Arm description:

- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations
- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

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

Dosage and administration details:

A 1-week ± 3 days run-in period was followed by five single-day randomized treatment periods separated by wash-out periods of 14±7 days. A safety follow-up phone contact was made 7 ±3 days after the last treatment visit or premature discontinuation, for safety purposes.
During the run-in period and during the wash-out periods, patients were treated with BDP pMDI HFA 50 µg extrafine (Ventolair®, Teva), 1 inhalation twice daily (daily dose: BDP 100 µg) administered with AeroChamber Plus™ spacer device.

Number of subjects in period 1	Sequence A/B/C/D/E	Sequence B/C/D/E/A	Sequence C/D/E/A/B
Started	13	13	13
Completed	12	13	12
Not completed	1	0	1
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	1	-	-

Number of subjects in period 1	Sequence D/E/A/B/C	Sequence E/A/B/C/D
Started	11	9
Completed	10	9
Not completed	1	0
Consent withdrawn by subject	1	-
Adverse event, non-fatal	-	-

Baseline characteristics

Reporting groups

Reporting group title	Sequence A/B/C/D/E
-----------------------	--------------------

Reporting group description:

- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations
- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic

Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.. Each patient will have 6 inhalations at each

Reporting group title	Sequence B/C/D/E/A
-----------------------	--------------------

Reporting group description:

- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations

Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

Reporting group title	Sequence C/D/E/A/B
-----------------------	--------------------

Reporting group description:

- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations
- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations

Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

Reporting group title	Sequence D/E/A/B/C
-----------------------	--------------------

Reporting group description:

- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
 - Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
 - Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations
 - Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
 - Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

Reporting group title	Sequence E/A/B/C/D
-----------------------	--------------------

Reporting group description:

- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations

- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

Reporting group values	Sequence A/B/C/D/E	Sequence B/C/D/E/A	Sequence C/D/E/A/B
Number of subjects	13	13	13
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	8.5	9.4	8.6
standard deviation	± 1.9	± 1.4	± 1.3
Gender categorical Units: Subjects			
Female	2	4	6
Male	11	9	7

Reporting group values	Sequence D/E/A/B/C	Sequence E/A/B/C/D	Total
Number of subjects	11	9	59
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			0 0 0 0 0 0 0 0 0
Age continuous Units: years			
arithmetic mean	8.8	9	-
standard deviation	± 1.7	± 1.7	-

Gender categorical			
Units: Subjects			
Female	4	2	18
Male	7	7	41

End points

End points reporting groups

Reporting group title	Sequence A/B/C/D/E
-----------------------	--------------------

Reporting group description:

- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations
- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic

Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.. Each patient will have 6 inhalations at each

Reporting group title	Sequence B/C/D/E/A
-----------------------	--------------------

Reporting group description:

- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations

Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

Reporting group title	Sequence C/D/E/A/B
-----------------------	--------------------

Reporting group description:

- Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations
- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations

Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

Reporting group title	Sequence D/E/A/B/C
-----------------------	--------------------

Reporting group description:

- Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
 - Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
 - Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations
 - Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
 - Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
- Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

Reporting group title	Sequence E/A/B/C/D
-----------------------	--------------------

Reporting group description:

- Treatment E (Ref): placebo pMDI with spacer, 6 inhalations in the morning at the clinic
- Treatment A (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations

- Treatment B (Exp): CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations
 - Treatment C (Exp): CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations
 - Treatment D (Ref): formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations
 Drug administration was done in the morning of each visit day at the clinic between 7.00 and 9.00 a.m.

Subject analysis set title	CHF 1535 50/6 µg - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised patients who received at least one dose of study medication and with any post-dose efficacy evaluations for a given treatment period.

Subject analysis set title	CHF 1535 100/12 µg - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised patients who will receive at least one dose of study medication and with any post-dose efficacy evaluations for a given treatment period.

Subject analysis set title	CHF 1535 200/24 µg - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised patients who will receive at least one dose of study medication and with any post-dose efficacy evaluations for a given treatment period.

Subject analysis set title	BDP 100 µg + FF 12 µg - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised patients who will receive at least one dose of study medication and with any post-dose efficacy evaluations for a given treatment period.

Subject analysis set title	Placebo - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised patients who will receive at least one dose of study medication and with any post-dose efficacy evaluations for a given treatment period.

Subject analysis set title	CHF 1535 50/6 µg - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised patients who took at least one dose of study medication.

Subject analysis set title	CHF 1535 100/12 µg - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised patients who took at least one dose of study medication.

Subject analysis set title	CHF 1535 200/24 µg - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised patients who took at least one dose of study medication.

Subject analysis set title	BDP 100 µg + FF 12 µg - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised patients who took at least one dose of study medication.

Subject analysis set title	Placebo - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised patients who took at least one dose of study medication.

Primary: FEV1 AUC0-12h standardised by time

End point title	FEV1 AUC0-12h standardised by time
End point description:	
FEV1 AUC corrected by time measured over 12 hours (10 min pre-dose and 10 min, 30 min, 1, 2, 4, 6, 8, 10, 12 hours postdose) following the morning dose of study medication.	
End point type	Primary
End point timeframe:	
At each visit from Visit 1 (screening visit, run-in period) to Visit 6 (from Visit 2 to Visit 6: treatment period)	

End point values	CHF 1535 50/6 µg - ITT	CHF 1535 100/12 µg - ITT	CHF 1535 200/24 µg - ITT	BDP 100 µg + FF 12 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	58	57	58	59
Units: liters				
arithmetic mean (standard deviation)	1.789 (± 0.388)	1.81 (± 0.405)	1.82 (± 0.416)	1.821 (± 0.416)

End point values	Placebo - ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	57			
Units: liters				
arithmetic mean (standard deviation)	1.738 (± 0.365)			

Statistical analyses

Statistical analysis title	CHF1535 100/12 µg vs BDP 100 µg + FF 12 µg
Comparison groups	CHF 1535 100/12 µg - ITT v BDP 100 µg + FF 12 µg - ITT
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.909
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.047
upper limit	0.042

Statistical analysis title	CHF 1535 50/6 µg vs placebo
Comparison groups	CHF 1535 50/6 µg - ITT v Placebo - ITT
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.048
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.045
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.089

Statistical analysis title	CHF 1535 100/12 µg vs placebo
Comparison groups	CHF 1535 100/12 µg - ITT v Placebo - ITT
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.076
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.032
upper limit	0.121

Statistical analysis title	CHF1535 200/24 µg vs placebo
Comparison groups	CHF 1535 200/24 µg - ITT v Placebo - ITT
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.086
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.041
upper limit	0.131

Statistical analysis title	BDP 100 µg + FF 12 µg vs placebo
Comparison groups	Placebo - ITT v BDP 100 µg + FF 12 µg - ITT
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.079
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.034
upper limit	0.123

Secondary: Peak FEV1

End point title	Peak FEV1
End point description:	Peak FEV1 is intended as the maximum value of the post-dose measurements during a 12 hour interval
End point type	Secondary
End point timeframe:	At each visit from Visit 1 (screening visit, run-in period) to Visit 6 (from Visit 2 to Visit 6: treatment period)

End point values	CHF 1535 50/6 µg - ITT	CHF 1535 100/12 µg - ITT	CHF 1535 200/24 µg - ITT	BDP 100 µg + FF 12 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	58	57	58	59
Units: liters				
arithmetic mean (standard deviation)	1.923 (± 0.4)	2 (± 0.427)	1.971 (± 0.404)	1.961 (± 0.426)

End point values	Placebo - ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	57			
Units: liters				
arithmetic mean (standard deviation)	1.879 (± 0.371)			

Statistical analyses

Statistical analysis title	CHF1535 100/12 µg vs BDP 100 µg + FF 12 µg
Comparison groups	CHF 1535 100/12 µg - ITT v BDP 100 µg + FF 12 µg - ITT
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.198
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.034
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.018
upper limit	0.086

Statistical analysis title	CHF1535 50/6 µg vs placebo
Comparison groups	CHF 1535 50/6 µg - ITT v Placebo - ITT
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.015
upper limit	0.089

Statistical analysis title	CHF1535 100/12 µg vs placebo
Comparison groups	Placebo - ITT v CHF 1535 100/12 µg - ITT

Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.119
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.067
upper limit	0.171

Statistical analysis title	CHF1535 200/24 µg vs placebo
Comparison groups	Placebo - ITT v CHF 1535 200/24 µg - ITT
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.094
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.042
upper limit	0.146

Statistical analysis title	BDP 100 µg + FF 12 µg vs placebo
Comparison groups	Placebo - ITT v BDP 100 µg + FF 12 µg - ITT
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.085
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.033
upper limit	0.137

Secondary: FEV1 at 12 h post-dose

End point title	FEV1 at 12 h post-dose
End point description:	
End point type	Secondary
End point timeframe:	
At each visit from Visit 1 (screening visit, run-in period) to Visit 6 (from Visit 2 to Visit 6: treatment period)	

End point values	CHF 1535 50/6 µg - ITT	CHF 1535 100/12 µg - ITT	CHF 1535 200/24 µg - ITT	BDP 100 µg + FF 12 µg - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	58	57	58	59
Units: liters				
arithmetic mean (standard deviation)	1.721 (± 0.423)	1.754 (± 0.395)	1.799 (± 0.432)	1.794 (± 0.424)

End point values	Placebo - ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	57			
Units: liters				
arithmetic mean (standard deviation)	1.733 (± 0.368)			

Statistical analyses

Statistical analysis title	CHF1535 100/12 µg vs BDP 100 µg + FF 12 µg
Comparison groups	CHF 1535 100/12 µg - ITT v BDP 100 µg + FF 12 µg - ITT
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.24
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.098
upper limit	0.025

Statistical analysis title	CHF1535 50/6 µg vs placebo
----------------------------	----------------------------

Comparison groups	CHF 1535 50/6 µg - ITT v Placebo - ITT
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.76
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.071
upper limit	0.052

Statistical analysis title	CHF1535 100/12 µg vs placebo
Comparison groups	Placebo - ITT v CHF 1535 100/12 µg - ITT
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.283
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.028
upper limit	0.094

Statistical analysis title	CHF1535 200/24 µg vs placebo
Comparison groups	Placebo - ITT v CHF 1535 200/24 µg - ITT
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.078
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.017
upper limit	0.139

Statistical analysis title	BDP 100 µg + FF 12 µg vs placebo
Comparison groups	Placebo - ITT v BDP 100 µg + FF 12 µg - ITT
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.009
upper limit	0.131

Secondary: Pre-dose heart rate

End point title	Pre-dose heart rate
End point description:	
End point type	Secondary
End point timeframe:	
At each visit from Visit 1 (screening visit, run-in period) to Visit 6 (from Visit 2 to Visit 6: treatment period)	

End point values	CHF 1535 50/6 µg - Safety	CHF 1535 100/12 µg - Safety	CHF 1535 200/24 µg - Safety	BDP 100 µg + FF 12 µg - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	58	57	58	59
Units: beats/min				
arithmetic mean (standard deviation)	80.2 (± 13.7)	80.3 (± 13.1)	80.4 (± 14.2)	81.7 (± 12.6)

End point values	Placebo - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	57			
Units: beats/min				
arithmetic mean (standard deviation)	81.5 (± 15.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Post-dose heart rate

End point title	Post-dose heart rate
-----------------	----------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

30 minutes post-dose at each clinic visit from Visit 2 to Visit 6

End point values	CHF 1535 50/6 µg - Safety	CHF 1535 100/12 µg - Safety	CHF 1535 200/24 µg - Safety	BDP 100 µg + FF 12 µg - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	58	57	58	59
Units: beats/min				
arithmetic mean (standard deviation)	79 (± 11.9)	80.7 (± 12.7)	81.6 (± 14.1)	80.1 (± 14.1)

End point values	Placebo - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	57			
Units: beats/min				
arithmetic mean (standard deviation)	79.7 (± 13.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose systolic blood pressure

End point title	Pre-dose systolic blood pressure
-----------------	----------------------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

Sitting systolic blood pressure at each visit from Visit 1 (screening visit, run-in period) to Visit 6 (from Visit 2 to Visit 6: treatment period).

End point values	CHF 1535 50/6 µg - Safety	CHF 1535 100/12 µg - Safety	CHF 1535 200/24 µg - Safety	BDP 100 µg + FF 12 µg - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	58	57	58	59
Units: mmHg				
arithmetic mean (standard deviation)	102.1 (± 6.7)	101.4 (± 6.8)	101.2 (± 7)	101.3 (± 6.7)

End point values	Placebo - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	57			
Units: mmHg				
arithmetic mean (standard deviation)	102 (± 6.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Post-dose systolic blood pressure

End point title	Post-dose systolic blood pressure
-----------------	-----------------------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

30 minutes post-dose, sitting systolic blood pressure at each visit from Visit 2 to Visit 6 (treatment period).

End point values	CHF 1535 50/6 µg - Safety	CHF 1535 100/12 µg - Safety	CHF 1535 200/24 µg - Safety	BDP 100 µg + FF 12 µg - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	58	57	58	59
Units: mmHg				
arithmetic mean (standard deviation)	102.2 (± 6.5)	101.9 (± 7.2)	101.4 (± 7.4)	102.2 (± 6.2)

End point values	Placebo - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	57			
Units: mmHg				
arithmetic mean (standard deviation)	102.5 (± 6.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose distolic blood pressure

End point title	Pre-dose distolic blood pressure
-----------------	----------------------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

Pre-dose, sitting diastolic blood pressure at each visit from Visit 1 (screening visit, run-in) to Visit 6 (from Visit 2 to Visit 6: treatment period).

End point values	CHF 1535 50/6 µg - Safety	CHF 1535 100/12 µg - Safety	CHF 1535 200/24 µg - Safety	BDP 100 µg + FF 12 µg - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	58	57	58	59
Units: mmHg				
arithmetic mean (standard deviation)	66.2 (± 6.4)	65.2 (± 6.6)	65.8 (± 6.9)	65.9 (± 6.7)

End point values	Placebo - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	57			
Units: mmHg				
arithmetic mean (standard deviation)	66.3 (± 6.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Post-dose diastolic blood pressure

End point title	Post-dose diastolic blood pressure
-----------------	------------------------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

30 minutes post-dose, sitting diastolic blood pressure at each visit from Visit 2 to Visit 6 (treatment period).

End point values	CHF 1535 50/6 µg - Safety	CHF 1535 100/12 µg - Safety	CHF 1535 200/24 µg - Safety	BDP 100 µg + FF 12 µg - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	58	57	58	59
Units: mmHg				
arithmetic mean (standard deviation)	65.7 (± 5.9)	66.1 (± 5.8)	65.6 (± 6.3)	65.9 (± 6.3)

End point values	Placebo - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	57			
Units: mmHg				
arithmetic mean (standard deviation)	66.1 (± 5.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose QTcF

End point title	Pre-dose QTcF
-----------------	---------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

15 minutes pre-dose at each visit from Visit 1 (screening visit, run-in period) to Visit 6 (from Visit 2 to Visit 6: treatment period).

End point values	CHF 1535 50/6 µg - Safety	CHF 1535 100/12 µg - Safety	CHF 1535 200/24 µg - Safety	BDP 100 µg + FF 12 µg - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	58	57	58	59
Units: msec				
arithmetic mean (standard deviation)	405.4 (± 12.6)	400.9 (± 13.6)	401.4 (± 14.9)	402.4 (± 15.4)

End point values	Placebo - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	57			
Units: msec				
arithmetic mean (standard deviation)	402.6 (± 14.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: 30 min post-dose QTcF

End point title	30 min post-dose QTcF
-----------------	-----------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

30 minutes post-dose at each visit from Visit 2 to Visit 6 (treatment period).

End point values	CHF 1535 50/6 µg - Safety	CHF 1535 100/12 µg - Safety	CHF 1535 200/24 µg - Safety	BDP 100 µg + FF 12 µg - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	58	57	58	59
Units: msec				
arithmetic mean (standard deviation)	404.3 (± 14)	405.5 (± 13.2)	406.4 (± 16.4)	402.5 (± 18.1)

End point values	Placebo - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	57			
Units: msec				
arithmetic mean (standard deviation)	401.1 (± 15.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: 1 hour post-dose QTcF

End point title	1 hour post-dose QTcF
-----------------	-----------------------

End point description:

End point type	Secondary
End point timeframe:	
1 hour post-dose at each visit from Visit 2 to Visit 6 (treatment period).	

End point values	CHF 1535 50/6 µg - Safety	CHF 1535 100/12 µg - Safety	CHF 1535 200/24 µg - Safety	BDP 100 µg + FF 12 µg - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	58	57	58	59
Units: msec				
arithmetic mean (standard deviation)	405.7 (± 12.8)	400.7 (± 16.1)	406.4 (± 16.3)	402.8 (± 14.5)

End point values	Placebo - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	57			
Units: msec				
arithmetic mean (standard deviation)	402.2 (± 14.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: 2 hour QTcF

End point title	2 hour QTcF
End point description:	
End point type	Secondary
End point timeframe:	
2 hours post-dose at each visit from Visit 2 to Visit 6 (treatment period).	

End point values	CHF 1535 50/6 µg - Safety	CHF 1535 100/12 µg - Safety	CHF 1535 200/24 µg - Safety	BDP 100 µg + FF 12 µg - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	58	57	58	59
Units: msec				
arithmetic mean (standard deviation)	403.2 (± 13.4)	400.8 (± 12.9)	405.1 (± 16.7)	402.5 (± 13.8)

End point values	Placebo - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	57			
Units: msec				
arithmetic mean (standard deviation)	403.1 (± 15.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: 6 hour post-dose QTcF

End point title	6 hour post-dose QTcF
-----------------	-----------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

6 hours post-dose at each visit from Visit 2 to Visit 6 (treatment period).

End point values	CHF 1535 50/6 µg - Safety	CHF 1535 100/12 µg - Safety	CHF 1535 200/24 µg - Safety	BDP 100 µg + FF 12 µg - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	58	57	58	59
Units: msec				
arithmetic mean (standard deviation)	402.5 (± 13.8)	402.1 (± 15.9)	403.2 (± 14.1)	402 (± 15.3)

End point values	Placebo - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	57			
Units: msec				
arithmetic mean (standard deviation)	402 (± 15.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: 12 hour post-dose QTcF

End point title	12 hour post-dose QTcF
-----------------	------------------------

End point description:

End point type	Secondary
End point timeframe:	
12 hours post-dose at each visit from Visit 2 to Visit 6 (treatment period).	

End point values	CHF 1535 50/6 µg - Safety	CHF 1535 100/12 µg - Safety	CHF 1535 200/24 µg - Safety	BDP 100 µg + FF 12 µg - Safety
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	58	57	58	59
Units: mesc				
arithmetic mean (standard deviation)	399.3 (± 12.6)	398.3 (± 13.3)	402.5 (± 13.8)	398.6 (± 12.3)

End point values	Placebo - Safety			
Subject group type	Subject analysis set			
Number of subjects analysed	57			
Units: mesc				
arithmetic mean (standard deviation)	399.1 (± 15.3)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

At each visit from Visit 1 (screening visit, run-in period) to Visit 6 (from Visit 2 to Visit 6: treatment period) to follow-up.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Safety population - CHF 1535 50/6 µg
-----------------------	--------------------------------------

Reporting group description:

CHF 1535 50/6 administered via a pMDI with spacer, 1 inhalation (dose: BDP 50 µg/FF 6 µg) + placebo HFA pMDI with spacer, 5 inhalations.

Reporting group title	Safety population - CHF 1535 100/12 µg
-----------------------	--

Reporting group description:

CHF 1535 50/6 administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg/FF 12 µg) + placebo HFA pMDI with spacer, 4 inhalations

Reporting group title	Safety population - CHF 1535 200/24 µg
-----------------------	--

Reporting group description:

CHF 1535 50/6 (dose: BDP 200 µg/FF 24 µg) administered via a pMDI with spacer, 4 inhalations (dose: BDP 200 µg/FF 24 µg) + placebo HFA pMDI with spacer, 2 inhalations

Reporting group title	Safety population - BDP 100 µg + FF 12 µg
-----------------------	---

Reporting group description:

Formoterol 6 µg HFA administered via a pMDI with spacer, 2 inhalations (dose: FF 12 µg) + extrafine BDP 50 µg, administered via a pMDI with spacer, 2 inhalations (dose: BDP 100 µg) + placebo HFA pMDI with spacer, 2 inhalations

Reporting group title	Safety population - Placebo
-----------------------	-----------------------------

Reporting group description:

Placebo pMDI with spacer, 6 inhalations in the morning at the clinic

Serious adverse events	Safety population - CHF 1535 50/6 µg	Safety population - CHF 1535 100/12 µg	Safety population - CHF 1535 200/24 µg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 58 (0.00%)	0 / 57 (0.00%)	0 / 58 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Safety population - BDP 100 µg + FF 12 µg	Safety population - Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Safety population - CHF 1535 50/6 µg	Safety population - CHF 1535 100/12 µg	Safety population - CHF 1535 200/24 µg
Total subjects affected by non-serious adverse events subjects affected / exposed	2 / 58 (3.45%)	3 / 57 (5.26%)	4 / 58 (6.90%)
Nervous system disorders Tremor subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	0 / 57 (0.00%) 0	1 / 58 (1.72%) 1
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Throat irritation subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0 1 / 58 (1.72%) 1 0 / 58 (0.00%) 0	0 / 57 (0.00%) 0 1 / 57 (1.75%) 1 1 / 57 (1.75%) 1	0 / 58 (0.00%) 0 0 / 58 (0.00%) 0 0 / 58 (0.00%) 0
Skin and subcutaneous tissue disorders Urticaria subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	0 / 57 (0.00%) 0	0 / 58 (0.00%) 0
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Respiratory tract infection	0 / 58 (0.00%) 0 0 / 58 (0.00%) 0	0 / 57 (0.00%) 0 0 / 57 (0.00%) 0	0 / 58 (0.00%) 0 2 / 58 (3.45%) 2

subjects affected / exposed	0 / 58 (0.00%)	1 / 57 (1.75%)	1 / 58 (1.72%)
occurrences (all)	0	1	1
Sinusitis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 57 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Safety population - BDP 100 µg + FF 12 µg	Safety population - Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 59 (5.08%)	4 / 57 (7.02%)	
Nervous system disorders			
Tremor			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	
occurrences (all)	0	0	
Throat irritation			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	1 / 59 (1.69%)	2 / 57 (3.51%)	
occurrences (all)	1	2	
Respiratory tract infection			

subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	
occurrences (all)	0	0	
Sinusitis			
subjects affected / exposed	0 / 59 (0.00%)	0 / 57 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 July 2012	This substantial amendment was introduced: 1. To modify the inclusion criterion n.6 about reversibility test at the screening visit lowering the positive threshold to 12% improvement with 200 µg salbutamol from pre-dose value instead of 15% in this children population under stable inhaled corticosteroid therapy; 2. To increase the time window between the 12-hour spirometry visits, and the relevant tolerance, from 7±3 to 14±7 days, in order to improve the acceptability of the study by patients and their parents, and to better match the availability of study personnel at the sites; 3. To provide also parents/patients with instructions for cleaning of AeroChamber Plus™ spacers in case of delay in attending clinic visits; 4. To decrease the number of participating Countries, keeping the same number of involved investigational sites; 5. To update the planned study start and end; 6. To allow the concomitant treatment with leukotriene antagonists if taken at stable dose in the 4 weeks prior to study entry and to be continued at the same dose throughout all the study period; 7. To correct some typing errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported