Clinical trial results:
A SINGLE CENTRE DOUBLE-BLIND, RANDOMISED 3 PERIOD CROSS OVER STUDY TO COMPARE SAFETY ASSESSED BY KNEMOMETRY AND URINARY CORTISOL MEASUREMENTS OF BECLOMETHASONE DIPROPIONATE HFA pMDI 100 AND 200 µg B.I.D. USING AEROCHAMBER PLUS™ SPACING DEVICE AND BECLOMETHASONE DIPROPIONATE HFA pMDI 200 µg B.I.D. USING THE VOLUMATIC™ SPACING DEVICE IN CHILDREN WITH MILD ASTHMA DURING A 2–WEEK TREATMENT PERIOD

Summary

EudraCT number	2007-003412-59
Trial protocol	DK
Global end of trial date	27 December 2007

Results information

Result version number	v1 (current)
This version publication date	10 November 2017
First version publication date	10 November 2017

Trial information

Trial identification

Sponsor protocol code	CCD-0704-PR-0024

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici S.p.A.
Sponsor organisation address	Via Palermo 26/A, Parma, Italy, 43122
Public contact	Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., +39 0521 2791, ClinicalTrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., +39 0521 2791, ClinicalTrials_info@chiesi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	03 December 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 December 2007
Global end of trial reached?	Yes
Global end of trial date	27 December 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to compare lower leg growth rate (LLGR), measured by knemometry, during a 2-week treatment period with BDP HFA pMDI 200 µg b.i.d. using AeroChamber Plus™ spacing device versus BDP HFA pMDI 200 µg b.i.d. using Volumatic™ spacing device.

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:

During the one-week training period the patients have familiarized with the actuators, the AeroChamber(TM) spacer and Volumatic (TM) spacer devices and the procedures to take place during the study. Patients were be off inhalation of corticosteroid treatment in the training period.

Actual start date of recruitment	17 September 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 26
Worldwide total number of subjects	26
EEA total number of subjects	26

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	19
Adolescents (12-17 years)	7
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of thirty (30) outpatients were enrolled.

Pre-assignment

Screening details:

Children (males and females) 6-14 years old (inclusive), with a clinical diagnosis of mild asthma during at least two months prior to screening visit were selected.

Pre-assignment period milestones

Number of subjects started	26
Intermediate milestone: Number of subjects	Run In- Placebo HFA pMDI: 26
Number of subjects completed	26

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence A (treatments A-B-C)

Arm description:

- Treatment A: BDP HFA pMDI (100 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment B: BDP HFA pMDI (50 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment C: BDP HFA pMDI (100 µg / actuation) via Volumatic™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d., for 2 weeks.

A run-in period with Placebo HFA pMDI (2 inhalations bid, via AeroChamber Plus1M spacer and via Volumatic(TM) spacer in the morning and in the evening for 2 weeks) preceded the first active section. The second and the third active sections were preceded by a 2-week wash-out period.

Arm type	Experimental
Investigational medicinal product name	BDP HFA pMDI
Investigational medicinal product code	
Other name	beclomethasone dipropionate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Treatment A: BDP hydrofluoroalcane (HFA) by pressurized metered-dose inhaler (pMDI) via AeroChamber Plus™ spacer, 2 inhalations b.i.d. (100 µg / actuation) for two weeks.
Treatment B: BDP HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d. (50 µg / actuation) for two weeks.
Treatment C: BDP HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d. (100 µg / actuation) for 2 weeks.

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

Dosage and administration details:

Treatment A: placebo hydrofluoroalcane (HFA) by pressurized metered-dose inhaler (pMDI) via Volumatic™ spacer, 2 inhalations b.i.d. for 2 weeks.
Treatment B: placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d. for 2 weeks.
Treatment C: placebo HFA pMDI via Aerochamber Plus™ spacer, 2 inhalations b.i.d. for 2 weeks.

Arm title	Sequence B (treatments A-C-B)

Arm description:

- Treatment A: BDP HFA pMDI (100 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment C: BDP HFA pMDI (100 µg / actuation) via Volumatic™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment B: BDP HFA pMDI (50 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
A run-in period with Placebo HFA pMDI (2 inhalations bid, via AeroChamber Plus1M spacer and via Volumatic(TM) spacer in the morning and in the evening for 2 weeks) preceded the first active section. The second and the third active sections were preceded by a 2-week wash-out period.

Arm type	Experimental
Investigational medicinal product name	BDP HFA pMDI
Investigational medicinal product code	
Other name	beclomethasone dipropionate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Treatment A: BDP hydrofluoroalcane (HFA) by pressurized metered-dose inhaler (pMDI) via AeroChamber Plus™ spacer, 2 inhalations b.i.d. (100 µg / actuation) for two weeks.
Treatment C: BDP HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d. (100 µg / actuation) for 2 weeks.
Treatment B: BDP HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d. (50 µg / actuation) for two weeks.

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

Dosage and administration details:

Treatment A: placebo hydrofluoroalcane (HFA) by pressurized metered-dose inhaler (pMDI) via Volumatic™ spacer, 2 inhalations b.i.d. for 2 weeks.
Treatment C: placebo HFA pMDI via Aerochamber Plus™ spacer, 2 inhalations b.i.d. for 2 weeks.
Treatment B: placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d. for 2 weeks.

Arm title	Sequence C (treatments B-A-C)

Arm description:

- Treatment B: BDP HFA pMDI (50 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment A: BDP HFA pMDI (100 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment C: BDP HFA pMDI (100 µg / actuation) via Volumatic™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d., for 2 weeks.
A run-in period with Placebo HFA pMDI (2 inhalations bid, via AeroChamber Plus1M spacer and via Volumatic(TM) spacer in the morning and in the evening for 2 weeks) preceded the first active section. The second and the third active sections were preceded by a 2-week wash-out period.

Arm type	Experimental
Investigational medicinal product name	BDP HFA pMDI
Investigational medicinal product code	
Other name	beclomethasone dipropionate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Treatment B: BDP hydrofluoroalcane (HFA) by pressurized metered-dose inhaler (pMDI) via AeroChamber Plus™ spacer, 2 inhalations b.i.d. (50 µg / actuation) for two weeks.
Treatment A: BDP HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d. (100 µg / actuation) for two weeks.
Treatment C: BDP HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d. (100 µg / actuation) for 2 weeks.

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

Dosage and administration details:

Treatment B: placebo hydrofluoroalcane (HFA) by pressurized metered-dose inhaler (pMDI) via Volumatic™ spacer, 2 inhalations b.i.d. for 2 weeks.
Treatment A: placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d. for 2 weeks.
Treatment C: placebo HFA pMDI via Aerochamber Plus™ spacer, 2 inhalations b.i.d. for 2 weeks.

Arm title	Sequence D (treatments B-C-A)

Arm description:

- Treatment B: BDP HFA pMDI (50 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment C: BDP HFA pMDI (100 µg / actuation) via Volumatic™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment A: BDP HFA pMDI (100 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
A run-in period with Placebo HFA pMDI (2 inhalations bid, via AeroChamber Plus1M spacer and via Volumatic(TM) spacer in the morning and in the evening for 2 weeks) preceded the first active section. The second and the third active sections were preceded by a 2-week wash-out period.

Arm type	Experimental
Investigational medicinal product name	BDP HFA pMDI
Investigational medicinal product code	
Other name	Beclomethasone dipropionate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Treatment B: BDP hydrofluoroalcane (HFA) by pressurized metered-dose inhaler (pMDI) via AeroChamber Plus™ spacer, 2 inhalations b.i.d. (50 µg / actuation) for two weeks.
Treatment C: BDP HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d. (100 µg / actuation) for 2 weeks.
Treatment A: BDP HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d. (100 µg / actuation) for two weeks.

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

Dosage and administration details:

Treatment B: placebo hydrofluoroalcane (HFA) by pressurized metered-dose inhaler (pMDI) via Volumatic™ spacer, 2 inhalations b.i.d. for 2 weeks.
Treatment C: placebo HFA pMDI via Aerochamber Plus™ spacer, 2 inhalations b.i.d. for 2 weeks.
Treatment A: placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d. for 2 weeks.

Arm title	Sequence E (treatments C-A-B)

Arm description:

- Treatment C: BDP HFA pMDI (100 µg / actuation) via Volumatic™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment A: BDP HFA pMDI (100 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment B: BDP HFA pMDI (50 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.

A run-in period with Placebo HFA pMDI (2 inhalations bid, via AeroChamber Plus1M spacer and via Volumatic(TM) spacer in the morning and in the evening for 2 weeks) preceded the first active section. The second and the third active sections were preceded by a 2-week wash-out period.

Arm type	Experimental
Investigational medicinal product name	BDP HFA pMDI
Investigational medicinal product code	
Other name	Beclomethasone dipropionate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Treatment C: BDP hydrofluoroalcane (HFA) by pressurized metered-dose inhaler (pMDI) via Volumatic™ spacer, 2 inhalations b.i.d. (100 µg / actuation) for 2 weeks.
Treatment A: BDP HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d. (100 µg / actuation) for two weeks.
Treatment B: BDP HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d. (50 µg / actuation) for two weeks.

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

Dosage and administration details:

Treatment C: placebo hydrofluoroalcane (HFA) by pressurized metered-dose inhaler (pMDI) via Aerochamber Plus™ spacer, 2 inhalations b.i.d. for 2 weeks.
Treatment A: placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d. for 2 weeks.
Treatment B: placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d. for 2 weeks.

Arm title	Sequence F (treatments C-B-A)

Arm description:

- Treatment C: BDP HFA pMDI (100 µg / actuation) via Volumatic™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment B: BDP HFA pMDI (50 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment A: BDP HFA pMDI (100 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
A run-in period with Placebo HFA pMDI (2 inhalations bid, via AeroChamber Plus1M spacer and via Volumatic(TM) spacer in the morning and in the evening for 2 weeks) preceded the first active section. The second and the third active sections were preceded by a 2-week wash-out period.

Arm type	Experimental
Investigational medicinal product name	BDP HFA pMDI
Investigational medicinal product code	
Other name	beclomethasone dipropionate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Treatment C: BDP hydrofluoroalcane (HFA) by pressurized metered-dose inhaler (pMDI) via Volumatic™ spacer, 2 inhalations b.i.d. (100 µg / actuation) for 2 weeks.
Treatment B: BDP HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d. (50 µg / actuation) for two weeks.
Treatment A: BDP HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d. (100 µg / actuation) for two weeks.

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

Dosage and administration details:

Treatment C: placebo hydrofluoroalcane (HFA) by pressurized metered-dose inhaler (pMDI) via

Aerochamber Plus™ spacer, 2 inhalations b.i.d. for 2 weeks.
Treatment B: placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d. for 2 weeks.
Treatment A: placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d. for 2 weeks.

Number of subjects in period 1	Sequence A (treatments A-B-C)	Sequence B (treatments A-C-B)	Sequence C (treatments B-A-C)
Started	3	4	5
Completed	3	4	5

Number of subjects in period 1	Sequence D (treatments B-C-A)	Sequence E (treatments C-A-B)	Sequence F (treatments C-B-A)
Started	4	5	5
Completed	4	5	5

Baseline characteristics

Reporting groups

Reporting group title	Overall trial by sequence

Reporting group description: -

Reporting group values	Overall trial by sequence	Total	
Number of subjects	26	26	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	9.8		
standard deviation	± 10	-	
Gender categorical Units: Subjects			
Female	11	11	
Male	15	15	

Subject analysis sets

Subject analysis set title	Treatment A - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-To-Treat analysis set (ITT), consisted of data from all patients, who were randomised and exposed to at least one dose of study product in the treatment period.

Subject analysis set title	Treatment B - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-To-Treat analysis set (ITT), consisted of data from all patients, who were randomised and exposed to at least one dose of study product in the treatment period.

Subject analysis set title	Treatment C - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-To-Treat analysis set (ITT), consisted of data from all patients, who were randomised and exposed to at least one dose of study product in the treatment period.

Subject analysis set title	Run-in Placebo - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-To-Treat analysis set (ITT), consisted of data from all patients, who were randomised and exposed to at least one dose of study product in the treatment period.

Reporting group values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population
Number of subjects	26	26	26
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	9.8	9.8	9.8
standard deviation	± 10	± 10	± 10
Gender categorical			
Units: Subjects			
Female	11	11	11
Male	15	15	15

Reporting group values	Run-in Placebo - ITT population		
Number of subjects	26		
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	9.8		
standard deviation	± 10		
Gender categorical			
Units: Subjects			
Female	11		
Male	15		

End points

End points reporting groups

Reporting group title	Sequence A (treatments A-B-C)

Reporting group description:

- Treatment A: BDP HFA pMDI (100 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment B: BDP HFA pMDI (50 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment C: BDP HFA pMDI (100 µg / actuation) via Volumatic™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d., for 2 weeks.

A run-in period with Placebo HFA pMDI (2 inhalations bid, via AeroChamber Plus1M spacer and via Volumatic(TM) spacer in the morning and in the evening for 2 weeks) preceded the first active section. The second and the third active sections were preceded by a 2-week wash-out period.

Reporting group title	Sequence B (treatments A-C-B)

Reporting group description:

- Treatment A: BDP HFA pMDI (100 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment C: BDP HFA pMDI (100 µg / actuation) via Volumatic™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment B: BDP HFA pMDI (50 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.

A run-in period with Placebo HFA pMDI (2 inhalations bid, via AeroChamber Plus1M spacer and via Volumatic(TM) spacer in the morning and in the evening for 2 weeks) preceded the first active section. The second and the third active sections were preceded by a 2-week wash-out period.

Reporting group title	Sequence C (treatments B-A-C)

Reporting group description:

- Treatment B: BDP HFA pMDI (50 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment A: BDP HFA pMDI (100 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment C: BDP HFA pMDI (100 µg / actuation) via Volumatic™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d., for 2 weeks.

A run-in period with Placebo HFA pMDI (2 inhalations bid, via AeroChamber Plus1M spacer and via Volumatic(TM) spacer in the morning and in the evening for 2 weeks) preceded the first active section. The second and the third active sections were preceded by a 2-week wash-out period.

Reporting group title	Sequence D (treatments B-C-A)

Reporting group description:

- Treatment B: BDP HFA pMDI (50 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment C: BDP HFA pMDI (100 µg / actuation) via Volumatic™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment A: BDP HFA pMDI (100 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.

A run-in period with Placebo HFA pMDI (2 inhalations bid, via AeroChamber Plus1M spacer and via Volumatic(TM) spacer in the morning and in the evening for 2 weeks) preceded the first active section. The second and the third active sections were preceded by a 2-week wash-out period.

Reporting group title	Sequence E (treatments C-A-B)

Reporting group description:

- Treatment C: BDP HFA pMDI (100 µg / actuation) via Volumatic™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment A: BDP HFA pMDI (100 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment B: BDP HFA pMDI (50 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.

A run-in period with Placebo HFA pMDI (2 inhalations bid, via AeroChamber Plus1M spacer and via Volumatic(TM) spacer in the morning and in the evening for 2 weeks) preceded the first active section. The second and the third active sections were preceded by a 2-week wash-out period.

Reporting group title	Sequence F (treatments C-B-A)

Reporting group description:

- Treatment C: BDP HFA pMDI (100 µg / actuation) via Volumatic™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d., for 2 weeks.

- Treatment B: BDP HFA pMDI (50 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment A: BDP HFA pMDI (100 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
A run-in period with Placebo HFA pMDI (2 inhalations bid, via AeroChamber Plus1M spacer and via Volumatic(TM) spacer in the morning and in the evening for 2 weeks) preceded the first active section. The second and the third active sections were preceded by a 2-week wash-out period.

Subject analysis set title	Treatment A - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-To-Treat analysis set (ITT), consisted of data from all patients, who were randomised and exposed to at least one dose of study product in the treatment period.

Subject analysis set title	Treatment B - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-To-Treat analysis set (ITT), consisted of data from all patients, who were randomised and exposed to at least one dose of study product in the treatment period.

Subject analysis set title	Treatment C - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-To-Treat analysis set (ITT), consisted of data from all patients, who were randomised and exposed to at least one dose of study product in the treatment period.

Subject analysis set title	Run-in Placebo - ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intention-To-Treat analysis set (ITT), consisted of data from all patients, who were randomised and exposed to at least one dose of study product in the treatment period.

Primary: Lower leg growth rate measured by knemometry

End point title	Lower leg growth rate measured by knemometry

End point description:

Lower leg growth rate (LLGR) measured by knemometry during a 2-week treatment period with BDP HFA pMDI 200 µg b.i.d. via AeroChamber Plus™ spacer versus BDP HFA pMDI 200 µg b.i.d. via Volumatic™ spacer.

End point type	Primary

End point timeframe:

At Visit 2 during training period and at Visit 3 (randomisation), Visit 4 (week 2), Visit 5 (week 4), Visit 6 (week 6), Visit 7 (week 8) and Visit 8 (end of treatment) during the active period.

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Run-in Placebo - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	26	26	26	26
Units: mm/wk				
arithmetic mean (standard deviation)	0.23 (± 0.325)	0.3 (± 0.303)	0.26 (± 0.288)	0.39 (± 0.24)

Statistical analyses

Statistical analysis title	Treatment A vs Treatment C
Comparison groups	Treatment A - ITT population v Treatment C - ITT population

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Mean difference (final values)
Point estimate	-0.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.13

Notes:

[1] - The LLGR was analyzed using ANOVA with treatments and periods as fixed effects, patients as a random effect and the baseline LLGR as a covariate. The difference 100 µg AeroChamber – 100 µg Volumatic for adjusted treatment means was presented with a two-sided 95% confidence interval. If the left endpoint of this interval is greater than or equal to -0.2 mm/week non-inferiority is declared.

Secondary: Pre-dose morning PEF

End point title	Pre-dose morning PEF

End point description:

The parameter was measured at home daily during each study period.
At the training visit, a Patient Diary Card was handed out to the patient. The patient would follow instructions for measuring PEF (morning and evening) with a Mini-Wright Peak Flow Meter and scoring asthma symptoms.

End point type	Secondary

End point timeframe:

At screening, at Visit 2 during training period and at Visit 3 (randomisation), Visit 4 (week 2), Visit 5 (week 4), Visit 6 (week 6), Visit 7 (week 8) and Visit 8 (end of treatment) during the active period.

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Run-in Placebo - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	26	26	26	26
Units: L/min)				
arithmetic mean (standard deviation)	253 (± 58.2)	257.3 (± 62.8)	260.7 (± 59.1)	249.1 (± 56.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose evening PEF

End point title	Pre-dose evening PEF

End point description:

The parameter was measured at home daily during each study period.
At the training visit, a Patient Diary Card was handed out to the patient. The patient would follow instructions for measuring PEF (morning and evening) with a Mini-Wright Peak Flow Meter and scoring asthma symptoms.

End point type	Secondary

End point timeframe:

At screening, at Visit 2 during training period and at Visit 3 (randomisation), Visit 4 (week 2), Visit 5

(week 4), Visit 6 (week 6), Visit 7 (week 8) and Visit 8 (end of treatment) during the active period.

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Run-in Placebo - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	26	26	26	26
Units: L/min				
arithmetic mean (standard deviation)	254.8 (± 58)	257.3 (± 62.9)	263.4 (± 62.1)	248.8 (± 55.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Asthma symptom score (Total)

End point title	Asthma symptom score (Total)

End point description:

At the training visit, a Patient Diary Card was handed out to the patient. The patient would follow instructions for measuring PEF (morning and evening) with a Mini-Wright Peak Flow Meter and scoring asthma symptoms.

End point type	Secondary

End point timeframe:

At Visit 2 during training period and at Visit 3 (randomisation), Visit 4 (week 2), Visit 5 (week 4), Visit 6 (week 6), Visit 7 (week 8) till the end of treatment during the active period.

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Run-in Placebo - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	26	26	26	26
Units: score				
arithmetic mean (standard deviation)	0.23 (± 0.63)	0.21 (± 0.62)	0.21 (± 0.6)	0.29 (± 0.64)

Statistical analyses

No statistical analyses for this end point

Secondary: Daily use of rescue medication

End point title	Daily use of rescue medication

End point description:

Inhaled terbutaline was administered as rescue medication. A minimum period of 4 hours should elapse between the use of rescue terbutaline and the spirometric measurements

End point type	Secondary

End point timeframe:

Throughout the study from training period to End of Treatment.

End point values	Treatment A - ITT population	Treatment B - ITT population	Treatment C - ITT population	Run-in Placebo - ITT population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	26	25	24	24
Units: number of doses				
arithmetic mean (standard deviation)	0.14 (± 0.42)	0.03 (± 0.09)	0.05 (± 0.14)	0.14 (± 0.29)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

At each visit in both the training period (Visits 1 and 2) and the active period (Visits 3 throug Visit 8).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	8.1

Reporting groups

Reporting group title	Sequence A (treatments A-B-C)

Reporting group description:

- Treatment A: BDP HFA pMDI (100 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment B: BDP HFA pMDI (50 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment C: BDP HFA pMDI (100 µg / actuation) via Volumatic™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d., for 2 weeks.

Each active section was preceded by a 2-week wash-out period.

Reporting group title	Sequence B (treatments A-C-B)

Reporting group description:

- Treatment A: BDP HFA pMDI (100 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment C: BDP HFA pMDI (100 µg / actuation) via Volumatic™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment B: BDP HFA pMDI (50 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.

Each active section was preceded by a 2-week wash-out period.

Reporting group title	Sequence C (treatments B-A-C)

Reporting group description:

- Treatment B: BDP HFA pMDI (50 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment A: BDP HFA pMDI (100 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment C: BDP HFA pMDI (100 µg / actuation) via Volumatic™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d., for 2 weeks.

Each active section was preceded by a 2-week wash-out period.

Reporting group title	Sequence D (treatments B-C-A)

Reporting group description:

- Treatment B: BDP HFA pMDI (50 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment C: BDP HFA pMDI (100 µg / actuation) via Volumatic™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment A: BDP HFA pMDI (100 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.

Each active section was preceded by a 2-week wash-out period.

Reporting group title	Sequence E (treatments C-A-B)

Reporting group description:

- Treatment C: BDP HFA pMDI (100 µg / actuation) via Volumatic™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment A: BDP HFA pMDI (100 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment B: BDP HFA pMDI (50 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.

Each active section was preceded by a 2-week wash-out period.

Reporting group title	Sequence F (treatments C-B-A)

Reporting group description:

- Treatment C: BDP HFA pMDI (100 µg / actuation) via Volumatic™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via AeroChamber Plus™ spacer, 2 inhalations b.i.d., for 2 weeks.

- Treatment B: BDP HFA pMDI (50 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
- Treatment A: BDP HFA pMDI (100 µg / actuation) via AeroChamber Plus™ spacer, 2 inhalations b.i.d., + placebo HFA pMDI via Volumatic™ spacer, 2 inhalations b.i.d., for 2 weeks.
Each active section was preceded by a 2-week wash-out period.

Serious adverse events	Sequence A (treatments A-B-C)	Sequence B (treatments A-C-B)	Sequence C (treatments B-A-C)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Sequence D (treatments B-C-A)	Sequence E (treatments C-A-B)	Sequence F (treatments C-B-A)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 0.03 %

Non-serious adverse events	Sequence A (treatments A-B-C)	Sequence B (treatments A-C-B)	Sequence C (treatments B-A-C)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	1 / 5 (20.00%)
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Middle ear effusion			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Pharyngolaryngeal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Laryngitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Acute tonsillitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Viral pharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 4 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Sequence D (treatments B-C-A)	Sequence E (treatments C-A-B)	Sequence F (treatments C-B-A)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	0 / 4 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Middle ear effusion			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal			

disorders			
Pharyngolaryngeal pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Laryngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Acute tonsillitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Viral pharyngitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

There are no limitations nor caveats applicable to this summary of results.

Notes: