Clinical trial results:
A Single Dose, Randomised, Double Blind, Double Dummy, Placebo Controlled, 3-way Crossover Clinical Study, comparing the Onset of Relief from Methacholine-induced Bronchoconstriction with CHF1535 100/6 g NEXThaler® versus CHF1535 100/6 g pMDI in Asthmatic Patients.

Summary

EudraCT number	2016-003672-47
Trial protocol	GB
Global end of trial date	19 September 2017

Results information

Result version number	v1 (current)
This version publication date	28 September 2018
First version publication date	28 September 2018

Trial information

Trial identification

Sponsor protocol code	CCD-01535BD1-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03108534
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici S.p.A.
Sponsor organisation address	Via Palermo 26/A, Parma, Italy, 43126
Public contact	Chiesi Farmaceutici S.p.A., Clinical Trial Transparency, Chiesi Farmaceutici S.p.A., +39 0521 2791, clinicaltrials_info@chiesi.com
Scientific contact	Chiesi Farmaceutici S.p.A., 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 September 2017
Global end of trial reached?	Yes
Global end of trial date	19 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate, in terms of pulmonary function, the non-inferiority of CHF1535 100/6 µg NEXThaler® vs CHF1535 100/6 µg pMDI on the onset of relief from methacholine-induced bronchospasm in asthmatic subjects on low-medium doses of Inhaled corticosteroids (ICS) or ICS with long-acting β2 agonist (LABA) fixed or free combination.

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:

Patients could continue their previous therapy with ICS or ICS/LABA with ICS at medium-low doses during the overall trial duration. In case they were in treatment with ICS/LABA fixed combination, they were switched to the free components in order to allow the LABA withdrawal before each visit.

Evidence for comparator:

CHF1535 100/6 µg pMDI

Actual start date of recruitment	28 February 2017
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	United Kingdom: 65
Worldwide total number of subjects	65
EEA total number of subjects	65

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	65
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The 65 subjects who positively passed screening were randomised to one of the six treatment sequences: ABC (11), ACB (9), BAC (12), BCA (9), CAB (12), CBA (12) where A stands for the Test treatment CHF1535 100/6 µg NEXThaler®, B for CHF1535 100/6 µg pMDI and C for placebo. 60 of the randomised subjects completed the study.

Pre-assignment

Screening details:

In total, 181 subjects diagnosed with asthma were screened of whom 116 (64.1%) failed screening.

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, Carer

Blinding implementation details:

The randomisation list was provided to the labelling facility but was not available to the subjects, investigators, monitors or employees of the centre involved in the management of the study before unblinding of the data, unless in case of emergency.
The Sponsor's clinical team was also blinded during the study as they did not have direct access to the randomisation list.

Arms

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

Arm description:

A - test treatment (CHF1535 100/6 µg NEXThaler®): One inhalation of CHF1535 100/6 µg NEXThaler® + one inhalation of CHF1535 100/6 µg pMDI matched placebo;
B -Reference treatment (CHF1535 100/6 µg pMDI): One inhalation of CHF1535 100/6 µg pMDI + one inhalation of CHF1535 100/6 µg NEXThaler® matched placebo;
C - Placebo: One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo + one inhalation of CHF1535 100/6 µg pMDI matched placebo.

Arm type	experimental - active comparator - placebo
Investigational medicinal product name	CHF1535 NEXThaler
Investigational medicinal product code	
Other name	Beclometasone dipropionate + formoterol fumarate
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of CHF1535 100/6 µg NEXThaler®;
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

Investigational medicinal product name	CHF1535 pMDI
Investigational medicinal product code	
Other name	Beclometasone dipropionate + formoterol fumarate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of CHF1535 100/6 µg pMDI;
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

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

Dosage and administration details:

One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo.
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

Investigational medicinal product name	CHF1535 pMDI Placebo
Investigational medicinal product code	
Other name	placebo
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of CHF1535 100/6 µg pMDI matched placebo.
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

Arm title	Sequence A-C-B

Arm description:

A - test treatment (CHF1535 100/6 µg NEXThaler®): One inhalation of CHF1535 100/6 µg NEXThaler® + one inhalation of CHF1535 100/6 µg pMDI matched placebo;
C - Placebo: One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo + one inhalation of CHF1535 100/6 µg pMDI matched placebo.
B -Reference treatment (CHF1535 100/6 µg pMDI): One inhalation of CHF1535 100/6 µg pMDI + one inhalation of CHF1535 100/6 µg NEXThaler® matched placebo;

Arm type	experimental - placebo - active comparator
Investigational medicinal product name	CHF1535 NEXThaler
Investigational medicinal product code	
Other name	Beclometasone dipropionate + formoterol fumarate
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of CHF1535 100/6 µg NEXThaler;
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

Investigational medicinal product name	CHF1535 pMDI
Investigational medicinal product code	
Other name	Beclometasone dipropionate + formoterol fumarate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of CHF1535 100/6 µg pMDI;
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

Investigational medicinal product name	CHF 1535 NEXThaler Placebo
Investigational medicinal product code	
Other name	placebo

Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo.
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

Investigational medicinal product name	CHF1535 pMDI Placebo
Investigational medicinal product code	
Other name	placebo
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of CHF1535 100/6 µg pMDI matched placebo.
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

Arm title	Sequence B-A-C

Arm description:

B -Reference treatment (CHF1535 100/6 µg pMDI): One inhalation of CHF1535 100/6 µg pMDI + one inhalation of CHF1535 100/6 µg NEXThaler® matched placebo;
A - test treatment (CHF1535 100/6 µg NEXThaler®): One inhalation of CHF1535 100/6 µg NEXThaler® + one inhalation of CHF1535 100/6 µg pMDI matched placebo;
C - Placebo: One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo + one inhalation of CHF1535 100/6 µg pMDI matched placebo.

Arm type	active comparator - experimental - placebo
Investigational medicinal product name	CHF1535 NEXThaler
Investigational medicinal product code	
Other name	Beclometasone dipropionate + formoterol fumarate
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of CHF1535 100/6 µg NEXThaler®.
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

Investigational medicinal product name	CHF1535 pMDI
Investigational medicinal product code	
Other name	Beclometasone dipropionate + formoterol fumarate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of CHF1535 100/6 µg pMDI;
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

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

Dosage and administration details:

One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo.
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least

30 seconds.

Investigational medicinal product name	CHF1535 pMDI Placebo
Investigational medicinal product code	
Other name	placebo
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of CHF1535 100/6 µg pMDI matched placebo.
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

Arm title	Sequence B-C-A

Arm description:

B -Reference treatment (CHF1535 100/6 µg pMDI): One inhalation of CHF1535 100/6 µg pMDI + one inhalation of CHF1535 100/6 µg NEXThaler® matched placebo;
C - Placebo: One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo + one inhalation of CHF1535 100/6 µg pMDI matched placebo.
A - test treatment (CHF1535 100/6 µg NEXThaler®): One inhalation of CHF1535 100/6 µg NEXThaler® + one inhalation of CHF1535 100/6 µg pMDI matched placebo;

Arm type	Active comparator - placebo - experimental
Investigational medicinal product name	CHF1535 NEXThaler
Investigational medicinal product code	
Other name	Beclometasone dipropionate + formoterol fumarate
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of CHF1535 100/6 µg NEXThaler®;
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

Investigational medicinal product name	CHF1535 pMDI
Investigational medicinal product code	
Other name	Beclometasone dipropionate + formoterol fumarate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of CHF1535 100/6 µg pMDI;
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

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

Dosage and administration details:

One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo.
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

Investigational medicinal product name	CHF1535 pMDI Placebo
Investigational medicinal product code	
Other name	placebo
Pharmaceutical forms	Inhalation solution

Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of CHF1535 100/6 µg pMDI matched placebo.
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

Arm title	Sequence C-A-B

Arm description:

C - Placebo: One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo + one inhalation of CHF1535 100/6 µg pMDI matched placebo.
A - test treatment (CHF1535 100/6 µg NEXThaler®): One inhalation of CHF1535 100/6 µg NEXThaler® + one inhalation of CHF1535 100/6 µg pMDI matched placebo;
B -Reference treatment (CHF1535 100/6 µg pMDI): One inhalation of CHF1535 100/6 µg pMDI + one inhalation of CHF1535 100/6 µg NEXThaler® matched placebo;

Arm type	placebo - experimental - active comparator
Investigational medicinal product name	CHF1535 NEXThaler
Investigational medicinal product code	
Other name	Beclometasone dipropionate + formoterol fumarate
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of CHF1535 100/6 µg NEXThaler®;
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

Investigational medicinal product name	CHF1535 pMDI
Investigational medicinal product code	
Other name	Beclometasone dipropionate + formoterol fumarate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of CHF1535 100/6 µg pMDI;
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

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

Dosage and administration details:

One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo.
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

Investigational medicinal product name	CHF1535 pMDI Placebo
Investigational medicinal product code	
Other name	placebo
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of CHF1535 100/6 µg pMDI matched placebo.
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

Arm title	Sequence C-B-A

Arm description:

C - Placebo: One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo + one inhalation of CHF1535 100/6 µg pMDI matched placebo.
B -Reference treatment (CHF1535 100/6 µg pMDI): One inhalation of CHF1535 100/6 µg pMDI + one inhalation of CHF1535 100/6 µg NEXThaler® matched placebo;
A - test treatment (CHF1535 100/6 µg NEXThaler®): One inhalation of CHF1535 100/6 µg NEXThaler® + one inhalation of CHF1535 100/6 µg pMDI matched placebo;

Arm type	placebo - active comparator - experimental
Investigational medicinal product name	CHF1535 NEXThaler
Investigational medicinal product code	
Other name	Beclometasone dipropionate + formoterol fumarate
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of CHF1535 100/6 µg NEXThaler®;
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

Investigational medicinal product name	CHF1535 pMDI
Investigational medicinal product code	
Other name	Beclometasone dipropionate + formoterol fumarate
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of CHF1535 100/6 µg pMDI;
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

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

Dosage and administration details:

One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo.
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

Investigational medicinal product name	CHF1535 pMDI Placebo
Investigational medicinal product code	
Other name	placebo
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

One inhalation of CHF1535 100/6 µg pMDI matched placebo.
The subjects took the study drug in an upright position and were instructed to hold their breath for 5 to 10 seconds or for as long as was comfortable. Each inhalation was separated by at least 30 seconds.

Number of subjects in period 1	Sequence A-B-C	Sequence A-C-B	Sequence B-A-C
Started	11	9	12
Completed	9	8	12
Not completed	2	1	0
Due to an AE of lower respiratory tract infection	-	1	-
Subject had a drop in FEV1 >45% at Visit 3	-	-	-
Subject did not drop to 30% FEV1 at Visit 2	-	-	-
Lost to follow-up	1	-	-
Subject did not reach 65% FEV1 at Visit 2	1	-	-

Number of subjects in period 1	Sequence B-C-A	Sequence C-A-B	Sequence C-B-A
Started	9	12	12
Completed	9	12	10
Not completed	0	0	2
Due to an AE of lower respiratory tract infection	-	-	-
Subject had a drop in FEV1 >45% at Visit 3	-	-	1
Subject did not drop to 30% FEV1 at Visit 2	-	-	1
Lost to follow-up	-	-	-
Subject did not reach 65% FEV1 at Visit 2	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Sequence A-B-C
Reporting group description:	
A - test treatment (CHF1535 100/6 µg NEXThaler®): One inhalation of CHF1535 100/6 µg NEXThaler® + one inhalation of CHF1535 100/6 µg pMDI matched placebo; B -Reference treatment (CHF1535 100/6 µg pMDI): One inhalation of CHF1535 100/6 µg pMDI + one inhalation of CHF1535 100/6 µg NEXThaler® matched placebo; C - Placebo: One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo + one inhalation of CHF1535 100/6 µg pMDI matched placebo.	
Reporting group title	Sequence A-C-B
Reporting group description:	
A - test treatment (CHF1535 100/6 µg NEXThaler®): One inhalation of CHF1535 100/6 µg NEXThaler® + one inhalation of CHF1535 100/6 µg pMDI matched placebo; C - Placebo: One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo + one inhalation of CHF1535 100/6 µg pMDI matched placebo. B -Reference treatment (CHF1535 100/6 µg pMDI): One inhalation of CHF1535 100/6 µg pMDI + one inhalation of CHF1535 100/6 µg NEXThaler® matched placebo;	
Reporting group title	Sequence B-A-C
Reporting group description:	
B -Reference treatment (CHF1535 100/6 µg pMDI): One inhalation of CHF1535 100/6 µg pMDI + one inhalation of CHF1535 100/6 µg NEXThaler® matched placebo; A - test treatment (CHF1535 100/6 µg NEXThaler®): One inhalation of CHF1535 100/6 µg NEXThaler® + one inhalation of CHF1535 100/6 µg pMDI matched placebo; C - Placebo: One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo + one inhalation of CHF1535 100/6 µg pMDI matched placebo.	
Reporting group title	Sequence B-C-A
Reporting group description:	
B -Reference treatment (CHF1535 100/6 µg pMDI): One inhalation of CHF1535 100/6 µg pMDI + one inhalation of CHF1535 100/6 µg NEXThaler® matched placebo; C - Placebo: One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo + one inhalation of CHF1535 100/6 µg pMDI matched placebo. A - test treatment (CHF1535 100/6 µg NEXThaler®): One inhalation of CHF1535 100/6 µg NEXThaler® + one inhalation of CHF1535 100/6 µg pMDI matched placebo;	
Reporting group title	Sequence C-A-B
Reporting group description:	
C - Placebo: One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo + one inhalation of CHF1535 100/6 µg pMDI matched placebo. A - test treatment (CHF1535 100/6 µg NEXThaler®): One inhalation of CHF1535 100/6 µg NEXThaler® + one inhalation of CHF1535 100/6 µg pMDI matched placebo; B -Reference treatment (CHF1535 100/6 µg pMDI): One inhalation of CHF1535 100/6 µg pMDI + one inhalation of CHF1535 100/6 µg NEXThaler® matched placebo;	
Reporting group title	Sequence C-B-A
Reporting group description:	
C - Placebo: One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo + one inhalation of CHF1535 100/6 µg pMDI matched placebo. B -Reference treatment (CHF1535 100/6 µg pMDI): One inhalation of CHF1535 100/6 µg pMDI + one inhalation of CHF1535 100/6 µg NEXThaler® matched placebo; A - test treatment (CHF1535 100/6 µg NEXThaler®): One inhalation of CHF1535 100/6 µg NEXThaler® + one inhalation of CHF1535 100/6 µg pMDI matched placebo;	

Reporting group values	Sequence A-B-C	Sequence A-C-B	Sequence B-A-C
Number of subjects	11	9	12

Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	11	9	12
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	34.5	42.6	44.2
standard deviation	± 11.3	± 10.8	± 10.1
Gender categorical Units: Subjects			
Female	2	4	3
Male	9	5	9

Reporting group values	Sequence B-C-A	Sequence C-A-B	Sequence C-B-A
Number of subjects	9	12	12
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	9	12	12
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	37.6	45.9	41.8
standard deviation	± 10.5	± 8.1	± 11.8
Gender categorical Units: Subjects			
Female	7	6	3
Male	2	6	9

Reporting group values	Total		
Number of subjects	65		
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)	65		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	25		
Male	40		

End points

End points reporting groups

Reporting group title	Sequence A-B-C

Reporting group description:

A - test treatment (CHF1535 100/6 µg NEXThaler®): One inhalation of CHF1535 100/6 µg NEXThaler® + one inhalation of CHF1535 100/6 µg pMDI matched placebo;
B -Reference treatment (CHF1535 100/6 µg pMDI): One inhalation of CHF1535 100/6 µg pMDI + one inhalation of CHF1535 100/6 µg NEXThaler® matched placebo;
C - Placebo: One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo + one inhalation of CHF1535 100/6 µg pMDI matched placebo.

Reporting group title	Sequence A-C-B

Reporting group description:

A - test treatment (CHF1535 100/6 µg NEXThaler®): One inhalation of CHF1535 100/6 µg NEXThaler® + one inhalation of CHF1535 100/6 µg pMDI matched placebo;
C - Placebo: One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo + one inhalation of CHF1535 100/6 µg pMDI matched placebo.
B -Reference treatment (CHF1535 100/6 µg pMDI): One inhalation of CHF1535 100/6 µg pMDI + one inhalation of CHF1535 100/6 µg NEXThaler® matched placebo;

Reporting group title	Sequence B-A-C

Reporting group description:

B -Reference treatment (CHF1535 100/6 µg pMDI): One inhalation of CHF1535 100/6 µg pMDI + one inhalation of CHF1535 100/6 µg NEXThaler® matched placebo;
A - test treatment (CHF1535 100/6 µg NEXThaler®): One inhalation of CHF1535 100/6 µg NEXThaler® + one inhalation of CHF1535 100/6 µg pMDI matched placebo;
C - Placebo: One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo + one inhalation of CHF1535 100/6 µg pMDI matched placebo.

Reporting group title	Sequence B-C-A

Reporting group description:

B -Reference treatment (CHF1535 100/6 µg pMDI): One inhalation of CHF1535 100/6 µg pMDI + one inhalation of CHF1535 100/6 µg NEXThaler® matched placebo;
C - Placebo: One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo + one inhalation of CHF1535 100/6 µg pMDI matched placebo.
A - test treatment (CHF1535 100/6 µg NEXThaler®): One inhalation of CHF1535 100/6 µg NEXThaler® + one inhalation of CHF1535 100/6 µg pMDI matched placebo;

Reporting group title	Sequence C-A-B

Reporting group description:

C - Placebo: One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo + one inhalation of CHF1535 100/6 µg pMDI matched placebo.
A - test treatment (CHF1535 100/6 µg NEXThaler®): One inhalation of CHF1535 100/6 µg NEXThaler® + one inhalation of CHF1535 100/6 µg pMDI matched placebo;
B -Reference treatment (CHF1535 100/6 µg pMDI): One inhalation of CHF1535 100/6 µg pMDI + one inhalation of CHF1535 100/6 µg NEXThaler® matched placebo;

Reporting group title	Sequence C-B-A

Reporting group description:

C - Placebo: One inhalation of CHF1535 100/6 µg NEXThaler® matched placebo + one inhalation of CHF1535 100/6 µg pMDI matched placebo.
B -Reference treatment (CHF1535 100/6 µg pMDI): One inhalation of CHF1535 100/6 µg pMDI + one inhalation of CHF1535 100/6 µg NEXThaler® matched placebo;
A - test treatment (CHF1535 100/6 µg NEXThaler®): One inhalation of CHF1535 100/6 µg NEXThaler® + one inhalation of CHF1535 100/6 µg pMDI matched placebo;

Subject analysis set title	CHF1535 NEXThaler (Treatment A) - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention-to-treat population (ITT): all randomised subjects who received at least one dose of the study treatment and with at least one available evaluation of efficacy after randomisation;

Subject analysis set title	CHF1535pMDI (Treatment B) - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention-to-treat population (ITT): all randomised subjects who received at least one dose of the study treatment and with at least one available evaluation of efficacy after randomisation;

Subject analysis set title	Placebo (Treatment C) - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention-to-treat population (ITT): all randomised subjects who received at least one dose of the study treatment and with at least one available evaluation of efficacy after randomisation;

Subject analysis set title	CHF1535 NEXThaler (Treatment A) - PP
Subject analysis set type	Per protocol

Subject analysis set description:

Per-protocol population (PP): all subjects from the ITT population without any major protocol violations (i.e. wrong inclusions, poor compliance, non-permitted medications).

Subject analysis set title	CHF1535pMDI (Treatment B) - PP
Subject analysis set type	Per protocol

Subject analysis set description:

Per-protocol population (PP): all subjects from the ITT population without any major protocol violations (i.e. wrong inclusions, poor compliance, non-permitted medications).

Subject analysis set title	Placebo (Treatment C) - PP
Subject analysis set type	Per protocol

Subject analysis set description:

Per-protocol population (PP): all subjects from the ITT population without any major protocol violations (i.e. wrong inclusions, poor compliance, non-permitted medications).

Primary: Change in FEV1 from post diluent to 5 minutes after study drug intake

End point title	Change in FEV1 from post diluent to 5 minutes after study drug intake

End point description:

For eligible subjects at treatment period: FEV1 before and during methacholine challenge as part of the methacholine challenge test procedure (number of times could vary based on the subject's individual response to methacholine).

End point type	Primary

End point timeframe:

At Visits 1, 2 and 3

End point values	CHF1535 NEXThaler (Treatment A) - ITT	CHF1535pMDI (Treatment B) - ITT	Placebo (Treatment C) - ITT	CHF1535 NEXThaler (Treatment A) - PP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	63	62	63	60
Units: Liters				
arithmetic mean (standard deviation)	-0.527 (± 0.238)	-0.497 (± 0.257)	-0.730 (± 0.246)	-0.527 (± 0.240)

End point values	CHF1535pMDI (Treatment B)	Placebo (Treatment C)		

	- PP	- PP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57	60		
Units: Liters				
arithmetic mean (standard deviation)	-0.502 (± 0.262)	-0.723 (± 0.249)		

Statistical analyses

Statistical analysis title	CHF1535 NEXThaler vs CHF1535 pMDI

Statistical analysis description:

The value N=125, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	CHF1535 NEXThaler (Treatment A) - ITT v CHF1535pMDI (Treatment B) - ITT
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.939 [2]
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.065

Notes:

[1] - The pre-defined non-inferiority margin for testing non-inferiority hypothesis was NIm= -0.120 L.

[2] - From ANCOVA Model including treatment, period and patient as fixed effects and post-diluent FEV1 and FEV1 at the end of methacholine challenge test as covariates.

Statistical analysis title	CHF1535 NEXThaler vs Placebo

Statistical analysis description:

The value N=126, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	CHF1535 NEXThaler (Treatment A) - ITT v Placebo (Treatment C) - ITT
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001 [4]
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.224
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.162
upper limit	0.286

Notes:

[3] - Conventional p-value to claim superiority of one arm vs. the other: p < 0.05.

[4] - From ANCOVA Model including treatment, period and patient as fixed effects and post-diluent FEV1 and FEV1 at the end of methacholine challenge test as covariates.

Statistical analysis title	CHF1535 pMDI vs Placebo

Statistical analysis description:

The value N=125, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	CHF1535pMDI (Treatment B) - ITT v Placebo (Treatment C) - ITT
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.001 [6]
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.222
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.283

Notes:

[5] - Conventional p-value to claim superiority of one arm vs. the other: p < 0.05.

[6] - From ANCOVA Model including treatment, period and patient as fixed effects and post-diluent FEV1 and FEV1 at the end of methacholine challenge test as covariates.

Statistical analysis title	CHF1535 NEXThaler vs CHF1535 pMDI

Statistical analysis description:

The value N=117, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	CHF1535 NEXThaler (Treatment A) - PP v CHF1535pMDI (Treatment B) - PP
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
P-value	= 0.766 [8]
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.056
upper limit	0.075

Notes:

[7] - The pre-defined non-inferiority margin for testing non-inferiority hypothesis was NIm= -0.120 L

[8] - From ANCOVA Model including treatment, period and patient as fixed effects and post-diluent FEV1 and FEV1 at the end of methacholine challenge test as covariates.

Statistical analysis title	CHF1535 NEXThaler vs placebo

Statistical analysis description:

The value N=120, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	CHF1535 NEXThaler (Treatment A) - PP v Placebo (Treatment C) - PP
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.001 [10]
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.224
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.159
upper limit	0.288

Notes:

[9] - Conventional p-value to claim superiority of one arm vs. the other: $p < 0.05$.

[10] - From ANCOVA Model including treatment, period and patient as fixed effects and post-diluent FEV1 and FEV1 at the end of methacholine challenge test as covariates.

Statistical analysis title	CHF1535 pMDI vs placebo

Statistical analysis description:

The value N=117, shown below, is generated automatically and is due to innate error of the EudraCT database system.

Comparison groups	CHF1535pMDI (Treatment B) - PP v Placebo (Treatment C) - PP
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.001 [12]
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.214
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.149
upper limit	0.278

Notes:

[11] - Conventional p-value to claim superiority of one arm vs. the other: $p < 0.05$.

[12] - From ANCOVA Model including treatment, period and patient as fixed effects and post-diluent FEV1 and FEV1 at the end of methacholine challenge test as covariates.

Secondary: Change in FEV1 from post-diluent at 1, 10, 20 and 30 minutes after drug intake

End point title	Change in FEV1 from post-diluent at 1, 10, 20 and 30 minutes after drug intake

End point description:

For eligible subjects at treatment period: FEV1 before and during methacholine challenge as part of the methacholine challenge test procedure (number of times could vary based on the subject's individual response to methacholine). After study drug intake at the following time points (FEV1 only): 1, 5, 10, 20 and 30 minutes post-dose.

Data from minute 1-post-dose measurements are reported here. A table with results including all the timepoints (1, 10, 20, and 30 minutes) is attached.

End point type	Secondary

End point timeframe:

At visits 1, 2 and 3.

End point values	CHF1535 NEXThaler (Treatment A) - ITT	CHF1535pMDI (Treatment B) - ITT	Placebo (Treatment C) - ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	63	62	63	
Units: Liters				
arithmetic mean (confidence interval 95%)	-0.645 (-0.684 to -0.605)	-0.647 (-0.687 to -0.608)	-0.842 (-0.881 to -0.802)	

Attachments (see zip file)	Tabella 9_ANCOVA Model on the Change in FEV1.pdf

Statistical analyses

Statistical analysis title	CHF135 NEXThaler vs CHF1535 pMDI

Statistical analysis description:

Change in FEV1 (L) from post-diluent to 1, 10, 20 and 30 minutes after drug intake was analysed separately for each post-dose time point using the same statistical model considered for the primary efficacy variable.

Comparison groups	CHF1535 NEXThaler (Treatment A) - ITT v CHF1535pMDI (Treatment B) - ITT
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.919 [14]
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0053
upper limit	0.059

Notes:

[13] - Inequality.

[14] - From ANCOVA model including treatment, period and patient as fixed effects and post-diluent FEV1 and FEV1 at the end of methacholine challenge test as covariates.

Statistical analysis title	CHF135 NEXThaler vs Placebo

Statistical analysis description:

Change in FEV1 (L) from post-diluent to 1, 10, 20 and 30 minutes after drug intake was analysed separately for each post-dose time point using the same statistical model considered for the primary efficacy variable.

Comparison groups	CHF1535 NEXThaler (Treatment A) - ITT v Placebo (Treatment C) - ITT

Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	< 0.001 [16]
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.197
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.141
upper limit	0.253

Notes:

[15] - Inequality.

[16] - From ANCOVA model including treatment, period and patient as fixed effects and post-diluent FEV1 and FEV1 at the end of methacholine challenge test as covariates.

Statistical analysis title	CHF135 pMDI vs Placebo

Statistical analysis description:

Change in FEV1 (L) from post-diluent to 1, 10, 20 and 30 minutes after drug intake was analysed separately for each post-dose time point using the same statistical model considered for the primary efficacy variable.

Comparison groups	CHF1535pMDI (Treatment B) - ITT v Placebo (Treatment C) - ITT
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	< 0.001 [18]
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.194
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.139
upper limit	0.25

Notes:

[17] - Inequality.

[18] - From ANCOVA model including treatment, period and patient as fixed effects and post-diluent FEV1 and FEV1 at the end of methacholine challenge test as covariates.

Secondary: Time to recovery in FEV1

End point title	Time to recovery in FEV1

End point description:

Recovery and "time to" are defined as follows:
- Recovery: return to 85% of the post-diluent value. Recovery is reached for values > 85%;
- "Time to": datetime at which % recovery in FEV1 vs. post-diluent > 85% - datetime of last inhalation, in min.

Reported data come from confirmatory analysis, which was performed on all subjects, those who recovered with their time to recovery at any time and those who did not recover with time to recovery extrapolated.

End point type	Secondary

End point timeframe:

The FEV1 was collected at the post-diluent timepoint and at 1, 5, 10, 20 and 30 minutes after drug intake.

End point values	CHF1535 NEXThaler (Treatment A) - ITT	CHF1535pMDI (Treatment B) - ITT	Placebo (Treatment C) - ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	63	62	63	
Units: min				
median (inter-quartile range (Q1-Q3))	8.01 (4.46 to 16.69)	7.52 (3.50 to 17.07)	28.17 (13.28 to 38.43)	

Statistical analyses

Statistical analysis title	CHF1535 NEXThaler vs CHF1535 pMDI

Statistical analysis description:

A hazard ratio < 1 indicates that patients treated with CHF1535 pMDI or Placebo are at lower probability of recovering in FEV1 than CHF1535 NEXThaler treated patients.
To be applied for any Cox model.

Comparison groups	CHF1535 NEXThaler (Treatment A) - ITT v CHF1535pMDI (Treatment B) - ITT
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.75 [20]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.673
upper limit	1.733

Notes:

[19] - Inequality.

[20] - From a Cox proportional hazard model stratified by subject and with treatment as factor.

Statistical analysis title	CHF1535 NEXThaler vs Placebo

Statistical analysis description:

A hazard ratio < 1 indicates that patients treated with CHF1535 pMDI or Placebo are at lower probability of recovering in FEV1 than CHF1535 NEXThaler treated patients.
To be applied for any Cox model.

Comparison groups	CHF1535 NEXThaler (Treatment A) - ITT v Placebo (Treatment C) - ITT
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	< 0.001 [22]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.229

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	0.403

Notes:

[21] - Inequality.

[22] - From a Cox proportional hazard model stratified by subject and with treatment as factor.

Secondary: FEV1 AUC0-10min normalised by time

End point title	FEV1 AUC0-10min normalised by time

End point description:

The area under the FEV1 vs. time curve observed from end of challenge to 10 min after methacholine challenge. The area was computed using the linear trapezoidal rule.
Values are reported as adjusted means.

End point type	Secondary

End point timeframe:

Timepoints considered for evaluation of AUC were: FEV1 values at 1, 5, 10 min after drug intake.

End point values	CHF1535 NEXThaler (Treatment A) - ITT	CHF1535pMDI (Treatment B) - ITT	Placebo (Treatment C) - ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	63	61	63	
Units: liter				
arithmetic mean (standard error)	2.26 (± 0.02)	2.25 (± 0.02)	2.07 (± 0.02)	

Statistical analyses

Statistical analysis title	CHF1535 NEXThaler vs CHF1535 pMDI
Comparison groups	CHF1535 NEXThaler (Treatment A) - ITT v CHF1535pMDI (Treatment B) - ITT
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.656 [24]
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.06

Notes:

[23] - Inequality.

[24] - From an ANCOVA model including treatment, period and subject as fixed effects, FEV1 post-diluent and FEV1 at the end of the methacholine challenge test as covariates.

Statistical analysis title	CHF1535 NEXThaler vs Placebo
Comparison groups	CHF1535 NEXThaler (Treatment A) - ITT v Placebo (Treatment C) - ITT
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	< 0.001 [26]
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	0.23

Notes:

[25] - Inequality.

[26] - From an ANCOVA model including treatment, period and subject as fixed effects, FEV1 post-diluent and FEV1 at the end of the methacholine challenge test as covariates.

Statistical analysis title	CHF1535 pMDI vs Placebo
Comparison groups	CHF1535pMDI (Treatment B) - ITT v Placebo (Treatment C) - ITT
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	< 0.001 [28]
Method	ANCOVA
Parameter estimate	Adjusted mean difference
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	0.22

Notes:

[27] - Inequality.

[28] - From an ANCOVA model including treatment, period and subject as fixed effects, FEV1 post-diluent and FEV1 at the end of the methacholine challenge test as covariates.

Secondary: Change in Borg scale from the end of methacholine challenge test to 1, 3, 5, 10, 20 and 30 minutes after study drug intake

End point title	Change in Borg scale from the end of methacholine challenge test to 1, 3, 5, 10, 20 and 30 minutes after study drug intake

End point description:

Assessments were performed at the following time points: post-diluent, post-challenge and at 1, 3, 5, 10, 20 and 30 minutes post-dose.

Data from minute 1-post-dose measurements are reported here. A table with the results including all the timepoints (1, 3, 5, 10, 20, and 30 minutes) is attached.

End point type	Secondary

End point timeframe:

At 1, 3, 5, 10, 20 and 30 minutes post-dose.

End point values	CHF1535 NEXThaler (Treatment A) - ITT	CHF1535pMDI (Treatment B) - ITT	Placebo (Treatment C) - ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	63	62	63	
Units: score				
arithmetic mean (confidence interval 95%)	-0.788 (-1.015 to -0.561)	-1.146 (-1.376 to -0.915)	-0.597 (-0.824 to -0.369)	

Attachments (see zip file)	Table 10_ANCOVA Model on the Change in Borg Scale.pdf

Statistical analyses

Statistical analysis title	CHF1535 NEXThaler vs CHF1535 pMDI
Comparison groups	CHF1535 NEXThaler (Treatment A) - ITT v CHF1535pMDI (Treatment B) - ITT
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	= 0.031 [30]
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.358
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.034
upper limit	0.681

Notes:

[29] - Inequality.

[30] - From an ANCOVA model with treatment, period and subject included as fixed effects, Borg scale post-diluent and Borg Scale at the end of methacholine challenge test as covariates.

Statistical analysis title	CHF1535 NEXThaler vs placebo
Comparison groups	CHF1535 NEXThaler (Treatment A) - ITT v Placebo (Treatment C) - ITT
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	= 0.242 [32]
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.191

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.513
upper limit	0.131

Notes:

[31] - Inequality.

[32] - From an ANCOVA model with treatment, period and subject included as fixed effects, Borg scale post-diluent and Borg Scale at the end of methacholine challenge test as covariates.

Statistical analysis title	CHF1535 pMDI vs placebo
Comparison groups	CHF1535pMDI (Treatment B) - ITT v Placebo (Treatment C) - ITT
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	< 0.001 [34]
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	-0.549
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	-0.227

Notes:

[33] - Inequality.

[34] - From an ANCOVA model with treatment, period and subject included as fixed effects, Borg scale post-diluent and Borg Scale at the end of methacholine challenge test as covariates.

Secondary: Time to recovery in Borg scale

End point title	Time to recovery in Borg scale

End point description:

Time (min) needed to reach 50% decrease from the post-methacholine value. Recovery is calculated as % Change in Borg scale from the post-methacholine value.

End point type	Secondary

End point timeframe:

The Borg Scale was collected at the end of methacholine challenge test (before drug intake) and at 1, 3, 5, 10, 20 and 30 min after drug intake.

End point values	CHF1535 NEXThaler (Treatment A) - ITT	CHF1535pMDI (Treatment B) - ITT	Placebo (Treatment C) - ITT	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	63	62	63	
Units: minutes				
median (inter-quartile range (Q1-Q3))	4.25 (2.50 to 10.0)	4.00 (1.00 to 8.75)	10.0 (3.00 to 20.0)	

Statistical analyses

Statistical analysis title	CHF1535 NEXThaler vs CHF1535 pMDI
Comparison groups	CHF1535 NEXThaler (Treatment A) - ITT v CHF1535pMDI (Treatment B) - ITT
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	= 0.609 [36]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.128
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.712
upper limit	1.787

Notes:

[35] - Inequality.

[36] - From a Cox proportional hazard model stratified by subject and with treatment as factor.

Statistical analysis title	CHF1535 NEXThaler vs placebo
Comparison groups	CHF1535 NEXThaler (Treatment A) - ITT v Placebo (Treatment C) - ITT
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	= 0.042 [38]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.607
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.374
upper limit	0.983

Notes:

[37] - Inequality.

[38] - From a Cox proportional hazard model stratified by subject and with treatment as factor.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event assessment was made at each Visit, from Visit 0 (screening visit), to Visit 3, through Visits 1 and 2, and subsequent follow-up phone call (5 to 14 days after the last administration).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	CHF1535 NEXthaler (Treatment A) - safety
Reporting group description: -	
Reporting group title	CHF1535 pMDI (Treatment B) - safety
Reporting group description: -	
Reporting group title	Placebo (Treatment C) - safety

Reporting group description: -

Serious adverse events	CHF1535 NEXthaler (Treatment A) - safety	CHF1535 pMDI (Treatment B) - safety	Placebo (Treatment C) - safety
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	0 / 63 (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: 1.6 %

Non-serious adverse events	CHF1535 NEXthaler (Treatment A) - safety	CHF1535 pMDI (Treatment B) - safety	Placebo (Treatment C) - safety
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 63 (6.35%)	4 / 62 (6.45%)	5 / 63 (7.94%)
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 63 (1.59%)
occurrences (all)	0	0	1
Limb injury			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 63 (1.59%)
occurrences (all)	0	0	1
Nervous system disorders			

Dizziness			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 63 (1.59%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 63 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 63 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 63 (3.17%)	0 / 62 (0.00%)	0 / 63 (0.00%)
occurrences (all)	2	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 63 (1.59%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 63 (1.59%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 63 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 63 (1.59%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	1 / 63 (1.59%)	1 / 62 (1.61%)	0 / 63 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 63 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 March 2017	The aim of this substantial amendment is to modify the required wash-out period prior to screening of the following non-permitted concomitant medications: - Long-acting anticholinergics from '8 weeks prior to screening' to '4 weeks prior to screening' - Leukotriene modifiers from '8 weeks prior to screening' to '4 weeks prior to screening'

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

There are no limitations or caveats to this summary of results.

Notes: