Clinical trial results:
A phase II, multicentre, double blind, randomised, 5-way cross-over study to test the non-inferiority of the acute bronchodilator effect of CHF 1535 200/6 µg NEXThaler® versus CHF 1535 100/6 µg NEXThaler® in partially controlled and uncontrolled adult asthmatic patients.

Summary

EudraCT number	2013-004826-27
Trial protocol	GB
Global end of trial date	14 October 2014

Results information

Result version number	v1 (current)
This version publication date	11 July 2016
First version publication date	09 August 2015

Trial information

Trial identification

Sponsor protocol code	CCD-01535BA1-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02000609
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 Manager, Chiesi Farmaceutici S.p.A., clinicalTrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency Manager, Chiesi Farmaceutici S.p.A., 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	14 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 October 2014
Global end of trial reached?	Yes
Global end of trial date	14 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority in terms of acute bronchodilator effect (FEV1 AUC0-12h) between a single dose of CHF 1535 NEXThaler® 200 + 6 µg and a single dose of CHF 1535 NEXThaler® 100 + 6 µg at two dose levels (1 and 4 inhalations) in partially-controlled and uncontrolled adult asthmatic patients.

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:

BDP HFA 100 µg (QVAR), 2 inhalations bid (total daily dose BDP 400 µg)

Evidence for comparator: -

Actual start date of recruitment	10 April 2014
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: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

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)	60
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Sixty subjects were randomised to one of the 5 treatment sequences and received study drugs: A-B-C-D-E (N=11), B-C-D-E-A (N=11), C-D-E-A-B (N=14), D-E-A-B-C (N=13) and E-A-B-C-D (N=11). Fifty eight (96.7%) subjects completed the study. Two (3.3%) subjects discontinued the study prematurely; 1 (1.7%) subject withdrew consent after randomisation.

Pre-assignment

Screening details:

In total, 208 subjects were screened. One hundred forty-eight subjects were not randomised (i.e., screening failures), of whom 140 subjects were not eligible to enter the study, 3 subjects withdrew consent before randomisation, 1 subject was lost to follow-up and 4 subjects were not randomized for other reasons.

Period 1

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

Blinding implementation details:

This was a double-blind study. The randomisation list was provided to the labelling facility but was not be 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-D-E

Arm description:

Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;
• Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;
• Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;
• Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;
• Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.

Arm type	experimental - active comparator - placebo
Investigational medicinal product name	CHF1535 DPI (BDP 100 µ + FF 6 µ) - CHF1535 DPI (BDP 200 µ + FF 6 µ) - CHF1535 DPI placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Test treatments:
CHF 1535 inhalation powder (fixed combination of BDP 200 µg plus FF 6 µg per actuation) administered via the NEXThaler® dry powder inhaler (DPI) at two dose levels.
• Treatment B: 1 inhalation (total dose BDP 200 µg / FF 6 µg);
• Treatment D: 4 inhalations (total dose BDP 800 µg / FF 24 µg).

Reference treatments:
• Treatment A: 1 inhalation (total dose BDP 100 µg / FF 6 µg);
• Treatment C: 4 inhalations (total dose BDP 400 µg / FF 24 µg).
• Treatment E: placebo.

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

Arm description:

• Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;
• Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;
• Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;
• Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.
• Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;

Arm type	experimental - active comparator - placebo
Investigational medicinal product name	CHF1535 DPI (BDP 100 µ + FF 6 µ) - CHF1535 DPI (BDP 200 µ + FF 6 µ) - CHF1535 DPI placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Test treatments:
CHF 1535 inhalation powder (fixed combination of BDP 200 µg plus FF 6 µg per actuation) administered via the NEXThaler® dry powder inhaler (DPI) at two dose levels.
• Treatment B: 1 inhalation (total dose BDP 200 µg / FF 6 µg);
• Treatment D: 4 inhalations (total dose BDP 800 µg / FF 24 µg).

Reference treatments:
• Treatment A: 1 inhalation (total dose BDP 100 µg / FF 6 µg);
• Treatment C: 4 inhalations (total dose BDP 400 µg / FF 24 µg).
• Treatment E: placebo.

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

Arm description:

• Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;
• Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;
• Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.
• Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;
• Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;

Arm type	experimental - active comparator - placebo

Investigational medicinal product name	CHF1535 DPI (BDP 100 µ + FF 6 µ) - CHF1535 DPI (BDP 200 µ + FF 6 µ) - CHF1535 DPI placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Test treatments:
CHF 1535 inhalation powder (fixed combination of BDP 200 µg plus FF 6 µg per actuation) administered via the NEXThaler® dry powder inhaler (DPI) at two dose levels.
• Treatment B: 1 inhalation (total dose BDP 200 µg / FF 6 µg);
• Treatment D: 4 inhalations (total dose BDP 800 µg / FF 24 µg).

Reference treatments:
• Treatment A: 1 inhalation (total dose BDP 100 µg / FF 6 µg);
• Treatment C: 4 inhalations (total dose BDP 400 µg / FF 24 µg).
• Treatment E: placebo.

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

Arm description:

• Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;
• Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.
• Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;
• Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;
• Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;

Arm type	experimental - active comparator - placebo
Investigational medicinal product name	CHF1535 DPI (BDP 100 µ + FF 6 µ) - CHF1535 DPI (BDP 200 µ + FF 6 µ) - CHF1535 DPI placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Test treatments:
CHF 1535 inhalation powder (fixed combination of BDP 200 µg plus FF 6 µg per actuation) administered via the NEXThaler® dry powder inhaler (DPI) at two dose levels.
• Treatment B: 1 inhalation (total dose BDP 200 µg / FF 6 µg);
• Treatment D: 4 inhalations (total dose BDP 800 µg / FF 24 µg).

Reference treatments:
• Treatment A: 1 inhalation (total dose BDP 100 µg / FF 6 µg);
• Treatment C: 4 inhalations (total dose BDP 400 µg / FF 24 µg).
• Treatment E: placebo.

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

Arm description:

• Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.
• Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;
• Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;
• Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler®

BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;
• Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;

Arm type	experimental - active comparator - placebo
Investigational medicinal product name	CHF1535 DPI (BDP 100 µ + FF 6 µ) - CHF1535 DPI (BDP 200 µ + FF 6 µ) - CHF1535 DPI placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Test treatments:
CHF 1535 inhalation powder (fixed combination of BDP 200 µg plus FF 6 µg per actuation) administered via the NEXThaler® dry powder inhaler (DPI) at two dose levels.
• Treatment B: 1 inhalation (total dose BDP 200 µg / FF 6 µg);
• Treatment D: 4 inhalations (total dose BDP 800 µg / FF 24 µg).

Reference treatments:
• Treatment A: 1 inhalation (total dose BDP 100 µg / FF 6 µg);
• Treatment C: 4 inhalations (total dose BDP 400 µg / FF 24 µg).
• Treatment E: placebo.

Number of subjects in period 1	Sequence A-B-C-D-E	Sequence B-C-D-E-A	Sequence C-D-E-A-B
Started	11	11	14
Completed	10	11	14
Not completed	1	0	0
personal issues	1	-	-
Consent withdrawn by subject	-	-	-

Number of subjects in period 1	Sequence D-E-A-B-C	Sequence E-A-B-C-D
Started	13	11
Completed	12	11
Not completed	1	0
personal issues	-	-
Consent withdrawn by subject	1	-

Reporting groups

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

Reporting group description:

Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;
• Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;
• Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;
• Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;
• Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.

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

Reporting group description:

• Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;
• Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;
• Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;
• Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.
• Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;

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

Reporting group description:

• Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;
• Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;
• Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.
• Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;
• Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;

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

Reporting group description:

• Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;
• Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.
• Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;
• Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg

NEXThaler®;
• Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;

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

Reporting group description:

• Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.
• Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;
• Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;
• Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;
• Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;

Reporting group values	Sequence A-B-C-D-E	Sequence B-C-D-E-A	Sequence C-D-E-A-B
Number of subjects	11	11	14
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	43.4	36.2	35.8
standard deviation	± 14.5	± 9.6	± 13.9
Gender categorical Units: Subjects			
Female	4	5	7
Male	7	6	7

Reporting group values	Sequence D-E-A-B-C	Sequence E-A-B-C-D	Total
Number of subjects	13	11	60
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	35	40.9	
standard deviation	± 9.2	± 11	-
Gender categorical			
Units: Subjects			
Female	7	5	28
Male	6	6	32

Subject analysis sets

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

Subject analysis set description:

All randomised subjects who received at least one dose of the study drug and who had at least one available evaluation of efficacy after randomisation.

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

Subject analysis set description:

All randomised subjects who received at least one dose of the study drug and who had at least one available evaluation of efficacy after randomisation.

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

Subject analysis set description:

All randomised subjects who received at least one dose of the study drug and who had at least one available evaluation of efficacy after randomisation.

Subject analysis set title	Treatment D - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised subjects who received at least one dose of the study drug and who had at least one available evaluation of efficacy after randomisation.

Subject analysis set title	Treatment E - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised subjects who received at least one dose of the study drug and who had at least one available evaluation of efficacy after randomisation.

Subject analysis set title	Treatment A - PP
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects from the ITT population without any major protocol violations (i.e., wrong inclusions, poor compliance, non-permitted medications). Since a cross-over design was used, the exclusion from the PP-population was defined on a per-period basis.

Subject analysis set title	Treatment B - PP
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects from the ITT population without any major protocol violations (i.e., wrong inclusions, poor compliance, non-permitted medications). Since a cross-over design was used, the exclusion from the PP-population was defined on a per-period basis.

Subject analysis set title	Treatment C - PP
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects from the ITT population without any major protocol violations (i.e., wrong inclusions, poor compliance, non-permitted medications). Since a cross-over design was used, the exclusion from the PP-population was defined on a per-period basis.

Subject analysis set title	Treatment D - PP
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects from the ITT population without any major protocol violations (i.e., wrong inclusions, poor compliance, non-permitted medications). Since a cross-over design was used, the exclusion from the PP-population was defined on a per-period basis.

Subject analysis set title	Treatment E - PP
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects from the ITT population without any major protocol violations (i.e., wrong inclusions, poor compliance, non-permitted medications). Since a cross-over design was used, the exclusion from the PP-population was defined on a per-period basis.

Subject analysis set title	Treatment A - safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised subjects who received at least one dose of study drug.

Subject analysis set title	Treatment B - safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised subjects who received at least one dose of study drug.

Subject analysis set title	Treatment C - safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised subjects who received at least one dose of study drug.

Subject analysis set title	Treatment D - safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised subjects who received at least one dose of study drug.

Subject analysis set title	Treatment E - safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised subjects who received at least one dose of study drug.

Reporting group values	Treatment A - ITT	Treatment B - ITT	Treatment C - ITT
Number of subjects	60	58	58
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			

Age continuous Units: years arithmetic mean standard deviation	± 	± 	±
Gender categorical Units: Subjects			
Female	28	27	27
Male	32	31	31

Reporting group values	Treatment D - ITT	Treatment E - ITT	Treatment A - PP
Number of subjects	59	59	60
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	± 	± 	±
Gender categorical Units: Subjects			
Female	28	28	28
Male	31	31	32

Reporting group values	Treatment B - PP	Treatment C - PP	Treatment D - PP
Number of subjects	57	58	59
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	± 	± 	±

Gender categorical Units: Subjects			
Female	26	27	28
Male	31	31	31

Reporting group values	Treatment E - PP	Treatment A - safety	Treatment B - safety
Number of subjects	59	60	58
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender categorical Units: Subjects			
Female	28	28	27
Male	31	32	31

Reporting group values	Treatment C - safety	Treatment D - safety	Treatment E - safety
Number of subjects	58	59	59
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender categorical Units: Subjects			
Female	27	28	28
Male	31	31	31

End points reporting groups

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

Reporting group description:

Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;
• Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;
• Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;
• Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;
• Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.

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

Reporting group description:

• Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;
• Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;
• Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;
• Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.
• Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;

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

Reporting group description:

• Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;
• Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;
• Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.
• Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;
• Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;

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

Reporting group description:

• Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;
• Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.
• Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;
• Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg

NEXThaler®;
• Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;

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

Reporting group description:

• Treatment E: placebo NEXThaler®, 1 inhalation plus placebo NEXThaler®, 3 inhalations, further referred to as placebo NEXThaler®.
• Treatment A: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 100 µg / FF 6 µg) further referred to as BDP/FF 100/6 µg NEXThaler®;
• Treatment B: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus placebo CHF 1535 NEXThaler®, 3 inhalations (total dose: BDP 200 µg / FF 6 µg) further referred to as BDP/FF 200/6 µg NEXThaler®;
• Treatment C: CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 100 µg / FF 6 µg, 3 inhalations (total dose: BDP 400 µg / FF 24 µg) further referred to as BDP/FF 400/24 µg NEXThaler®;
• Treatment D: CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 1 inhalation plus CHF 1535 NEXThaler® BDP 200 µg / FF 6 µg, 3 inhalations (total dose: BDP 800 µg / FF 24 µg) further referred to as BDP/FF 800/24 µg NEXThaler®;

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

Subject analysis set description:

All randomised subjects who received at least one dose of the study drug and who had at least one available evaluation of efficacy after randomisation.

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

Subject analysis set description:

All randomised subjects who received at least one dose of the study drug and who had at least one available evaluation of efficacy after randomisation.

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

Subject analysis set description:

All randomised subjects who received at least one dose of the study drug and who had at least one available evaluation of efficacy after randomisation.

Subject analysis set title	Treatment D - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised subjects who received at least one dose of the study drug and who had at least one available evaluation of efficacy after randomisation.

Subject analysis set title	Treatment E - ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised subjects who received at least one dose of the study drug and who had at least one available evaluation of efficacy after randomisation.

Subject analysis set title	Treatment A - PP
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects from the ITT population without any major protocol violations (i.e., wrong inclusions, poor compliance, non-permitted medications). Since a cross-over design was used, the exclusion from the PP-population was defined on a per-period basis.

Subject analysis set title	Treatment B - PP
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects from the ITT population without any major protocol violations (i.e., wrong inclusions, poor compliance, non-permitted medications). Since a cross-over design was used, the exclusion from the PP-population was defined on a per-period basis.

Subject analysis set title	Treatment C - PP
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects from the ITT population without any major protocol violations (i.e., wrong inclusions, poor compliance, non-permitted medications). Since a cross-over design was used, the exclusion from the PP-population was defined on a per-period basis.

Subject analysis set title	Treatment D - PP
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects from the ITT population without any major protocol violations (i.e., wrong inclusions, poor compliance, non-permitted medications). Since a cross-over design was used, the exclusion from the PP-population was defined on a per-period basis.

Subject analysis set title	Treatment E - PP
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects from the ITT population without any major protocol violations (i.e., wrong inclusions, poor compliance, non-permitted medications). Since a cross-over design was used, the exclusion from the PP-population was defined on a per-period basis.

Subject analysis set title	Treatment A - safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised subjects who received at least one dose of study drug.

Subject analysis set title	Treatment B - safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised subjects who received at least one dose of study drug.

Subject analysis set title	Treatment C - safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised subjects who received at least one dose of study drug.

Subject analysis set title	Treatment D - safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised subjects who received at least one dose of study drug.

Subject analysis set title	Treatment E - safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised subjects who received at least one dose of study drug.

Primary: FEV1 AUC0-12h/12h

End point title	FEV1 AUC0-12h/12h

End point description:

FEV1 AUC0-12h was measured standardised by time (L)

End point type	Primary

End point timeframe:

FEV1 was measured from visit 3 to visit 7, at the following timepoints: at pre-dose within 60 min of the dose and at 10 min, 30 min, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h and 12 h post-dose.

End point values	Treatment A - PP	Treatment B - PP	Treatment C - PP	Treatment D - PP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	57	58	59
Units: Liters				
arithmetic mean (confidence interval 95%)	2.754 (2.722 to 2.786)	2.783 (2.749 to 2.818)	2.87 (2.837 to 2.903)	2.897 (2.863 to 2.93)

End point values	Treatment E - PP			
Subject group type	Subject analysis set			
Number of subjects analysed	59			
Units: Liters				
arithmetic mean (confidence interval 95%)	2.477 (2.444 to 2.51)			

Statistical analyses

Statistical analysis title	Treatment B vs Treatment A
Comparison groups	Treatment A - PP v Treatment B - PP
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.224
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.018
upper limit	0.076

Statistical analysis title	Treatment D vs Treatment C
Comparison groups	Treatment D - PP v Treatment C - PP
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.258
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.027

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.073

Statistical analysis title	Treatment D vs Treatment E
Comparison groups	Treatment E - PP v Treatment D - PP
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.374
upper limit	0.466

Notes:

[1] - Assay sensitivity analysis

Statistical analysis title	Treatment C vs Treatment E
Comparison groups	Treatment C - PP v Treatment E - PP
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.393
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.347
upper limit	0.439

Notes:

[2] - Assy sensitivity analysis

Statistical analysis title	Treatment B vs Treatment E
Comparison groups	Treatment B - PP v Treatment E - PP

Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.306
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.259
upper limit	0.354

Notes:

[3] - Assay sensitivity analysis

Statistical analysis title	Treatment A vs Treatment E
Comparison groups	Treatment A - PP v Treatment E - PP
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.277
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.231
upper limit	0.324

Notes:

[4] - Assay sensitivity analysis

Statistical analysis title	Treatment C vs Treatment A
Comparison groups	Treatment A - PP v Treatment C - PP
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.116
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.069
upper limit	0.162

Notes:

[5] - dose-effect analysis

Statistical analysis title	Treatment D vs Treatment B

Comparison groups	Treatment D - PP v Treatment B - PP
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.113
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.066
upper limit	0.161

Notes:

[6] - dose-effect analysis

Secondary: FEV1 AUC0-4h/4h

End point title	FEV1 AUC0-4h/4h

End point description:

FEV1 AUC0-4h standardised by time (L)

End point type	Secondary

End point timeframe:

FEV1 was measured from visit 3 to visit 7 (treatment visits) at the following timepoints: at pre-dose within 60 min of the dose and at 10 min, 30 min, 1 h, 2 h, 3 h, 4 h post-dose.

End point values	Treatment A - ITT	Treatment B - ITT	Treatment C - ITT	Treatment D - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	58	58	59
Units: Liters				
arithmetic mean (confidence interval 95%)	2.773 (2.742 to 2.804)	2.802 (2.77 to 2.834)	2.887 (2.855 to 2.919)	2.9 (2.869 to 2.931)

End point values	Treatment E - ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	59			
Units: Liters				
arithmetic mean (confidence interval 95%)	2.52 (2.488 to 2.551)			

Statistical analyses

Statistical analysis title	Treatment B vs Treatment A
Comparison groups	Treatment A - ITT v Treatment B - ITT

Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.015
upper limit	0.074

Statistical analysis title	Treatment D vs Treatment C
Comparison groups	Treatment C - ITT v Treatment D - ITT
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.013
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.031
upper limit	0.057

Statistical analysis title	Treatment D vs Treatment E
Comparison groups	Treatment D - ITT v Treatment E - ITT
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.336
upper limit	0.424

Notes:

[7] - Sensitivity analysis

Statistical analysis title	Treatment C vs Treatment E
Comparison groups	Treatment C - ITT v Treatment E - ITT

Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.367
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.323
upper limit	0.412

Notes:

[8] - sensitivity analysis

Statistical analysis title	Treatment B vs Treatment E
Comparison groups	Treatment B - ITT v Treatment E - ITT
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.283
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.238
upper limit	0.327

Notes:

[9] - sensitivity analisys

Statistical analysis title	Treatment A vs Treatment E
Comparison groups	Treatment E - ITT v Treatment A - ITT
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.253
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.208
upper limit	0.298

Notes:

[10] - sensitivity analysis

Statistical analysis title	Treatment C vs Treatment A

Comparison groups	Treatment A - ITT v Treatment C - ITT
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.114
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.159

Notes:

[11] - Dose-effect analysis

Statistical analysis title	Treatment D vs Treatment B
Comparison groups	Treatment B - ITT v Treatment D - ITT
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.098
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.053
upper limit	0.142

Notes:

[12] - Dose-effect analysis

Secondary: FEV1 AUC4-12h/8h

End point title	FEV1 AUC4-12h/8h

End point description:

FEV1 AUC4-12h was measured in a standardised by time (L) way.

End point type	Secondary

End point timeframe:

FEV1 was measured from visit 3 to visit 7 (treatment visits) at the following time points: pre-dose within 60 min of the dose and at 10
min, 30 min, 1 h, 2 h, 3 h, 4 h post-dose.

End point values	Treatment A - ITT	Treatment B - ITT	Treatment C - ITT	Treatment D - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	58	58	59
Units: Liters				
arithmetic mean (confidence interval 95%)	2.74 (2.706 to 2.775)	2.768 (2.732 to 2.803)	2.857 (2.821 to 2.892)	2.89 (2.855 to 2.926)

End point values	Treatment E - ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	59			
Units: Liters				
arithmetic mean (confidence interval 95%)	2.449 (2.413 to 2.484)			

Statistical analyses

Statistical analysis title	Treatment B vs Treatment A
Comparison groups	Treatment A - ITT v Treatment B - ITT
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.027
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.022
upper limit	0.077

Statistical analysis title	Treatment D vs Treatment C
Comparison groups	Treatment D - ITT v Treatment C - ITT
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.016
upper limit	0.083

Statistical analysis title	Treatment D vs Treatment E
Comparison groups	Treatment D - ITT v Treatment E - ITT
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.442
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.392
upper limit	0.491

Notes:

[13] - sensitivity analysis

Statistical analysis title	Treatment C vs Treatment E
Comparison groups	Treatment C - ITT v Treatment E - ITT
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.408
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.359
upper limit	0.458

Notes:

[14] - sensitivity analysis

Statistical analysis title	Treatment B vs Treatment E
Comparison groups	Treatment E - ITT v Treatment B - ITT
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.319

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.269
upper limit	0.369

Notes:

[15] - Sensitivity analisys

Statistical analysis title	Treatment A vs Treatment E
Comparison groups	Treatment A - ITT v Treatment E - ITT
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.292
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.242
upper limit	0.342

Notes:

[16] - Sensitivity analysis

Statistical analysis title	Treatment C vs Treatment A
Comparison groups	Treatment C - ITT v Treatment A - ITT
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.117
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.067
upper limit	0.167

Notes:

[17] - Dose-effect analysis

Statistical analysis title	Treatment D vs Treatment B
Comparison groups	Treatment D - ITT v Treatment B - ITT

Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.123
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.073
upper limit	0.172

Notes:

[18] - Dose-effect analysis

Secondary: Peak FEV1

End point title	Peak FEV1

End point description:

Maximum FEV1 value over 12h post-dose

End point type	Secondary

End point timeframe:

FEV1 was measured over 12 hours after single administration

End point values	Treatment A - ITT	Treatment B - ITT	Treatment C - ITT	Treatment D - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	58	58	59
Units: Liters				
arithmetic mean (confidence interval 95%)	2.898 (2.865 to 2.93)	2.919 (2.886 to 2.953)	3.008 (2.975 to 3.041)	3.023 (2.991 to 3.056)

End point values	Treatment E - ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	59			
Units: Liters				
arithmetic mean (confidence interval 95%)	2.641 (2.608 to 2.673)			

Statistical analyses

Statistical analysis title	Treatment B vs Treatment A
Comparison groups	Treatment A - ITT v Treatment B - ITT

Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.022
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.024
upper limit	0.068

Statistical analysis title	Treatment D vs Treatment C
Comparison groups	Treatment C - ITT v Treatment D - ITT
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.061

Statistical analysis title	Treatment D vs Treatment E
Comparison groups	Treatment D - ITT v Treatment E - ITT
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.383
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.337
upper limit	0.429

Notes:

[19] - Sensitivity analysis

Statistical analysis title	Treatment C vs Treatment E
Comparison groups	Treatment C - ITT v Treatment E - ITT

Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.367
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.321
upper limit	0.413

Notes:

[20] - Sensitivity analysis

Statistical analysis title	Treatment B vs Treatment E
Comparison groups	Treatment B - ITT v Treatment E - ITT
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.279
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.232
upper limit	0.325

Notes:

[21] - Sensitivity analysis

Statistical analysis title	Treatment A vs Treatment E
Comparison groups	Treatment A - ITT v Treatment E - ITT
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.257
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.211
upper limit	0.303

Notes:

[22] - Sensitivity anlysis

Statistical analysis title	Treatment C vs Treatment A

Comparison groups	Treatment C - ITT v Treatment A - ITT
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.064
upper limit	0.157

Notes:

[23] - Dose-effect analysis

Statistical analysis title	Treatment D vs Treatment B
Comparison groups	Treatment B - ITT v Treatment D - ITT
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.104
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.058
upper limit	0.15

Notes:

[24] - Dose-effect analysis

Secondary: Peak FVC

End point title	Peak FVC

End point description:

maximum FEV1 value over 12h post-dose

End point type	Secondary

End point timeframe:

FVC was measured over 12 hours after single administration

End point values	Treatment A - ITT	Treatment B - ITT	Treatment C - ITT	Treatment D - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	58	58	59
Units: Liters				
arithmetic mean (confidence interval 95%)	4.121 (4.09 to 4.153)	4.149 (4.116 to 4.182)	4.172 (4.14 to 4.205)	4.187 (4.155 to 4.22)

End point values	Treatment E - ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	59			
Units: Liters				
arithmetic mean (confidence interval 95%)	4.014 (3.982 to 4.046)			

Statistical analyses

Statistical analysis title	Treatment B vs Treatment A
Comparison groups	Treatment A - ITT v Treatment B - ITT
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.018
upper limit	0.073

Statistical analysis title	Treatment D vs Treatment C
Comparison groups	Treatment C - ITT v Treatment D - ITT
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.06

Statistical analysis title	Treatment D vs Treatment E
Comparison groups	Treatment D - ITT v Treatment E - ITT

Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.173
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.128
upper limit	0.218

Notes:

[25] - Sensitivity analysis

Statistical analysis title	Treatment C vs Treatment E
Comparison groups	Treatment C - ITT v Treatment E - ITT
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other[26]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.158
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.113
upper limit	0.204

Notes:

[26] - Sensitivity analysis

Statistical analysis title	Treatment B vs Treatment E
Comparison groups	Treatment B - ITT v Treatment E - ITT
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.135
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.089
upper limit	0.181

Notes:

[27] - SEnsitivity analysis

Statistical analysis title	Treatment A vs Treatment E

Comparison groups	Treatment A - ITT v Treatment E - ITT
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	other[28]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.107
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.062
upper limit	0.152

Notes:

[28] - Sensitivity analysis

Statistical analysis title	Treatment C vs Treatment A
Comparison groups	Treatment A - ITT v Treatment C - ITT
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	= 0.027
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.006
upper limit	0.096

Notes:

[29] - Dose-effect analysis

Statistical analysis title	Treatment D vs Treatment B
Comparison groups	Treatment D - ITT v Treatment B - ITT
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other[30]
P-value	= 0.102
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.038
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.008
upper limit	0.084

Notes:

[30] - Dose-effect analysis

Secondary: FVC AUC0-12/12h	
End point title	FVC AUC0-12/12h
End point description:	
AUC0-12h was measured in a standardised by time (L) way.	
End point type	Secondary
End point timeframe:	
FVC was measured at the following time points during treatment visits (visit 3 to visit 7): at pre-dose within 60 min of the dose and at 10 min, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h and 12 h post-dose.	

End point values	Treatment A - ITT	Treatment B - ITT	Treatment C - ITT	Treatment D - ITT
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	58	58	59
Units: LIters				
arithmetic mean (confidence interval 95%)	3.97 (3.941 to 3.998)	3.986 (3.956 to 4.016)	4.023 (3.993 to 4.053)	4.042 (4.013 to 4.072)

End point values	Treatment E - ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	59			
Units: LIters				
arithmetic mean (confidence interval 95%)	3.835 (3.805 to 3.864)			

Statistical analyses

Statistical analysis title	Treatment B vs Treatment A
Comparison groups	Treatment B - ITT v Treatment A - ITT
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.025
upper limit	0.058

Statistical analysis title	Treatment D vs Treatment C
Comparison groups	Treatment C - ITT v Treatment D - ITT

Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.019
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.022
upper limit	0.06

Statistical analysis title	Treatment D vs Treatment E
Comparison groups	Treatment D - ITT v Treatment E - ITT
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.208
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.166
upper limit	0.249

Notes:

[31] - Sensitivity analysis

Statistical analysis title	Treatment C vs Treatment E
Comparison groups	Treatment C - ITT v Treatment E - ITT
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other[32]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.188
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.147
upper limit	0.23

Notes:

[32] - Sensitivity analysis

Statistical analysis title	Treatment B vs Treatment E
Comparison groups	Treatment B - ITT v Treatment E - ITT

Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.151
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.109
upper limit	0.193

Notes:

[33] - Sensitivity analysis

Statistical analysis title	Treatment A vs Treatment E
Comparison groups	Treatment A - ITT v Treatment E - ITT
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.135
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.094
upper limit	0.176

Notes:

[34] - Sensitivity analysis

Statistical analysis title	Treatment C vs Treatment A
Comparison groups	Treatment C - ITT v Treatment A - ITT
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	= 0.011
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.014
upper limit	0.098

Notes:

[35] - Dose-effect analysis

Statistical analysis title	Treatment D vs Treatment B

Comparison groups	Treatment D - ITT v Treatment B - ITT
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	other[36]
P-value	= 0.009
Method	ANCOVA
Parameter estimate	adjusted mean difference
Point estimate	0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.014
upper limit	0.098

Notes:

[36] - Dose-effect analysis

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From signature of informed consent until follow-up phone call.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Treatment A - safety population
Reporting group description: -	
Reporting group title	Treatment B - safety population
Reporting group description: -	
Reporting group title	Treatment C - safety population
Reporting group description: -	
Reporting group title	Treatment D - safety population
Reporting group description: -	
Reporting group title	Treatment E - safety population
Reporting group description: -	

Serious adverse events	Treatment A - safety population	Treatment B - safety population	Treatment C - safety population
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	0 / 58 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Treatment D - safety population	Treatment E - safety population	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Treatment A - safety population	Treatment B - safety population	Treatment C - safety population
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 60 (13.33%)	9 / 58 (15.52%)	5 / 58 (8.62%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Laceration			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	2 / 60 (3.33%)	4 / 58 (6.90%)	1 / 58 (1.72%)
occurrences (all)	2	4	2
Hypersomnia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	4 / 58 (6.90%)
occurrences (all)	0	0	4
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			

Seasonal allergy			
subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eye pruritus			
subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Ocular hyperaemia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Prostatomegaly			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	1 / 60 (1.67%)	1 / 58 (1.72%)	0 / 58 (0.00%)
occurrences (all)	1	1	0
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Rash			

subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	0 / 58 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Conjunctivitis bacterial			
subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	0 / 58 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Treatment D - safety population	Treatment E - safety population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 59 (15.25%)	13 / 59 (22.03%)	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	
occurrences (all)	0	0	
Fall			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	
occurrences (all)	0	0	

Laceration			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	2 / 59 (3.39%)	7 / 59 (11.86%)	
occurrences (all)	2	7	
Hypersomnia			
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Eye disorders			
Eye pruritus			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	
occurrences (all)	0	0	
Ocular hyperaemia			
subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Prostatomegaly			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	
occurrences (all)	0	0	
Rash			
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			

Conjunctivitis bacterial			
subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	1 / 59 (1.69%)	1 / 59 (1.69%)	
occurrences (all)	1	1	
Rhinitis			
subjects affected / exposed	1 / 59 (1.69%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	0 / 59 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 59 (0.00%)	0 / 59 (0.00%)	
occurrences (all)	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.

No limitations or caveats are applicable to this summary of results

Notes: