Clinical trial results:
Open label, prospective, exploratory study to investigate the effect of inhaled CHF5993 pMDI on central and peripheral airway dimensions in COPD patients by functional respiratory imaging

Summary

EudraCT number	2017-000438-79
Trial protocol	BE HU
Global end of trial date	31 January 2019

Results information

Result version number	v1 (current)
This version publication date	13 February 2020
First version publication date	13 February 2020

Trial information

Trial identification

Sponsor protocol code	CCD-05993AA1-16

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici S.p.A.
Sponsor organisation address	Via Palermo 26/A, Parma, Italy, 43122
Public contact	Clinical Trial Transparency, Chiesi Farmaceutici S.p.A, clinicaltrials_info@chiesi.com
Scientific contact	Clinical Trial Transparency, 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	24 September 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the effect of inhaled extrafine CHF5993 pMDI on airway volumes and resistance, by using functional respiratory imaging (FRI) in patients with chronic obstructive pulmonary disease (COPD), treated with a non extrafine extemporary triple combination for three months before entering the study.

The IMP has both bronchodilatory and anti-inflammatory properties and is used for the treatment of patients with severe COPD or with asthma. Each subject inhaled CHF5993 two times daily; total daily dose: 400 µg BDP, 24 µg FF, and 50 µg GB, for 24 weeks.

Functional Respiratory Imaging (FRI) with computational fluid dynamics (CFD) analysis was used to demonstrate the effect of the IMP on airway parameters in the distal and central regions of the lung and to image the deposition of the extrafine formulation into the deep lung. Lung imaging was obtained from computed tomography (CT) scans, taken upon inspiration and expiration.

Protection of trial subjects:

The clinical study was performed in accordance with the principles that have their origin in the declaration of Helsinki, and with local regulations. Furthermore, the study was performed in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) notes for guidance on Good Clinical Practice (GCP) (ICH/CPMP/135/95).

Before the start of the study, all subjects gave their written informed consent to participate in the study after having been informed of the nature and implications of the study. At completion of subject's participation in the study, it was the Investigator’s responsibility to prescribe the most appropriate treatment for the subject or to restore the initial therapy or to refer to the general practitioner.

Low-dose multislice CT scans were performed at pre-dose, at Visit 2 (Week 0), Visit 5 (Week 12), and Visit 8 (Week 24). At Visit 2, a scan of the upper airway was also performed.

Adverse events (AEs) and vital signs were recorded at all visits (from screening onward, during the treatment phase of 24 weeks). If the investigator deemed it necessary, a visit was scheduled at 7 days after the last drug administration. A follow-up call was scheduled for all subjects and it was performed 7 days after the last study drug administration.

Background therapy:

Permitted concomitant medications

1. Inhaled salbutamol administered as rescue medication. A minimum period of 6 h had to elapse between the use of rescue salbutamol and the spirometric measurements.
2. Long-acting antihistamines if taken at stable regimen at least 2 months prior to screening or if taken pro re nata (PRN).
3. Non-selective xanthine derivatives (e.g., theophylline) if taken at stable regimen for at least 1 month prior to screening and to be maintained constant during the study.

If the subject took concomitant medications, prior to the Visit 1 (screening visit), Visit 2, Visit 5, or Visit 8, the pre-specified washout periods for concomitant medications had to be respected.

Abbreviations used in this entry:

BDP=Beclometasone dipropionate
B17MP=Beclometasone 17-monopropionate (active metabolite of BDP)
CFD=Computational fluid dynamics

CHF 5993=Fixed combination of BDP, FF, and GB
COPD=Chronic obstructive pulmonary disease
CT=Computerised tomography
FEV1=Forced expiratory volume in the 1st second
FF=Formoterol fumarate
FRC=Functional residual capacity
FRI=Functional Respiratory Imaging
GB=Glycopyrronium bromide
HU=Hounsfield Units
IC=Inspiratory capacity
kPa=Kilopascal
MedDRA=Medical Dictionary for Regulatory Activities
µg=Microgram
PEF=Peak expiratory flow
pMDI=Pressurised metered dose inhaler
SGRQ=Saint George Respiratory Questionnaire
RV=Residual volume
s=Second
TLC=Total lung capacity
Voxel=Volume representing element (in Hounsfield units) is a single data point, on a regularly spaced, three-dimensional grid.

Evidence for comparator:

None used.

Actual start date of recruitment	20 November 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	Belgium: 14
Country: Number of subjects enrolled	Hungary: 7
Worldwide total number of subjects	21
EEA total number of subjects	21

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)	8
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adult male and female adult subjects with documented chronic obstructive pulmonary disease (COPD) for at least 12 months (GOLD, 2017 criteria), were evaluated according to the study inclusion and exclusion criteria. Signed Informed Consent Form was obtained prior to any study procedures.

Pre-assignment

Screening details:

At the screening visit (7 ± 3 days prior to baseline), subjects were selected to enter into the study according to the eligibility criteria. Overall, 32 subjects were screened; of these, 21 subjects were enrolled for treatment and evaluation.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Open-label study; not blinded.

Arms

Arm title	Subjects with COPD

Arm description:

Adult subjects with diagnosed and established COPD, who have been treated with a non-extrafine extemporary triple combination for three months, before entering the study. The aim of the study was to explore changes occurring in response to a long-term treatment with CHF 5993, which is an extrafine triple fixed-dose combination.

Arm type	Experimental
Investigational medicinal product name	CHF 5993 (100/6/12.5 µg), pMDI
Investigational medicinal product code	
Other name	BDP/FF/GB, Fixed combination of beclomethasone dipropionate, formoterol fumarate, glycopyrronium bromide
Pharmaceutical forms	Pressurised inhalation, solution
Routes of administration	Inhalation use

Dosage and administration details:

CHF 5993 is a fixed combination of BDP, FF, and GB.
Single actuation of the CHF 5993 pMDI contains: 100µg BDP/6µg FF/12.5µg GB.

Each subject inhaled CHF 5993 100/6/12.5 µg pMDI as two inhalations twice a day (two inhalations in the morning and two inhalations in the evening), giving a total daily dose of 400 µg BDP, 24 µg FF, and 50 µg GB.

Number of subjects in period 1	Subjects with COPD
Started	21
Completed	20
Not completed	1
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Subjects with COPD
Reporting group description:	
Adult subjects with diagnosed and established COPD, who have been treated with a non-extrafine extemporary triple combination for three months, before entering the study. The aim of the study was to explore changes occurring in response to a long-term treatment with CHF 5993, which is an extrafine triple fixed-dose combination.	

Reporting group values	Subjects with COPD	Total	
Number of subjects	21	21	
Age categorical Units: Subjects			
Adults (18-64 years)	8	8	
From 65-84 years	13	13	
Age continuous Units: years			
arithmetic mean	64.1		
standard deviation	± 10.1	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	11	11	
Race Units: Subjects			
Caucasian	21	21	
Smoking habits Units: Subjects			
Ex-smoker	9	9	
Current smoker	12	12	
Body mass index (BMI) Units: kg/m2			
arithmetic mean	24.44		
standard deviation	± 4.01	-	
Duration of smoking Units: years			
arithmetic mean	42.61		
standard deviation	± 10.56	-	
Number pack-years			
Pack-year = number of cigarettes per day x number of years/20			
Units: pack-years			
arithmetic mean	38.29		
standard deviation	± 12.48	-	

End points

End points reporting groups

Reporting group title	Subjects with COPD
Reporting group description:	
Adult subjects with diagnosed and established COPD, who have been treated with a non-extrafine extemporary triple combination for three months, before entering the study. The aim of the study was to explore changes occurring in response to a long-term treatment with CHF 5993, which is an extrafine triple fixed-dose combination.	
Subject analysis set title	Baseline, FRC
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects evaluated at baseline; lung level FRC	
Subject analysis set title	Week 12, FRC
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects evaluated at week 12; lung level FRC	
Subject analysis set title	Week 24, FRC
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects evaluated at week 24; lung level FRC	
Subject analysis set title	Baseline, TLC
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects evaluated at baseline; lung level TLC	
Subject analysis set title	Week 12, TLC
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects evaluated at week 12; lung level TLC	
Subject analysis set title	Week 24, TLC
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects evaluated at week 24; lung level TLC	
Subject analysis set title	Baseline
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects evaluated at baseline.	
Subject analysis set title	Week 24
Subject analysis set type	Per protocol
Subject analysis set description:	
Subjects evaluated at week 24.	

Primary: 1_Specific image-based airway volumes (siVaw); FRC and TLC

End point title	1_Specific image-based airway volumes (siVaw); FRC and TLC

End point description:

Specific image-based airway volumes (siVaw): Computerised tomography-based (CT-based) airway volumes, normalised by the lung volume.
Percent change from baseline to week 12 and 24 of treatment. Lung level: FRC and TLC.

The primary region evaluated was the distal lung region.
Percent change from baseline is presented using descriptive statistics (geometric mean and coefficient of variation).
Specific image-based airway volumes are the CT-based airway volumes normalised by the lung volume.

The siVaw as an FRI parameter is derived from the airway volume (iVaw). Because the airway volume is dependent on the lung volume, the airway volumes had to be made specific to facilitate the comparison between the study visits. The lung volume could be determined from the CT scans for both FRC and TLC, by identifying and grouping the voxels (a value in three-dimensional space) that represent the air in the lungs. The specificity was calculated by dividing the airway volume by the lung volume.

End point type	Primary

End point timeframe:

Baseline, week 12, week 24.

End point values	Baseline, FRC	Week 12, FRC	Week 24, FRC	Baseline, TLC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17[1]	18[2]	17	20
Units: ml/L				
geometric mean (geometric coefficient of variation)	0.548 (± 46.5)	0.606 (± 48.3)	0.567 (± 45.3)	1.242 (± 96.5)

Notes:

[1] - Per protocol population was used for all analyses groups

[2] - Geometric coefficient of variation is the coefficient of variation for all analyses

End point values	Week 12, TLC	Week 24, TLC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	19		
Units: ml/L				
geometric mean (geometric coefficient of variation)	1.332 (± 72.6)	1.341 (± 52.7)		

Statistical analyses

Statistical analysis title	1_Percent change from baseline at week 12; FRC

Statistical analysis description:

Percent change from baseline at week 12; within group comparison.
Lung level: FRC

The value N=35 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=17.

Comparison groups	Week 12, FRC v Baseline, FRC
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.701 [4]
Method	Mixed model for repeated measures
Parameter estimate	Adjusted % change geometric mean
Point estimate	5.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.56
upper limit	37.08

Notes:

[3] - The analysis type is a post treatment comparison versus baseline.

[4] - p-value and estimates are based on a mixed model for repeated measures (MMRM) including log (baseline), visit and its interaction as effects. Estimates are based on back transformed values.

Statistical analysis title	2_Percent change from baseline at week 24; FRC

Statistical analysis description:

Percent change from baseline at week 24; within group comparison.

The value N=34 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=17.

Comparison groups	Week 24, FRC v Baseline, FRC
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.781 [6]
Method	Mixed model for repeated measures
Parameter estimate	Adjusted % change geometric mean
Point estimate	3.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.97
upper limit	33.76

Notes:

[5] - The analysis type is a post treatment comparison versus baseline.

[6] - p-value and estimates are based on a mixed model for repeated measures (MMRM) including log (baseline), visit and its interaction as effects. Estimates are based on back transformed values.

Statistical analysis title	3_Percent change from baseline at week 12; TLC

Statistical analysis description:

Percent change from baseline at week 12; within group comparison.

The value N=39 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=20.

Comparison groups	Baseline, TLC v Week 12, TLC
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.261 [8]
Method	Mixed model for repeated measures
Parameter estimate	Adjusted % change geometric mean
Point estimate	7.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	23.87

Notes:

[7] - The analysis type is a post treatment comparison versus baseline.

[8] - p-value and estimates are based on a mixed model for repeated measures (MMRM) including log (baseline), visit and its interaction as effects. Estimates are based on back transformed values.

Statistical analysis title	4_Percent change from baseline at week 24; TLC

Statistical analysis description:

Percent change from baseline at week 24; within group comparison.

The value N=39 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=20.

Comparison groups	Week 24, TLC v Baseline, TLC
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.023 [10]
Method	Mixed model for repeated measures
Parameter estimate	Adjusted % change geometric mean
Point estimate	15.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.33
upper limit	31.41

Notes:

[9] - The analysis type is a post treatment comparison versus baseline.

[10] - p-value and estimates are based on a mixed model for repeated measures (MMRM) including log (baseline), visit and its interaction as effects. Estimates are based on back transformed values.

Primary: 2_Specific image-based airway resistance (siRaw); FRC and TLC

End point title	2_Specific image-based airway resistance (siRaw); FRC and TLC

End point description:

Specific image-based airway resistance (siRaw). Percent change from baseline to week 12 and 24 of treatment.
Lung level: FRC and TLC.

The primary region evaluated was the distal lung region. Analysis was done for the Functional Residual Capacity (FRC) and for the Total Lung Capacity (TLC). Results represent the actual values per time point for siRaw at baseline, week 12, and week 24. Percent change from baseline is presented using descriptive statistics (geometric mean and coefficient of variation).

Specific image-based airway resistance is the CFD-based airway resistance normalised by the lung volume and was determined using CFD. The specific airway resistance (siRaw) as an FRI parameter is derived from the airway resistance (iRaw). Because the airway resistance is dependent on the lung volume, the airway resistance had to be made specific to facilitate the comparison between the visits.

End point type	Primary

End point timeframe:

Baseline, week 12, week 24.

End point values	Baseline, FRC	Week 12, FRC	Week 24, FRC	Baseline, TLC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17[11]	18[12]	17	20
Units: kPa*s				
geometric mean (geometric coefficient of variation)	0.1481 (± 77.0)	0.2433 (± 77.6)	0.2412 (± 73.0)	0.2957 (± 74.7)

Notes:

[11] - Per protocol population was used for all analyses groups

[12] - Geometric coefficient of variation is the coefficient of variation for all analyses

End point values	Week 12, TLC	Week 24, TLC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	19		
Units: kPa*s				
geometric mean (geometric coefficient of variation)	0.2131 (± 80.2)	0.2265 (± 64.5)		

Statistical analyses

Statistical analysis title	1_Percent change from baseline at week 12; FRC

Statistical analysis description:

Percent change from baseline at week 12; within group comparison.
Lung level: FRC

The value N=35 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=17.

Comparison groups	Week 12, FRC v Baseline, FRC
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.027 [14]
Method	Mixed model for repeated measures
Parameter estimate	Adjusted % change geometric mean
Point estimate	65.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.86
upper limit	157.44

Notes:

[13] - The analysis type is a post treatment comparison versus baseline; see also 'Analysis type comment' for end point 1.
[14] - Further clarification is provided in the 'P-value comment' for end point 1.

Statistical analysis title	2_Percent change from baseline at week 24; FRC

Statistical analysis description:

Percent change from baseline at week 24; within group comparison.
Lung level: FRC

The value N=34 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=17.

Comparison groups	Week 24, FRC v Baseline, FRC
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.104 [16]
Method	Mixed model for repeated measures
Parameter estimate	Adjusted % change geometric mean
Point estimate	62.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.64
upper limit	196.72

Notes:

[15] - The analysis type is a post treatment comparison versus baseline; see also 'Analysis type comment' for end point 1.
[16] - Further clarification is provided in the 'P-value comment' for end point 1.

Statistical analysis title	3_Percent change from baseline at week 12; TLC

Statistical analysis description:

Percent change from baseline at week 24; within group comparison.
Lung level: TLC

The value N=39 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=20.

Comparison groups	Week 12, TLC v Baseline, TLC
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.052 [18]
Method	Mixed model for repeated measures
Parameter estimate	Adjusted % change geometric mean
Point estimate	-27.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.4
upper limit	0.36

Notes:

[17] - The analysis type is a post treatment comparison versus baseline; see also 'Analysis type comment' for end point 1.
[18] - Further clarification is provided in the 'P-value comment' for end point 1.

Statistical analysis title	4_Percent change from baseline at week 24; TLC

Statistical analysis description:

Percent change from baseline at week 24; within group comparison.
Lung level: TLC

The value N=39 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=20.

Comparison groups	Week 24, TLC v Baseline, TLC
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.05 [20]
Method	Mixed model for repeated measures
Parameter estimate	Adjusted % change geometric mean
Point estimate	-30.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-52.17
upper limit	0.08

Notes:

[19] - The analysis type is a post treatment comparison versus baseline; see also 'Analysis type comment' for end point 1.
[20] - Further clarification is provided in the 'P-value comment' for end point 1.

Secondary: 3_Internal Airflow Distribution

End point title	3_Internal Airflow Distribution

End point description:

Internal airflow distribution (Internal lobar airflow distribution).
Percent change from baseline to week 24 of treatment.
Percent change from baseline is presented using descriptive statistics (geometric mean and coefficient of variation).

Lobar volume (iVlobe) is an FRI-based ventilation parameter, obtained by identifying and grouping voxels that represent the air in the lungs. The lung volume could be determined from the scans at both FRC and TLC. The subject-specific airflow distribution could be established by assessing lobar volume expansion.

Results represent the actual values per time point, at baseline and week 24.
Lung level: Not applicable
Lung region: Upper lobes

End point type	Secondary

End point timeframe:

Baseline, week 24.

End point values	Baseline	Week 24		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[21]	18[22]		
Units: percent				
geometric mean (geometric coefficient of variation)	49.104 (± 27.0)	47.909 (± 25.5)		

Notes:

[21] - Per protocol population was used for all analyses groups

[22] - Geometric coefficient of variation is the coefficient of variation for all analyses

Statistical analyses

Statistical analysis title	1_Percent change from baseline at week 24

Statistical analysis description:

Percent change from baseline at week 24; within group comparison.

The value N=37 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=19.

Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.858 [24]
Method	Mixed model for repeated measures
Parameter estimate	Adjusted % change geometric mean
Point estimate	-0.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.56
upper limit	6.84

Notes:

[23] - The analysis type is a post treatment comparison versus baseline; see also the 'Analysis type comment' for end point 1.
[24] - Further clarification is provided in the 'P-value comment' for end point 1.

Secondary: 4_Air Trapping

End point title	4_Air Trapping

End point description:

Air trapping.
Percent change from baseline to week 24 of treatment.
Percent change from baseline is presented using descriptive statistics (geometric mean and coefficient of variation).

Air trapping, also called gas trapping, is an abnormal retention of air in the lungs. It is observed in obstructive lung diseases such as asthma and bronchiolitis obliterans syndrome, and in chronic obstructive pulmonary diseases such as emphysema and chronic bronchitis. FRI-based air trapping was defined as all the intrapulmonary voxels with Hounsfield Units (HU) between -1024 and -850, using the expiratory scans at FRC.

Results represent the actual values per time point, at baseline and week 24.
Lung level: FRC
Lung region: Total lung region

End point type	Secondary

End point timeframe:

Baseline, week 24.

End point values	Baseline	Week 24		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[25]	18[26]		
Units: percent				
geometric mean (geometric coefficient of variation)	53.782 (± 33.4)	53.900 (± 34.5)		

Notes:

[25] - Per protocol population was used for all analyses groups

[26] - Geometric coefficient of variation is the coefficient of variation for all analyses

Statistical analyses

Statistical analysis title	1_Percent change from baseline at week 24

Statistical analysis description:

Percent change from baseline at week 24; within group comparison.

The value N=37 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=19.

Comparison groups	Week 24 v Baseline

Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0.693 [28]
Method	Mixed model for repeated measures
Parameter estimate	Adjusted % change geometric mean
Point estimate	1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.28
upper limit	11.75

Notes:

[27] - The analysis type is a post treatment comparison versus baseline; see also the 'Analysis type comment' for end point 1.
[28] - Further clarification is provided in the 'P-value comment' for end point 1.

Secondary: 5_Emphysema (Low Attenuation Score)

End point title	5_Emphysema (Low Attenuation Score)

End point description:

Emphysema (Low Attenuation Score)
Percent change from baseline to week 24 of treatment.
Percent change from baseline is presented using descriptive statistics (geometric mean and coefficient of variation).

The low attenuation areas on CT scans have been reported to represent emphysematous changes of the lung. Emphysema is a long-term, progressive disease of the lungs that primarily causes shortness of breath due to over-inflation of the alveoli. FRI-based emphysema calculations were defined as all the intrapulmonary voxels with HU between -1024 and -950, using the inspiratory scans at TLC.

Results represent the actual values per time point, at baseline and week 24.
Lung level: TLC
Lung region: Total lung region

End point type	Secondary

End point timeframe:

Baseline, week 24.

End point values	Baseline	Week 24		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20[29]	19[30]		
Units: percent				
geometric mean (geometric coefficient of variation)	6.636 (± 105.4)	6.077 (± 100.6)		

Notes:

[29] - Per protocol population was used for all analyses groups

[30] - Geometric coefficient of variation is the coefficient of variation for all analyses

Statistical analyses

Statistical analysis title	1_Percent change from baseline at week 24

Statistical analysis description:

Percent change from baseline at week 24; within group comparison.

The value N=39 (Subjects in this analysis) shown below, is generated automatically and is due to an

innate error of the EudraCT database system. The correct value for subjects in the analysis is N=20.

Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	= 0.603 [32]
Method	Mixed model for repeated measures
Parameter estimate	Adjusted % change geometric mean
Point estimate	-5.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.4
upper limit	18.21

Notes:

[31] - The analysis type is a post treatment comparison versus baseline; see also the 'Analysis type comment' for end point 1.
[32] - Further clarification is provided in the 'P-value comment' for end point 1.

Secondary: 6_Airway Wall Volume

End point title	6_Airway Wall Volume

End point description:

Airway wall volume.
Percent change from baseline to week 24 of treatment.
Percent change from baseline is presented using descriptive statistics (geometric mean and coefficient of variation).

The airway wall volume (iVaww) consisted of all visible tissue in the CT scan that encompassed the airway wall. The airway wall volume can typically be described to the same generation level as the volume description of the airway lumen. This is where the airway diameter is around 1 2 mm.

Results represent the actual values per time point, at baseline and week 24.
Lung level: TLC
Lung region: Distal lung region

End point type	Secondary

End point timeframe:

Baseline, week 24.

End point values	Baseline	Week 24		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20[33]	19[34]		
Units: mL				
geometric mean (geometric coefficient of variation)	36.430 (± 54.9)	36.591 (± 54.9)		

Notes:

[33] - Per protocol population was used for all analyses groups

[34] - Geometric coefficient of variation is the coefficient of variation for all analyses

Statistical analyses

Statistical analysis title	1_Percent change from baseline at week 24

Statistical analysis description:

Percent change from baseline at week 24; within group comparison.

The value N=39 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=20.

Comparison groups	Baseline v Week 24
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	= 0.169 [36]
Method	Mixed model for repeated measures
Parameter estimate	Adjusted % change geometric mean
Point estimate	6.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	15.52

Notes:

[35] - The analysis type is a post treatment comparison versus baseline; see also the 'Analysis type comment' for end point 1.
[36] - Further clarification is provided in the 'P-value comment' for end point 1.

Secondary: 7_Blood Vessel Density

End point title	7_Blood Vessel Density

End point description:

Blood vessel density.
Percent change from baseline to week 24 of treatment.
Percent change from baseline is presented using descriptive statistics (geometric mean and coefficient of variation).

Blood vessel density (iVbv) was determined through segmentation and 3D reconstruction of the blood vessels. The segmentation was based on a HU threshold between -600 and 600 and was performed on the TLC scan. The blood vessel density can be considered a surrogate for perfusion. If a contrast agent was used, the HU threshold changed to capture voxels between 200 and 1873. The use of a contrast agent was not strictly required but recommended for patients with significant fibrosis or opaque (high attenuation) regions.

Results represent the actual values per time point, at baseline and week 24.
Lung level: TLC
Lung region: Distal lung region

End point type	Secondary

End point timeframe:

Baseline, week 24.

End point values	Baseline	Week 24		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20[37]	19[38]		
Units: percent				
geometric mean (geometric coefficient of variation)	2.145 (± 38.8)	2.146 (± 40.7)		

Notes:

[37] - Per protocol population was used for all analyses groups

[38] - Geometric coefficient of variation is the coefficient of variation for all analyses

Statistical analyses

Statistical analysis title	1_Percent change from baseline at week 24

Statistical analysis description:

Percent change from baseline at week 24; within group comparison.

The value N=39 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=20.

Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other[39]
P-value	= 0.82 [40]
Method	Mixed model for repeated measures
Parameter estimate	Adjusted % change geometric mean
Point estimate	-0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	4.38

Notes:

[39] - The analysis type is a post treatment comparison versus baseline; see also the 'Analysis type comment' for end point 1.
[40] - Further clarification is provided in the 'P-value comment' for end point 1.

Secondary: 8_Ventilation/Perfusion Matching

End point title	8_Ventilation/Perfusion Matching

End point description:

Ventilation/Perfusion matching.
Percent change from baseline to week 24 of treatment.
Percent change from baseline is presented using descriptive statistics (geometric mean and coefficient of variation).

By relating the regional ventilation to the regional perfusion, an assessment of the ventilation perfusion mismatch and potential reduction in the mismatch could be made.

Results represent the actual values per time point, at baseline and week 24.
Lung level: Not applicable
Lung region: Total lung region

End point type	Secondary

End point timeframe:

Baseline, week 24.

End point values	Baseline	Week 24		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[41]	18[42]		
Units: litre/litre				
geometric mean (geometric coefficient of variation)	12.164 (± 41.7)	11.842 (± 32.7)		

Notes:

[41] - Per protocol population was used for all analyses groups

[42] - Geometric coefficient of variation is the coefficient of variation for all analyses

Statistical analyses

Statistical analysis title	1_Percent change from baseline at week 24

Statistical analysis description:

Percent change from baseline at week 24; within group comparison.

The value N=37 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=19.

Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other[43]
P-value	= 0.627 [44]
Method	Mixed model for repeated measures
Parameter estimate	Adjusted % change geometric mean
Point estimate	-2.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.82
upper limit	10.49

Notes:

[43] - The analysis type is a post treatment comparison versus baseline; see also the 'Analysis type comment' for end point 1.
[44] - Further clarification is provided in the 'P-value comment' for end point 1.

Secondary: 9_Aerosol Deposition; BDP FF, GB

End point title	9_Aerosol Deposition; BDP FF, GB

End point description:

Aerosol deposition for BDP, FF, and GB.
Percent change from baseline to week 24 of treatment.
Percent change from baseline is presented using descriptive statistics (geometric mean and coefficient of variation).

Regional aerosol deposition was determined by simulating the flow in the patient-specific geometries using patient-specific boundary conditions by means of CFD. While solving the flow equations, simultaneously particles were released in the flow and the force mass balance of the individual particles was determined through additional discrete phase computations. When a calculated particle trajectory intersected with the airway wall, the particle was trapped in that location. This allowed determining the regional concentration of inhaled aerosols and consequently the effective lung dose of inhaled medication.

Results represent the actual values per time point, at baseline and week 24.
Lung level: TLC
Lung region: Peripheral lung region

End point type	Secondary

End point timeframe:

Baseline, week 24.

End point values	Baseline	Week 24		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20[45]	19[46]		
Units: microgram(s)				
geometric mean (geometric coefficient of variation)				
BDP	24.1242 (± 13.4)	24.0345 (± 17.0)		
FF	1.4103 (± 13.4)	1.4051 (± 17.0)		
GB	2.9772 (± 13.3)	2.9663 (± 16.9)		

Notes:

[45] - Per protocol population was used for all analyses groups

[46] - Geometric coefficient of variation is the coefficient of variation for all analyses

Statistical analyses

Statistical analysis title	1_Aerosol deposition -- BDP

Statistical analysis description:

Aerosol deposition, BDP
Percent change from baseline at week 24; within group comparison.

The value N=39 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=20.

Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other[47]
P-value	= 0.953 [48]
Method	Mixed model for repeated measures
Parameter estimate	Adjusted % change geometric mean
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.49
upper limit	11.13

Notes:

[47] - The analysis type is a post treatment comparison versus baseline; see also the 'Analysis type comment' for end point 1.
[48] - Further clarification is provided in the 'P-value comment' for end point 1.

Statistical analysis title	2_Aerosol deposition -- FF

Statistical analysis description:

Aerosol deposition, FF

Percent change from baseline at week 24; within group comparison.

The value N=39 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=19.

Comparison groups	Week 24 v Baseline

Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other[49]
P-value	= 0.952 [50]
Method	Mixed model for repeated measures
Parameter estimate	Adjusted % change geometric mean
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.43
upper limit	11.07

Notes:

[49] - The analysis type is a post treatment comparison versus baseline; see also the 'Analysis type comment' for end point 1.
[50] - Further clarification is provided in the 'P-value comment' for end point 1.

Statistical analysis title	3_Aerosol deposition -- GB

Statistical analysis description:

Aerosol deposition, GB

Percent change from baseline at week 24; within group comparison.

The value N=39 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=19.

Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other[51]
P-value	= 0.951 [52]
Method	Mixed model for repeated measures
Parameter estimate	Adjusted % change geometric mean
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.33
upper limit	10.96

Notes:

[51] - The analysis type is a post treatment comparison versus baseline; see also the 'Analysis type comment' for end point 1.
[52] - Further clarification is provided in the 'P-value comment' for end point 1.

Secondary: 10a_Dynamic lung volumes -- Spirometry: FEV1

End point title	10a_Dynamic lung volumes -- Spirometry: FEV1

End point description:

Dynamic lung volumes calculated by spirometry: Forced Expiratory Volume in one second (FEV1)

FEV1 is one of the lung function tests, obtained by spirometry. The volume of air that can be forced out in one second after taking a deep breath is an important measure of pulmonary function.For FEV1, the highest value (L) from three technically satisfactory attempts (1 minute apart) were recorded.

Descriptive statistics were used to calculate the results shown below, which represent the actual values per time point, at baseline and at pre-dose week 24.

End point type	Secondary

End point timeframe:

Baseline, pre dose at week 24.

End point values	Baseline	Week 24		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20[53]	20		
Units: litre(s)				
arithmetic mean (standard deviation)	1.057 (± 0.394)	1.113 (± 0.483)		

Notes:

[53] - Per protocol population was used for all analyses groups

Statistical analyses

Statistical analysis title	1_Change from baseline at week 24, FEV1

Statistical analysis description:

Change from baseline at week 24, FEV1.

Within group comparison.
Change from baseline is presented using descriptive statistics.

The value N=40 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=20.

Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[54]
P-value	= 0.296
Method	paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.052
upper limit	0.163

Notes:

[54] - The analysis type is a comparison versus baseline.

Secondary: 10b_Dynamic lung volumes -- Spirometry PEF

End point title	10b_Dynamic lung volumes -- Spirometry PEF

End point description:

Dynamic lung volumes, spirometry: Peak Expiratory Flow (PEF)

PEF is one of the lung function tests, obtained by spirometry. PEF is a person's maximum speed of expiration, as measured with a peak flow meter

Descriptive statistics were used to calculate the results shown below, which represent the actual values per time point, at baseline and at pre-dose week 24.

End point type	Secondary

End point timeframe:

Baseline, pre dose at week 24.

End point values	Baseline	Week 24		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20[55]	20		
Units: litre/s				
arithmetic mean (standard deviation)	2.829 (± 1.024)	2.862 (± 1.224)		

Notes:

[55] - Per protocol population was used for all analyses groups

Statistical analyses

Statistical analysis title	1_Change from baseline at week 24, PEF

Statistical analysis description:

Change from baseline at week 24, PEF.

Within group comparison.
Change from baseline is presented using descriptive statistics.

The value N=40 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=20.

Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[56]
P-value	= 0.777
Method	paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	0.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.208
upper limit	0.274

Notes:

[56] - The analysis type is a comparison versus baseline.

Secondary: 11_Static lung volumes -- Plethysmography: IC, TLC, RV

End point title	11_Static lung volumes -- Plethysmography: IC, TLC, RV

End point description:

Static lung volumes calculated by body plethysmography: Inspiratory capacity (IC), Total lung capacity (TLC), Residual volume (RV)

Body plethysmography is a well-established technique of lung function determination, providing measures of the lung that reflect a multitude of functional and structural aspects. It is an alternative method of measuring lung volume that takes advantage of the principle of Boyle's law i.e. the volume of gas at a constant temperature varies inversely with the pressure applied to it. The primary advantage of body plethysmography is that it can measure the total volume of air in the chest, including gas trapped in bullae. Another advantage is that this test can be performed quickly while patient is breathing at tidal volume.

Descriptive statistics were used to calculate the results shown below, which represent the actual values per time point.
The number of patients contributing to the end points is also shown.

End point type	Secondary

End point timeframe:

Baseline, pre dose at week 24.

End point values	Baseline	Week 24		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20[57]	19[58]		
Units: litre(s)				
arithmetic mean (standard deviation)				
Inspiratory capacity	1.421 (± 0.623)	1.573 (± 0.450)		
Total lung capacity	7.514 (± 1.584)	7.632 (± 1.304)		
Residual volume	5.043 (± 1.146)	5.077 (± 0.977)		

Notes:

[57] - Per protocol population was used for all analyses groups

Number of subjects
N=20
N=20
N=20

[58] -
Number of subjects
N=19
N=20
N=20

Statistical analyses

Statistical analysis title	1_Change from baseline at pre dose at week 24, IC

Statistical analysis description:

Change from baseline at pre dose on week 24, IC.

Within group comparison.
Change from baseline is presented using descriptive statistics.

The value N=39 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=19.

Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other[59]
P-value	= 0.068
Method	paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	0.173

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.014
upper limit	0.36
Variability estimate	Standard deviation
Dispersion value	0.388

Notes:

[59] - The analysis type is a comparison versus baseline.

Statistical analysis title	2_Change from baseline at pre dose at week 24, TLC

Statistical analysis description:

Change from baseline at pre dose at week 24, TLC

Within group comparison.
Change from baseline is presented using descriptive statistics.

The value N=39 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=20.

Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other[60]
P-value	= 0.486
Method	paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	0.118
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.228
upper limit	0.463
Variability estimate	Standard deviation
Dispersion value	0.739

Notes:

[60] - The analysis type is a comparison versus baseline.

Statistical analysis title	3_Change from baseline at pre dose at week 24, RV

Statistical analysis description:

Change from baseline at pre dose at week 24, RV

Within group comparison.
Change from baseline is presented using descriptive statistics.

The value N=39 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=20.

Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	other[61]
P-value	= 0.841
Method	paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	0.034

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.316
upper limit	0.384
Variability estimate	Standard deviation
Dispersion value	0.747

Notes:

[61] - The analysis type is a comparison versus baseline.

Secondary: 12_Saint George Respiratory Questionnaire (SGRQ)

End point title	12_Saint George Respiratory Questionnaire (SGRQ)

End point description:

Saint George Respiratory Questionnaire (SGRQ)

The SGRQ is an index designed to measure and quantify health-related health status in patients with chronic airflow limitation. Results obtained as a score from SGRQ have been shown to correlate well with established measures of symptom level, disease activity, and disability.

Three component are used to calculate the SGRQ score: Symptom level, Impacts, and Activity. A Total score is also calculated and this summarises the impact of the disease on overall health status. Scores are expressed as a percentage of overall impairment where 100 represents worst possible health status and 0 indicates best possible health status.

Results show the SGRQ score at baseline and at week 24 of treatment. The number of subjects (N) contributing to the data is also indicated.

End point type	Secondary

End point timeframe:

Baseline, week 24.

End point values	Baseline	Week 24		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19[62]	19[63]		
Units: score				
arithmetic mean (standard deviation)				
SGRQ total score	47.61 (± 15.25)	44.80 (± 19.86)		
SGRQ symptoms	53.67 (± 20.25)	50.08 (± 23.44)		
SGRQ impacts	34.48 (± 16.70)	36.29 (± 21.70)		
SGRQ activity	66.74 (± 18.44)	58.05 (± 22.34)		

Notes:

[62] - Per protocol population was used for all analyses groups
Number of subjects
N=19
N=19
N=19
N=20

[63] -
Number of subjects
N=19
N=19

N=20
N=19

Statistical analyses

Statistical analysis title	1_Change from baseline at week 24 - Total Score

Statistical analysis description:

Change from baseline at week 24; SGRQ Total score.

Within group comparison, using descriptive statistics.

The value N=38 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=19.

Comparison groups	Baseline v Week 24
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other[64]
P-value	= 0.291
Method	paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-2.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.22
upper limit	2.61
Variability estimate	Standard deviation
Dispersion value	11.23

Notes:

[64] - The analysis type is a comparison versus baseline.

Statistical analysis title	2_Change from baseline at week 24; SGRQ Symptoms

Statistical analysis description:

Change from baseline at week 24; SGRQ Symptoms score.

Within group comparison, using descriptive statistics.

The value N=38 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=19.

Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other[65]
P-value	= 0.403
Method	paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-3.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.39
upper limit	5.22
Variability estimate	Standard deviation
Dispersion value	18.27

Notes:

[65] - The analysis type is a comparison versus baseline.

Statistical analysis title	3_Change from baseline at week 24; SGRQ Impacts

Statistical analysis description:

Change from baseline at week 24; SGRQ Impacts.

Within group comparison, using descriptive statistics.

The value N=38 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=19.

Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other[66]
P-value	= 0.74
Method	paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.14
upper limit	7.11
Variability estimate	Standard deviation
Dispersion value	12.71

Notes:

[66] - The analysis type is a comparison versus baseline.

Statistical analysis title	4_Change from baseline at week 24; SGRQ Activity

Statistical analysis description:

Change from baseline at week 24; SGRQ Activity.

Within group comparison, using descriptive statistics.

The value N=38 (Subjects in this analysis) shown below, is generated automatically and is due to an innate error of the EudraCT database system. The correct value for subjects in the analysis is N=19.

Comparison groups	Week 24 v Baseline
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other[67]
P-value	= 0.131
Method	paired t-test
Parameter estimate	Mean difference (final values)
Point estimate	-8.31

Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.35
upper limit	2.74
Variability estimate	Standard deviation
Dispersion value	22.91

Notes:

[67] - The analysis type is a comparison versus baseline.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment period: from first treatment inhalation of IMP until study completion (24 weeks) or study discontinuation.

Adverse event reporting additional description:

Analyses of adverse events were based on the safety population, defined as all randomised subjects who received at least one dose of IMP.

Adverse events were analysed according to the treatment-emergent principle.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Subjects with COPD

Reporting group description: -

Serious adverse events	Subjects with COPD		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 21 (4.76%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Subjects with COPD		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 21 (61.90%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	4		
Headache			

subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	4		
Dyspnoea			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	10		
Oropharyngeal pain			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	5		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	8		
Back pain			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	8		
Muscle spasms			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None reported

Notes: