Clinical trial results:
Open label, prospective study to evaluate the effect of step-up from non-extrafine ICS/LABA DPI to extra fine triple therapy with CHF5993 DPI on airway geometry and lung ventilation using FRI in subjects with advanced COPD.

Summary

EudraCT number	2020-002356-20
Trial protocol	BE HU
Global end of trial date	03 January 2022

Results information

Result version number	v1 (current)
This version publication date	25 February 2023
First version publication date	25 February 2023

Trial information

Trial identification

Sponsor protocol code	CLI-05993BA1-08

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 Trasparency, Chiesi Farmaceutici S.p.A., clinicaltrials_info@chiesi.com
Scientific contact	Clinical Trial Trasparency, 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	27 January 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of stepping-up from fluticasone dipropionate (FP)/salmeterol (SLM) dry-powder inhaler (DPI) (SERETIDE™ DISKUS™) to extrafine beclometasone dipropionate (BDP)/formoterol fumarate (FF)/glycopyrronium bromide (GB) DPI (CHF5993) on airway geometry and lung ventilation.

The primary and secondary endpoints are shown in the database.

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. The study was carried out in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) notes for guidance on Good Clinical Practice (GCP) (ICH/CPMP/135/95).
All patients were to be well trained in the inhalation technique with In-Check Dial at screening to familiarise with the inhalation technique, in the attempt to yield repeatable inhalations.
During V1 (screening), all patients were to be trained on the proper use of SERETIDE™ DISKUS™ and CHF5993 NEXThaler® by using In-Check Dial.
During the training, two different assessments were to be performed: one set for DISKUS™ resistance, and the second set for NEXThaler®.

The study consisted of a screening visit (V1), followed by a 6 week run-in period. At the end of the run-in period (V2), patients were switched to the treatment period for 6 weeks (until V3). A follow-up call was planned after 2 weeks ± 2 days from V3 for males and women of non childbearing potential. The total study duration was approximately 14 weeks per patient.

Background therapy:

In the run-in period, patients were administered SERETIDE™ DISKUS™ 500/50 µg one inhalation b.i.d. (batch number: V66D), giving a total daily dose of 1 mg FP (Fluticasone dipropionate) and 100 µg SLM (Salmeterol).

Evidence for comparator: -

Actual start date of recruitment	11 June 2021
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: 8
Country: Number of subjects enrolled	Hungary: 17
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	12
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total, 45 patients were screened of whom 20 were screening failures. The other 25 patients were enrolled and received two inhalations b.i.d. of CHF5993 DPI 100/6/12.5 µg. All enrolled and treated patients completed the study, and 23 patients were included in the PP analysis set.

Pre-assignment

Screening details:

Screening visit was performed 6 weeks ± 2 days before Visit 2. The eligibility (inclusion/exclusion criteria) such as BMI, medical and smoking hystory, hystory of alcohol and drug abuse, vital signs, ECG test, pregnancy test, serology test, documented COVID-19 diagnosis, blood analysis, urine test, intake of concomitants medications were assessed.

Pre-assignment period milestones

Number of subjects started	45[1]
Number of subjects completed	25

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 1
Reason: Number of subjects	In-/exclusion criteria: 14
Reason: Number of subjects	Consent withdrawn by subject: 5

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: In total, 45 patients were screened of whom 20 were screening failures. The other 25 patients were enrolled and treated.

Period 1

Period 1 title	CHF5993 DPI 100/6/12.5 µg (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	CHF5993 DPI 100/6/12.5 µg

Arm description:

All patients (25 subjects) received CHF5993 as follows:
- Treatment period (6 weeks): two inhalations b.i.d. of CHF5993 DPI 100/6/12.5 µg, giving a total daily dose of BDP/FF/GB 400/24/50 µg.

After the screening visit (V1) that was to be performed 6 weeks ± 2 days before Visit 2 (V2), eligible patients were to undergo a 6-week run-in period with FP/SLM DPI 500/50 µg (SERETIDE™ DISKUS™). At the end of the run-in period (V2), patients were to be switched to the treatment period with BDP/FF/GB DPI (CHF5993) for 6 weeks until Visit 3 (V3).

Arm type	Experimental
Investigational medicinal product name	CHF5993 DPI 100/6/12.5 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Respiratory use

Dosage and administration details:

Carried out treatment included two inhalations b.i.d. of CHF5993 DPI 100/6/12.5 µg, giving a total daily dose of BDP/FF/GB 400/24/50 µg.

Number of subjects in period 1	CHF5993 DPI 100/6/12.5 µg
Started	25
Completed	25

Baseline characteristics

Reporting groups	
Reporting group title	CHF5993 DPI 100/6/12.5 µg

Reporting group description:

After the screening visit (V1) that was to be performed 6 weeks ± 2 days before Visit 2 (V2), eligible patients were to undergo a 6-week run-in period with FP/SLM DPI 500/50 µg (SERETIDE™ DISKUS™). At the end of the run-in period (V2), patients were to be switched to the treatment period with BDP/FF/GB DPI (CHF5993) for 6 weeks until Visit 3 (V3). During the treatment period all patients, (25 subjects) received two inhalations b.i.d. of CHF5993 DPI 100/6/12.5 µg, giving a total daily dose of BDP/FF/GB 400/24/50 µg. All enrolled and treated patients completed the study.

Reporting group values	CHF5993 DPI 100/6/12.5 µg	Total	
Number of subjects	25	25	
Age categorical Units: Subjects			
Adults (45-79 years)	25	25	
Age continuous Units: years			
arithmetic mean	65.0		
standard deviation	± 7.7	-	
Gender categorical Units: Subjects			
Female	9	9	
Male	16	16	
Race Units: Subjects			
White	25	25	
BMI Units: kg/m²			
arithmetic mean	27.71		
standard deviation	± 5.05	-	

End points

End points reporting groups

Reporting group title	CHF5993 DPI 100/6/12.5 µg

Reporting group description:

All patients (25 subjects) received CHF5993 as follows:
- Treatment period (6 weeks): two inhalations b.i.d. of CHF5993 DPI 100/6/12.5 µg, giving a total daily dose of BDP/FF/GB 400/24/50 µg.

After the screening visit (V1) that was to be performed 6 weeks ± 2 days before Visit 2 (V2), eligible patients were to undergo a 6-week run-in period with FP/SLM DPI 500/50 µg (SERETIDE™ DISKUS™). At the end of the run-in period (V2), patients were to be switched to the treatment period with BDP/FF/GB DPI (CHF5993) for 6 weeks until Visit 3 (V3).

Subject analysis set title	Baseline / V2 pre-dose, TLC
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects evaluated at Baseline / Visit 2 pre-dose; distal lung region at Total Lung Capacity, TLC.
The PP analysis set, defined as all patients from the safety set, excluding patients without any valid evaluation of FRI after the baseline or with important protocol deviations impacting the primary study endpoints, included 23 patients.

Subject analysis set title	V2 post-dose, TLC
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects evaluated at Visit 2 post-dose; distal lung region at Total Lung Capacity, TLC.
The PP analysis set, defined as all patients from the safety set, excluding patients without any valid evaluation of FRI after the baseline or with important protocol deviations impacting the primary study endpoints, included 23 patients.

Subject analysis set title	V3 pre-dose, TLC
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects evaluated at Visit 3 pre-dose; distal lung region at Total Lung Capacity, TLC.
The PP analysis set, defined as all patients from the safety set, excluding patients without any valid evaluation of FRI after the baseline or with important protocol deviations impacting the primary study endpoints, included 23 patients.

Subject analysis set title	V3 post-dose, TLC
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects evaluated at Visit 3 post-dose; distal lung region at Total Lung Capacity, TLC.
The PP analysis set, defined as all patients from the safety set, excluding patients without any valid evaluation of FRI after the baseline or with important protocol deviations impacting the primary study endpoints, included 23 patients.

Subject analysis set title	Baseline / V2 pre-dose, FRC
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects evaluated at Baseline / Visit 2 pre-dose; distal lung region at Functional Residual Capacity, FRC.
The PP analysis set, defined as all patients from the safety set, excluding patients without any valid evaluation of FRI after the baseline or with important protocol deviations impacting the primary study endpoints, included 23 patients.

Subject analysis set title	V2 post-dose, FRC
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects evaluated at Visit 2 post-dose; distal lung region at Functional Residual Capacity, FRC.
The PP analysis set, defined as all patients from the safety set, excluding patients without any valid evaluation of FRI after the baseline or with important protocol deviations impacting the primary study endpoints, included 23 patients.

Subject analysis set title	V3 pre-dose, FRC
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects evaluated at Visit 3 pre-dose; distal lung region at Functional Residual Capacity, FRC.
The PP analysis set, defined as all patients from the safety set, excluding patients without any valid evaluation of FRI after the baseline or with important protocol deviations impacting the primary study endpoints, included 23 patients.

Subject analysis set title	V3 post-dose, FRC
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects evaluated at Visit 3 post-dose; distal lung region at Functional Residual Capacity, FRC.
The PP analysis set, defined as all patients from the safety set, excluding patients without any valid evaluation of FRI after the baseline or with important protocol deviations impacting the primary study endpoints, included 23 patients.

Primary: Untrimmed siVaw for distal region at TLC – actual value for V2 pre-dose and V3 pre-dose

End point title	Untrimmed siVaw for distal region at TLC – actual value for V2 pre-dose and V3 pre-dose

End point description:

siVaw is Specific Image-Based Airway Volume (at Total Lung Capacity, TLC).
Primary efficacy endpoints were presented as the arithmetic mean and the standard deviation (SD).
The data were summarized by the descriptive statistics for actual values at each timepoint.

End point type	Primary

End point timeframe:

Multi-slice with multidetector computed tomography (MDCT) (inspiratory at TLC and expiratory at FRC) was to be performed pre-dose and within 60-120 min post-dose at V2 and V3. At V2, the upper airway (UA) was also to be be scanned at TLC, pre-dose.

End point values	Baseline / V2 pre-dose, TLC	V3 pre-dose, TLC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	23		
Units: percentage				
arithmetic mean (standard deviation)	1.4088 (± 0.6647)	1.3550 (± 0.6014)		

Statistical analyses

Statistical analysis title	Percent change from Baseline to V3 pre-dose; TLC

Statistical analysis description:

Overall, distal region value for primary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from baseline to pre-dose at V3 was back transformed and presented with its 95% confidence interval (CI) and related p-value.

The value N=46, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study.
The correct value for subjects in the analysis is N=23.

Comparison groups	V3 pre-dose, TLC v Baseline / V2 pre-dose, TLC

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.4521
Method	Mixed models analysis
Parameter estimate	Adjusted Mean Change
Point estimate	-3.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.44
upper limit	6.89

Notes:

[1] - The model included the logarithm of baseline (V2 pre-dose, but not for trimmed parameters) at TLC and visit (V2 post-dose, V3 pre-dose, V3 post-dose) as covariates, and the interaction between visit and logarithm of baseline (for untrimmed parameters).
The model parameters were estimated using the restricted maximum likelihood method with unstructured variance-covariance matrix and Kenward-Roger approximation to estimate denominator degrees of freedom.

Primary: Trimmed siRaw for distal region at TLC – actual value for V2 pre-dose and V3 pre-dose

End point title	Trimmed siRaw for distal region at TLC – actual value for V2 pre-dose and V3 pre-dose

End point description:

siRaw is the Specific Image-Based Airway Resistance (at Total Lung Capacity, TLC).
Primary efficacy endpoints were presented as the arithmetic mean and the standard deviation (SD).
The data were summarized by the descriptive statistics for actual values at each timepoint.

End point type	Primary

End point timeframe:

Multi-slice with multidetector computed tomography (MDCT) (inspiratory at TLC and expiratory at FRC) was to be performed pre-dose and within 60-120 min post-dose at V2 and V3. At V2, the upper airway (UA) was also to be be scanned at TLC, pre-dose.

End point values	Baseline / V2 pre-dose, TLC	V3 pre-dose, TLC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22[2]	22[3]		
Units: percentage				
arithmetic mean (standard deviation)				
TLC	0.7160 (± 0.4034)	0.8492 (± 0.5947)		

Notes:

[2] - PP population
number of patients/number of patients with data: 23/22
[3] - PP population
number of patients/number of patients with data: 23/22

Statistical analyses

Statistical analysis title	Percent change from Baseline to V3 pre-dose; TLC

Statistical analysis description:

Overall, distal region value for primary endpoints was log-transformed and analysed using a Mixed

Model for Repeated Measures (MMRM). The adjusted % change from baseline to pre-dose at V3 was back transformed and presented with its 95% confidence interval (CI) and related p-value.

The value N=44, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study.
The correct value for subjects in the analysis is N=22.

Comparison groups	V3 pre-dose, TLC v Baseline / V2 pre-dose, TLC
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.4871
Method	Mixed models analysis
Parameter estimate	Adjusted Mean Change
Point estimate	11.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.67
upper limit	56.02

Notes:

[4] - The model included the logarithm of baseline (V2 pre-dose, but not for trimmed parameters) at TLC and visit (V2 post-dose, V3 pre-dose, V3 post-dose) as covariates, and the interaction between visit and logarithm of baseline (for untrimmed parameters).
The model parameters were estimated using the restricted maximum likelihood method with unstructured variance-covariance matrix and Kenward-Roger approximation to estimate denominator degrees of freedom.

Secondary: Untrimmed siVaw for distal region at TLC and FRC – actual value for V2 pre-dose, V2 post-dose, V3 pre-dose and V3 post-dose

End point title	Untrimmed siVaw for distal region at TLC and FRC – actual value for V2 pre-dose, V2 post-dose, V3 pre-dose and V3 post-dose

End point description:

siVaw is Specific Image-Based Airway Volume (at Total Lung Capacity, TLC and Functional Residual Capacity, FRC).
Secondary efficacy endpoints were presented as the arithmetic mean and the standard deviation (SD).
The data were summarized by the descriptive statistics for actual values at each timepoint.

End point type	Secondary

End point timeframe:

Multi-slice with multidetector computed tomography (MDCT) (inspiratory at TLC and expiratory at FRC) was to be performed pre-dose and within 60-120 min post-dose at V2 and V3. At V2, the upper airway (UA) was also to be be scanned at TLC, pre-dose.

End point values	Baseline / V2 pre-dose, TLC	V2 post-dose, TLC	V3 pre-dose, TLC	V3 post-dose, TLC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	23	23	23
Units: percentage				
arithmetic mean (standard deviation)	1.4088 (± 0.6647)	1.8706 (± 0.4954)	1.3550 (± 0.6014)	1.9805 (± 0.6390)

End point values	Baseline / V2 pre-dose, FRC	V2 post-dose, FRC	V3 pre-dose, FRC	V3 post-dose, FRC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23	23	23	23
Units: percentage				
arithmetic mean (standard deviation)	0.6321 (± 0.3164)	1.0204 (± 0.3404)	0.6982 (± 0.3198)	1.0442 (± 0.3825)

Statistical analyses

Statistical analysis title	Percent change from Baseline to V2 post-dose; TLC

Statistical analysis description:

Overall, distal region value for secondary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from baseline to post-dose at V2 was back transformed and presented with its 95% confidence interval (CI) and related p-value.
The value N=46, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study.
The correct value for subjects in the analysis is N=23.

Comparison groups	V2 post-dose, TLC v Baseline / V2 pre-dose, TLC
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted Mean Change
Point estimate	39.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.9
upper limit	51.53

Statistical analysis title	Percent change from V3 post to V3 pre-dose; TLC

Statistical analysis description:

Overall, distal region value for secondary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from V3 post-dose to V3 pre-dose was back transformed and presented with its 95% confidence interval (CI) and related p-value.
The value N=46, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study.
The correct value for subjects in the analysis is N=23.

Comparison groups	V3 post-dose, TLC v V3 pre-dose, TLC
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted Mean Change
Point estimate	62.63

Confidence interval	
level	95 %
sides	2-sided
lower limit	41.78
upper limit	86.56

Statistical analysis title	Percent change from Baseline to V3 pre-dose; FRC

Statistical analysis description:

Overall, distal region value for secondary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from baseline to pre-dose at V3 was back transformed and presented with its 95% confidence interval (CI) and related p-value.

The value N=46, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study.
The correct value for subjects in the analysis is N=23.

Comparison groups	V3 pre-dose, FRC v Baseline / V2 pre-dose, FRC
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0636
Method	Mixed models analysis
Parameter estimate	Adjusted Mean Change
Point estimate	16.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.93
upper limit	36.44

Statistical analysis title	Percent change from Baseline to V2 post-dose; FRC

Statistical analysis description:

Overall, distal region value for secondary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from baseline to post-dose at V2 was back transformed and presented with its 95% confidence interval (CI) and related p-value.
The value N=46, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study.
The correct value for subjects in the analysis is N=23.

Comparison groups	V2 post-dose, FRC v Baseline / V2 pre-dose, FRC
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted Mean Change
Point estimate	77.87

Confidence interval	
level	95 %
sides	2-sided
lower limit	60.28
upper limit	97.39

Statistical analysis title	Percent change from V3 post to V3 pre-dose; FRC

Statistical analysis description:

Overall, distal region value for secondary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from V3 post-dose to V3 pre-dose was back transformed and presented with its 95% confidence interval (CI) and related p-value.
The value N=46, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study.
The correct value for subjects in the analysis is N=23.

Comparison groups	V3 post-dose, FRC v V3 pre-dose, FRC
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0011
Method	Mixed models analysis
Parameter estimate	Adjusted Mean Change
Point estimate	39.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.21
upper limit	67.43

Secondary: Trimmed siRaw for distal region at TLC and FRC – actual value for V2 pre-dose, V2 post-dose, V3 pre-dose and V3 post-dose

End point title	Trimmed siRaw for distal region at TLC and FRC – actual value for V2 pre-dose, V2 post-dose, V3 pre-dose and V3 post-dose

End point description:

siRaw is the Specific Image-Based Airway Resistance (at Total Lung Capacity, TLC and Functional Residual Capacity, FRC).
Secondary efficacy endpoints were presented as the arithmetic mean and the standard deviation (SD). The data were summarized by the descriptive statistics for actual values at each timepoint.

End point type	Secondary

End point timeframe:

Multi-slice with multidetector computed tomography (MDCT) (inspiratory at TLC and expiratory at FRC) was to be performed pre-dose and within 60-120 min post-dose at V2 and V3. At V2, the upper airway (UA) was also to be be scanned at TLC, pre-dose.

End point values	Baseline / V2 pre-dose, TLC	V2 post-dose, TLC	V3 pre-dose, TLC	V3 post-dose, TLC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	22[5]	23	22[6]	23
Units: percentage				
arithmetic mean (standard deviation)	0.7160 (± 0.4034)	0.3685 (± 0.1594)	0.8492 (± 0.5947)	0.3121 (± 0.1416)

Notes:

[5] - PP population
number of patients/number of patients with data: 23/22.
[6] - PP population
number of patients/number of patients with data: 23/22.

End point values	Baseline / V2 pre-dose, FRC	V2 post-dose, FRC	V3 pre-dose, FRC	V3 post-dose, FRC
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	22[7]	22[8]	22[9]	22[10]
Units: percentage				
arithmetic mean (standard deviation)	0.4981 (± 0.3383)	0.2200 (± 0.1664)	0.3625 (± 0.4733)	0.1889 (± 0.1453)

Notes:

[7] - PP population
number of patients/number of patients with data: 23/22.
[8] - PP population
number of patients/number of patients with data: 23/22.
[9] - PP population
number of patients/number of patients with data: 23/22.
[10] - PP population
number of patients/number of patients with data: 23/22.

Statistical analyses

Statistical analysis title	Percent change from Baseline to V2 post-dose; TLC

Statistical analysis description:

Overall, distal region value for secondary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from baseline to post-dose at V2 was back transformed and presented with its 95% confidence interval (CI) and related p-value.
The value N=45, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study.
The correct value for subjects in the analysis is N=22.

Comparison groups	V2 post-dose, TLC v Baseline / V2 pre-dose, TLC
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0002
Method	Mixed models analysis
Parameter estimate	Adjusted Mean Change
Point estimate	-51.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-64.56
upper limit	-32.44

Statistical analysis title	Percent change from V3 post to V3 pre-dose; TLC

Statistical analysis description:

Overall, distal region value for secondary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from V3 post-dose to V3 pre-dose was back transformed and presented with its 95% confidence interval (CI) and related p-value.
The value N=45, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study.
The correct value for subjects in the analysis is N=22.

Comparison groups	V3 post-dose, TLC v V3 pre-dose, TLC
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0009
Method	Mixed models analysis
Parameter estimate	Adjusted Mean Change
Point estimate	-57.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-72.88
upper limit	-32.52

Statistical analysis title	Percent change from Baseline to V3 pre-dose; FRC

Statistical analysis description:

Overall, distal region value for secondary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from baseline to pre-dose at V3 was back transformed and presented with its 95% confidence interval (CI) and related p-value.

The value N=44, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study.
The correct value for subjects in the analysis is N=22.

Comparison groups	Baseline / V2 pre-dose, FRC v V3 pre-dose, FRC
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0261
Method	Mixed models analysis
Parameter estimate	Adjusted Mean Change
Point estimate	-63.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-84.85
upper limit	-12.42

Statistical analysis title	Percent change from Baseline to V2 post-dose; FRC

Statistical analysis description:

Overall, distal region value for secondary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from baseline to post-dose at V2 was back transformed and presented with its 95% confidence interval (CI) and related p-value.
The value N=44, shown below, is generated automatically and is due to innate error of the EudraCT

database system and to the cross-over nature of the study.
The correct value for subjects in the analysis is N=22.

Comparison groups	V2 post-dose, FRC v Baseline / V2 pre-dose, FRC
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0006
Method	Mixed models analysis
Parameter estimate	Adjusted Mean Change
Point estimate	-66.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-81.4
upper limit	-41.27

Statistical analysis title	Percent change from V3 post to V3 pre-dose; FRC

Statistical analysis description:

Overall, distal region value for secondary endpoints was log-transformed and analysed using a Mixed Model for Repeated Measures (MMRM). The adjusted % change from V3 post-dose to V3 pre-dose was back transformed and presented with its 95% confidence interval (CI) and related p-value.
The value N=45, shown below, is generated automatically and is due to innate error of the EudraCT database system and to the cross-over nature of the study.
The correct value for subjects in the analysis is N=22.

Comparison groups	V3 pre-dose, FRC v V3 post-dose, FRC
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3855
Method	Mixed models analysis
Parameter estimate	Adjusted Mean Change
Point estimate	-29.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-68.62
upper limit	59.42

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs starting on or after first administration of study drug (CHF5993 DPI) were classified as Treatment-Emergent AEs (TEAEs).

Adverse event reporting additional description:

The safety data were summarised in 3 phases: 1)Screening: starting from date signing the ICF until first FP/SLM DPI administration date-1 min/day, 2)Run-in: starting from first FP/SLM DPI administration date until first CHF5993 DPI administration date–1 min/day, 3)Treatment: from first CHF5993 DPI administration date until date of last contact.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	CHF5993 DPI 100/6/12.5 µg - Safety set

Reporting group description:

The safety set, defined as all patients who received at least one dose of study drug (CHF5993 DPI), included 25 patients.

Serious adverse events	CHF5993 DPI 100/6/12.5 µg - Safety set		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	CHF5993 DPI 100/6/12.5 µg - Safety set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 25 (44.00%)		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Sciatica			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		

Gastrointestinal disorders Hiatus hernia subjects affected / exposed occurrences (all)	 1 / 25 (4.00%) 1		
Respiratory, thoracic and mediastinal disorders Pleural calcification subjects affected / exposed occurrences (all) Bronchiectasis subjects affected / exposed occurrences (all) Pulmonary fibrosis subjects affected / exposed occurrences (all)	 2 / 25 (8.00%) 2 1 / 25 (4.00%) 1 1 / 25 (4.00%) 1		
Hepatobiliary disorders Hepatic steatosis subjects affected / exposed occurrences (all)	 1 / 25 (4.00%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	 1 / 25 (4.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2021	The following changes have been implemented: -IMP storage conditions updated accordingly to EMA requirements; -Typo corrections.
09 August 2021	The following substantial changes have been implemented: -Blood chemistry updated considering the creatinine test replacing BUN analysis; -RSI is now referred to Summary of; -Product Characteristics instead of IB; -Sponsor medical expert contacts updated; -Typo corrections.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported