Clinical trial results:
A Double Blind, Multicentre, Randomised, Placebo-Controlled, 3-Way Cross-Over Study To Evaluate The Effect Of A Triple Combination Of Beclometasone Dipropionate And Formoterol Fumarate Plus Glycopyrronium (CHF5993) And A Dual Combination Of Beclometasone Dipropionate Plus Formoterol Fumarate (CHF1535) Both Administered Via pMDI On Lung Hyperinflation And Exercise Endurance Time In Subjects With Chronic Obstructive Pulmonary Disease (COPD).

Summary

EudraCT number	2020-004718-36
Trial protocol	DE HU PL
Global end of trial date	24 February 2023

Results information

Result version number	v1 (current)
This version publication date	10 March 2024
First version publication date	10 March 2024

Trial information

Trial identification

Sponsor protocol code	CLI-05993AA1-17

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	03 November 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of triple (CHF5993 100/6/10 µg) and dual (CHF1535 100/6 µg) ICS-containing combinations, both administered via pMDI, on exercise tolerance, lung hyperinflation and physical activity. A placebo-controlled design was selected to evaluate the effect of CHF5993 and CHF1535 on clinical parameters associated with cardiopulmonary exercise testing and to allow quantification of the response to study treatments.

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 Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) notes for guidance on Good Clinical Practice (GCP) (ICH E6 Version 2).
The samples were collected by qualified and well-trained healthcare professionals, investigators insured a close follow-up of safety signals, and that everything has been done to reduce the burden of study procedures (e.g. low volume of blood collection, no painful procedures, etc.).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 October 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	Poland: 73
Country: Number of subjects enrolled	Germany: 105
Country: Number of subjects enrolled	Hungary: 3
Worldwide total number of subjects	181
EEA total number of subjects	181

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	77
From 65 to 84 years	104
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 181 subjects were enrolled, of whom 106 were randomised into one of the 6 treatment sequences. Of the 106 randomised subjects, all received at least 1 dose of study treatment.

Pre-assignment

Screening details:

The screening visit (V1, Week -1) was planned to assess the eligibility of subjects and obtain ICF signature if not done at the pre-screening visit.
All inclusion/exclusion criteria, presented in the CSR synopsis, were assessed.

Period 1

Period 1 title	Treatment Period 1, Period 2, Period 3 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject, Monitor, Data analyst

Blinding implementation details:

The double-blind randomisation ensured that no systematic bias affected the treatment sequence allocation and subject/Investigator perceptions of the study treatments. The IRT system was used to assign all kits in order to have an inventory control and subject dosing tracking. The randomisation list was not available to subjects, Investigators, monitors or employees of the centre involved in the management of the clinical study before unblinding of the data, except in case of emergency.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Sequence 1: BDP/FF/G // BDP/FF // Placebo

Arm description:

The treatment sequence 1 BDP/FF/G // BDP/FF // Placebo consists of:
- First treatment period with CHF5993 (BDP/FF/G pMDI 100/6/10 µg), 2 inhalations twice daily (BID);
- Second treatment period with CHF1535 (BDP/FF pMDI 100/6 µg), 2 inhalations twice daily (BID);
- Third treatment period with CHF5993 Placebo, 2 inhalations twice daily (BID).

17 subjects were randomized into this treatment sequence and completed the study.

Arm type	Experimental
Investigational medicinal product name	CHF5993 (BDP/FF/G pMDI 100/6/10 µg), CHF1535 (BDP/FF pMDI 100/6 µg)
Investigational medicinal product code	
Other name	TRIMBOW® - CHF5993, FOSTER® - CHF1535
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

CHF5993 [TRIMBOW®, fixed combination of beclometasone dipropionate (BDP) 100 µg, plus formoterol fumarate (FF) 6 µg, plus glycopyrronium (G) 10 µg] and CHF1535 [FOSTER®, fixed combination of BDP 100 µg, plus FF 6 µg] are drug pressurised inhaler. They were given twice daily (BID), 2 inhalations (in the morning and in the evening).
The total daily doses (TDD) administered are:
- BDP/FF/G 400/24/40 µg for CHF5993 [TRIMBOW®];
- BDP/FF 400/24 µg for CHF1535 [FOSTER®].

The reference product is CHF5993 placebo, a drug pressurised inhaler. It was given twice daily (BID), 2 inhalations.

Arm title	Treatment Sequence 2: BDP/FF/G // Placebo // BDP/FF

Arm description:

The treatment sequence 2 BDP/FF/G // Placebo // BDP/FF consists of:

- First treatment period with CHF5993 (BDP/FF/G pMDI 100/6/10 µg), 2 inhalations twice daily (BID);
- Second treatment period with CHF5993 Placebo, 2 inhalations twice daily (BID);
- Third treatment period with CHF1535 (BDP/FF pMDI 100/6 µg), 2 inhalations twice daily (BID).

17 subjects were randomized into this treatment sequence, of whom 14 completed the study.
3 subjects discontinued for recording adverse events.

Arm type	Experimental
Investigational medicinal product name	CHF5993 (BDP/FF/G pMDI 100/6/10 µg), CHF1535 (BDP/FF pMDI 100/6 µg)
Investigational medicinal product code	
Other name	TRIMBOW® - CHF5993, FOSTER® - CHF1535
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

CHF5993 [TRIMBOW®, fixed combination of beclometasone dipropionate (BDP) 100 µg, plus formoterol fumarate (FF) 6 µg, plus glycopyrronium (G) 10 µg] and CHF1535 [FOSTER®, fixed combination of BDP 100 µg, plus FF 6 µg] are drug pressurised inhaler. They were given twice daily (BID), 2 inhalations (in the morning and in the evening).
The total daily doses (TDD) administered are:
- BDP/FF/G 400/24/40 µg for CHF5993 [TRIMBOW®];
- BDP/FF 400/24 µg for CHF1535 [FOSTER®].

The reference product is CHF5993 placebo, a drug pressurised inhaler. It was given twice daily (BID), 2 inhalations.

Arm title	Treatment Sequence 3: BDP/FF // BDP/FF/G // Placebo

Arm description:

The treatment sequence 3 BDP/FF // BDP/FF/G // Placebo consists of:
- First treatment period with CHF1535 (BDP/FF pMDI 100/6 µg), 2 inhalations twice daily (BID);
- Second treatment period with CHF5993 (BDP/FF/G pMDI 100/6/10 µg), 2 inhalations twice daily (BID);
- Third treatment period with CHF5993 Placebo, 2 inhalations twice daily (BID).

18 subjects were randomized into this treatment sequence and completed the study.

Arm type	Experimental
Investigational medicinal product name	CHF5993 (BDP/FF/G pMDI 100/6/10 µg), CHF1535 (BDP/FF pMDI 100/6 µg)
Investigational medicinal product code	
Other name	TRIMBOW® - CHF5993, FOSTER® - CHF1535
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

CHF5993 [TRIMBOW®, fixed combination of beclometasone dipropionate (BDP) 100 µg, plus formoterol fumarate (FF) 6 µg, plus glycopyrronium (G) 10 µg] and CHF1535 (FOSTER®, fixed combination of BDP 100 µg, plus FF 6 µg) are drug pressurised inhaler. They were given twice daily (BID), 2 inhalations (in the morning and in the evening).
The total daily doses (TDD) administered are:
- BDP/FF/G 400/24/40 µg for CHF5993 [TRIMBOW®];
- BDP/FF 400/24 µg for CHF1535 [FOSTER®].

The reference product is CHF5993 placebo, a drug pressurised inhaler. It was given twice daily (BID), 2 inhalations.

Arm title	Treatment Sequence 4: BDP/FF // Placebo // BDP/FF/G

Arm description:

The treatment sequence 4 BDP/FF // Placebo // BDP/FF/G consists of:
- First treatment period with CHF1535 (BDP/FF pMDI 100/6 µg), 2 inhalations twice daily (BID);
- Second treatment period with CHF5993 Placebo, 2 inhalations twice daily (BID);
- Third treatment period with CHF5993 (BDP/FF/G pMDI 100/6/10 µg), 2 inhalations twice daily (BID).

17 subjects were randomized into this treatment sequence, of whom 15 completed the study.
2 subjects discontinued for recording adverse events and COPD exacerbation.

Arm type	Experimental

Investigational medicinal product name	CHF5993 (BDP/FF/G pMDI 100/6/10 µg), CHF1535 (BDP/FF pMDI 100/6 µg)
Investigational medicinal product code	
Other name	TRIMBOW® - CHF5993, FOSTER® - CHF1535
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

CHF5993 [TRIMBOW®, fixed combination of beclometasone dipropionate (BDP) 100 µg, plus formoterol fumarate (FF) 6 µg, plus glycopyrronium (G) 10 µg] and CHF1535 (FOSTER®, fixed combination of BDP 100 µg, plus FF 6 µg) are drug pressurised inhaler. They were given twice daily (BID), 2 inhalations (in the morning and in the evening).
The total daily doses (TDD) administered are:
- BDP/FF/G 400/24/40 µg for CHF5993 [TRIMBOW®];
- BDP/FF 400/24 µg for CHF1535 [FOSTER®].

The reference product is CHF5993 placebo, a drug pressurised inhaler. It was given twice daily (BID), 2 inhalations.

Arm title	Treatment Sequence 5: Placebo // BDP/FF/G // BDP/FF

Arm description:

The treatment sequence 5 Placebo // BDP/FF/G // BDP/FF consists of:
- First treatment period with CHF5993 Placebo, 2 inhalations twice daily (BID);
- Second treatment period with CHF5993 (BDP/FF/G pMDI 100/6/10 µg), 2 inhalations twice daily (BID);
- Third treatment period with CHF1535 (BDP/FF pMDI 100/6 µg), 2 inhalations twice daily (BID).

18 subjects were randomized into this treatment sequence, of whom 15 completed the study.
3 subjects discontinued for recording adverse events and for consent withdrawal.

Arm type	Experimental
Investigational medicinal product name	CHF5993 (BDP/FF/G pMDI 100/6/10 µg), CHF1535 (BDP/FF pMDI 100/6 µg)
Investigational medicinal product code	
Other name	TRIMBOW® - CHF5993, FOSTER® - CHF1535
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

CHF5993 [TRIMBOW®, fixed combination of beclometasone dipropionate (BDP) 100 µg, plus formoterol fumarate (FF) 6 µg, plus glycopyrronium (G) 10 µg] and CHF1535 (FOSTER®, fixed combination of BDP 100 µg, plus FF 6 µg) are drug pressurised inhaler. They were given twice daily (BID), 2 inhalations (in the morning and in the evening).
The total daily doses (TDD) administered are:
- BDP/FF/G 400/24/40 µg for CHF5993 [TRIMBOW®];
- BDP/FF 400/24 µg for CHF1535 [FOSTER®].

The reference product is CHF5993 placebo, a drug pressurised inhaler. It was given twice daily (BID), 2 inhalations.

Arm title	Treatment Sequence 6: Placebo // BDP/FF // BDP/FF/G

Arm description:

The treatment sequence 6 Placebo // BDP/FF // BDP/FF/G consists of:
- First treatment period with CHF5993 Placebo, 2 inhalations twice daily (BID);
- Second treatment period with CHF1535 (BDP/FF pMDI 100/6 µg), 2 inhalations twice daily (BID);
- Third treatment period with CHF5993 (BDP/FF/G pMDI 100/6/10 µg), 2 inhalations twice daily (BID).

19 subjects were randomized into this treatment sequence, of whom 16 completed the study.
3 subjects discontinued for recording adverse events and COPD exacerbation.

Arm type	Experimental
Investigational medicinal product name	CHF5993 (BDP/FF/G pMDI 100/6/10 µg), CHF1535 (BDP/FF pMDI 100/6 µg)
Investigational medicinal product code	
Other name	TRIMBOW® - CHF5993, FOSTER® - CHF1535
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

CHF5993 [TRIMBOW®, fixed combination of beclometasone dipropionate (BDP) 100 µg, plus formoterol fumarate (FF) 6 µg, plus glycopyrronium (G) 10 µg] and CHF1535 (FOSTER®, fixed combination of BDP 100 µg, plus FF 6 µg) are drug pressurised inhaler. They were given twice daily (BID), 2 inhalations (in the morning and in the evening).
The total daily doses (TDD) administered are:
- BDP/FF/G 400/24/40 µg for CHF5993 [TRIMBOW®];
- BDP/FF 400/24 µg for CHF1535 [FOSTER®].

The reference product is CHF5993 placebo, a drug pressurised inhaler. It was given twice daily (BID), 2 inhalations.

Number of subjects in period 1[1]	Treatment Sequence 1: BDP/FF/G // BDP/FF // Placebo	Treatment Sequence 2: BDP/FF/G // Placebo // BDP/FF	Treatment Sequence 3: BDP/FF // BDP/FF/G // Placebo
Started	17	17	18
Completed	17	14	18
Not completed	0	3	0
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	3	-
COPD Exacerbation	-	-	-

Number of subjects in period 1[1]	Treatment Sequence 4: BDP/FF // Placebo // BDP/FF/G	Treatment Sequence 5: Placebo // BDP/FF/G // BDP/FF	Treatment Sequence 6: Placebo // BDP/FF // BDP/FF/G
Started	17	18	19
Completed	15	15	16
Not completed	2	3	3
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	1	2	2
COPD Exacerbation	1	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 181 subjects were enrolled, of whom 106 were randomised into one of the 6 treatment
sequences. Of the 106 randomised subjects, all received at least 1 dose of study treatment.

Baseline characteristics

Reporting groups

Reporting group title	Treatment Sequence 1: BDP/FF/G // BDP/FF // Placebo

Reporting group description:

The treatment sequence 1 BDP/FF/G // BDP/FF // Placebo consists of:
- First treatment period with CHF5993 (BDP/FF/G pMDI 100/6/10 µg), 2 inhalations twice daily (BID);
- Second treatment period with CHF1535 (BDP/FF pMDI 100/6 µg), 2 inhalations twice daily (BID);
- Third treatment period with CHF5993 Placebo, 2 inhalations twice daily (BID).

17 subjects were randomized into this treatment sequence and completed the study.

Reporting group title	Treatment Sequence 2: BDP/FF/G // Placebo // BDP/FF

Reporting group description:

The treatment sequence 2 BDP/FF/G // Placebo // BDP/FF consists of:
- First treatment period with CHF5993 (BDP/FF/G pMDI 100/6/10 µg), 2 inhalations twice daily (BID);
- Second treatment period with CHF5993 Placebo, 2 inhalations twice daily (BID);
- Third treatment period with CHF1535 (BDP/FF pMDI 100/6 µg), 2 inhalations twice daily (BID).

17 subjects were randomized into this treatment sequence, of whom 14 completed the study.
3 subjects discontinued for recording adverse events.

Reporting group title	Treatment Sequence 3: BDP/FF // BDP/FF/G // Placebo

Reporting group description:

The treatment sequence 3 BDP/FF // BDP/FF/G // Placebo consists of:
- First treatment period with CHF1535 (BDP/FF pMDI 100/6 µg), 2 inhalations twice daily (BID);
- Second treatment period with CHF5993 (BDP/FF/G pMDI 100/6/10 µg), 2 inhalations twice daily (BID);
- Third treatment period with CHF5993 Placebo, 2 inhalations twice daily (BID).

18 subjects were randomized into this treatment sequence and completed the study.

Reporting group title	Treatment Sequence 4: BDP/FF // Placebo // BDP/FF/G

Reporting group description:

The treatment sequence 4 BDP/FF // Placebo // BDP/FF/G consists of:
- First treatment period with CHF1535 (BDP/FF pMDI 100/6 µg), 2 inhalations twice daily (BID);
- Second treatment period with CHF5993 Placebo, 2 inhalations twice daily (BID);
- Third treatment period with CHF5993 (BDP/FF/G pMDI 100/6/10 µg), 2 inhalations twice daily (BID).

17 subjects were randomized into this treatment sequence, of whom 15 completed the study.
2 subjects discontinued for recording adverse events and COPD exacerbation.

Reporting group title	Treatment Sequence 5: Placebo // BDP/FF/G // BDP/FF

Reporting group description:

The treatment sequence 5 Placebo // BDP/FF/G // BDP/FF consists of:
- First treatment period with CHF5993 Placebo, 2 inhalations twice daily (BID);
- Second treatment period with CHF5993 (BDP/FF/G pMDI 100/6/10 µg), 2 inhalations twice daily (BID);
- Third treatment period with CHF1535 (BDP/FF pMDI 100/6 µg), 2 inhalations twice daily (BID).

18 subjects were randomized into this treatment sequence, of whom 15 completed the study.
3 subjects discontinued for recording adverse events and for consent withdrawal.

Reporting group title	Treatment Sequence 6: Placebo // BDP/FF // BDP/FF/G

Reporting group description:

The treatment sequence 6 Placebo // BDP/FF // BDP/FF/G consists of:
- First treatment period with CHF5993 Placebo, 2 inhalations twice daily (BID);
- Second treatment period with CHF1535 (BDP/FF pMDI 100/6 µg), 2 inhalations twice daily (BID);
- Third treatment period with CHF5993 (BDP/FF/G pMDI 100/6/10 µg), 2 inhalations twice daily (BID).

19 subjects were randomized into this treatment sequence, of whom 16 completed the study.
3 subjects discontinued for recording adverse events and COPD exacerbation.

Reporting group values	Treatment Sequence 1: BDP/FF/G // BDP/FF // Placebo	Treatment Sequence 2: BDP/FF/G // Placebo // BDP/FF	Treatment Sequence 3: BDP/FF // BDP/FF/G // Placebo
Number of subjects	17	17	18
Age categorical			
Units: Subjects			
Adults (18-64 years)	6	8	9
From 65-84 years	11	9	9
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	67.1	66.2	64.8
standard deviation	± 7.8	± 7.6	± 6.5
Gender categorical			
Units: Subjects			
Female	8	4	3
Male	9	13	15
Race			
Units: Subjects			
White	17	17	18
Asian	0	0	0
Black or African American	0	0	0
Other	0	0	0
Smoking Status			
Units: Subjects			
Ex-smoker	10	8	6
Current smoker	7	9	12
Weight			
Units: Kg			
arithmetic mean	74.06	76.02	87.23
standard deviation	± 18.97	± 11.19	± 15.44
BMI			
Units: kg/m2			
arithmetic mean	25.58	25.66	28.44
standard deviation	± 4.62	± 2.99	± 4.90

Reporting group values	Treatment Sequence 4: BDP/FF // Placebo // BDP/FF/G	Treatment Sequence 5: Placebo // BDP/FF/G // BDP/FF	Treatment Sequence 6: Placebo // BDP/FF // BDP/FF/G
Number of subjects	17	18	19
Age categorical			
Units: Subjects			
Adults (18-64 years)	9	8	11
From 65-84 years	8	10	8
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	65.6	65.1	63.6
standard deviation	± 7.0	± 9.5	± 4.9
Gender categorical			
Units: Subjects			
Female	7	10	8
Male	10	8	11

Race Units: Subjects			
White	17	18	19
Asian	0	0	0
Black or African American	0	0	0
Other	0	0	0
Smoking Status Units: Subjects			
Ex-smoker	6	7	10
Current smoker	11	11	9
Weight Units: Kg			
arithmetic mean	82.42	77.61	84.58
standard deviation	± 13.47	± 16.11	± 18.94
BMI Units: kg/m2			
arithmetic mean	27.78	26.75	28.36
standard deviation	± 3.42	± 4.21	± 5.09

Reporting group values	Total		
Number of subjects	106		
Age categorical Units: Subjects			
Adults (18-64 years)	51		
From 65-84 years	55		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	40		
Male	66		
Race Units: Subjects			
White	106		
Asian	0		
Black or African American	0		
Other	0		
Smoking Status Units: Subjects			
Ex-smoker	47		
Current smoker	59		
Weight Units: Kg			
arithmetic mean			
standard deviation	-		
BMI Units: kg/m2			
arithmetic mean			

standard deviation	-		

End points

End points reporting groups

Reporting group title	Treatment Sequence 1: BDP/FF/G // BDP/FF // Placebo

Reporting group description:

The treatment sequence 1 BDP/FF/G // BDP/FF // Placebo consists of:
- First treatment period with CHF5993 (BDP/FF/G pMDI 100/6/10 µg), 2 inhalations twice daily (BID);
- Second treatment period with CHF1535 (BDP/FF pMDI 100/6 µg), 2 inhalations twice daily (BID);
- Third treatment period with CHF5993 Placebo, 2 inhalations twice daily (BID).

17 subjects were randomized into this treatment sequence and completed the study.

Reporting group title	Treatment Sequence 2: BDP/FF/G // Placebo // BDP/FF

Reporting group description:

The treatment sequence 2 BDP/FF/G // Placebo // BDP/FF consists of:
- First treatment period with CHF5993 (BDP/FF/G pMDI 100/6/10 µg), 2 inhalations twice daily (BID);
- Second treatment period with CHF5993 Placebo, 2 inhalations twice daily (BID);
- Third treatment period with CHF1535 (BDP/FF pMDI 100/6 µg), 2 inhalations twice daily (BID).

17 subjects were randomized into this treatment sequence, of whom 14 completed the study.
3 subjects discontinued for recording adverse events.

Reporting group title	Treatment Sequence 3: BDP/FF // BDP/FF/G // Placebo

Reporting group description:

The treatment sequence 3 BDP/FF // BDP/FF/G // Placebo consists of:
- First treatment period with CHF1535 (BDP/FF pMDI 100/6 µg), 2 inhalations twice daily (BID);
- Second treatment period with CHF5993 (BDP/FF/G pMDI 100/6/10 µg), 2 inhalations twice daily (BID);
- Third treatment period with CHF5993 Placebo, 2 inhalations twice daily (BID).

18 subjects were randomized into this treatment sequence and completed the study.

Reporting group title	Treatment Sequence 4: BDP/FF // Placebo // BDP/FF/G

Reporting group description:

The treatment sequence 4 BDP/FF // Placebo // BDP/FF/G consists of:
- First treatment period with CHF1535 (BDP/FF pMDI 100/6 µg), 2 inhalations twice daily (BID);
- Second treatment period with CHF5993 Placebo, 2 inhalations twice daily (BID);
- Third treatment period with CHF5993 (BDP/FF/G pMDI 100/6/10 µg), 2 inhalations twice daily (BID).

17 subjects were randomized into this treatment sequence, of whom 15 completed the study.
2 subjects discontinued for recording adverse events and COPD exacerbation.

Reporting group title	Treatment Sequence 5: Placebo // BDP/FF/G // BDP/FF

Reporting group description:

The treatment sequence 5 Placebo // BDP/FF/G // BDP/FF consists of:
- First treatment period with CHF5993 Placebo, 2 inhalations twice daily (BID);
- Second treatment period with CHF5993 (BDP/FF/G pMDI 100/6/10 µg), 2 inhalations twice daily (BID);
- Third treatment period with CHF1535 (BDP/FF pMDI 100/6 µg), 2 inhalations twice daily (BID).

18 subjects were randomized into this treatment sequence, of whom 15 completed the study.
3 subjects discontinued for recording adverse events and for consent withdrawal.

Reporting group title	Treatment Sequence 6: Placebo // BDP/FF // BDP/FF/G

Reporting group description:

The treatment sequence 6 Placebo // BDP/FF // BDP/FF/G consists of:
- First treatment period with CHF5993 Placebo, 2 inhalations twice daily (BID);
- Second treatment period with CHF1535 (BDP/FF pMDI 100/6 µg), 2 inhalations twice daily (BID);
- Third treatment period with CHF5993 (BDP/FF/G pMDI 100/6/10 µg), 2 inhalations twice daily (BID).

19 subjects were randomized into this treatment sequence, of whom 16 completed the study.
3 subjects discontinued for recording adverse events and COPD exacerbation.

Subject analysis set title	BDP/FF/G
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects who took CHF5993 (BDP/FF/G pMDI 100/6/10 µg), 2 inhalations BID via pMDI (in the morning and in the evening).

Subject analysis set title	BDP/FF
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects who took CHF1535 (BDP/FF pMDI 100/6 µg) 2 inhalations BID via pMDI (in the morning and in the evening).

Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects who took CHF5993 Placebo, 2 inhalations BID via pMDI.

Primary: CHF5993 (BDP/FF/G) vs. Placebo - Change from baseline in 2h post-dose IC after 3 weeks of treatment

End point title	CHF5993 (BDP/FF/G) vs. Placebo - Change from baseline in 2h post-dose IC after 3 weeks of treatment

End point description:

This primary efficacy variable was analysed on the ITT population using a linear mixed model. The model included treatment and period as fixed effects, baseline value of the
current treatment period and baseline value averaged across all the treatment periods as covariates, and subject as a random effect.

End point type	Primary

End point timeframe:

Baseline value was defined as the pre-dose IC value collected at the beginning of each treatment period (i.e., V2, V4 and V6).

End point values	BDP/FF/G	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91[1]	89[2]		
Units: score				
arithmetic mean (standard deviation)	0.383 (± 0.323)	-0.024 (± 0.284)		

Notes:

[1] - Number of subjects with available data/Number of subjects in the ITT set: 91/99

[2] - Number of subjects with available data/Number of subjects in the ITT set: 89/105

Statistical analyses

Statistical analysis title	Change from baseline in 2h post-dose at week 3

Statistical analysis description:

An unstructured covariance matrix was assumed, and the Kenward-Roger adjustment was used for the degrees of freedom. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% CIs after 3 weeks of treatment were estimated by the model.
Data are presented as adjusted mean differences with their 95% two-sided Confidence Intervals, and p value.

Comparison groups	BDP/FF/G v Placebo

Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Adjusted Mean Difference
Point estimate	0.315
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	0.38

Primary: CHF1535 (BDP/FF) vs. Placebo - Change from baseline in 2h post-dose IC after 3 weeks of treatment

End point title	CHF1535 (BDP/FF) vs. Placebo - Change from baseline in 2h post-dose IC after 3 weeks of treatment

End point description:

This primary efficacy variable was analysed on the ITT population using a linear mixed model. The model included treatment and period as fixed effects, baseline value of the
current treatment period and baseline value averaged across all the treatment periods as covariates, and subject as a random effect.

End point type	Primary

End point timeframe:

Baseline value was defined as the pre-dose IC value collected at the beginning of each treatment period (i.e., V2, V4 and V6).

End point values	BDP/FF	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91[3]	89[4]		
Units: score				
arithmetic mean (standard deviation)	0.203 (± 0.275)	-0.024 (± 0.284)		

Notes:

[3] - Number of subjects with available data/Number of subjects in the ITT set: 91/99

[4] - Number of subjects with available data/Number of subjects in the ITT set: 89/105

Statistical analyses

Statistical analysis title	Change from baseline in 2h post-dose at week 3

Statistical analysis description:

An unstructured covariance matrix was assumed, and the Kenward-Roger adjustment was used for the degrees of freedom. The adjusted means in each treatment group, the adjusted mean difference between treatments and their 95% CIs after 3 weeks of treatment were estimated by the model.
Data are presented as adjusted mean differences with their 95% two-sided Confidence Intervals, and p value.

Comparison groups	BDP/FF v Placebo

Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Adjusted Mean Difference
Point estimate	0.223
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.285

Secondary: CHF5993 (BDP/FF/G) vs. Placebo - Change from baseline in IC at isotime after 3 weeks of treatment

End point title	CHF5993 (BDP/FF/G) vs. Placebo - Change from baseline in IC at isotime after 3 weeks of treatment

End point description:

Key-secondary variables were analysed using a linear model including treatment and period as fixed effects, baseline value of the current treatment period and baseline value averaged across all the treatment periods as covariates, and subject as a random effect.

End point type	Secondary

End point timeframe:

The baseline IC value was collected at isotime at the beginning of each treatment period [V2, V4 and V6].

End point values	BDP/FF/G	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92[5]	92[6]		
Units: score				
arithmetic mean (standard deviation)	0.266 (± 0.522)	-0.027 (± 0.435)		

Notes:

[5] - Number of subjects with available data/Number of subjects in the ITT set: 92/99

[6] - Number of subjects with available data/Number of subjects in the ITT set: 92/105

Statistical analyses

Statistical analysis title	Change from baseline in IC at isotime at week 3

Statistical analysis description:

An unstructured covariance matrix was assumed, and the Kenward-Roger adjustment was used for the degrees of freedom.
Data are presented as adjusted mean differences with their 95% two-sided Confidence Intervals, and p value.

Comparison groups	BDP/FF/G v Placebo

Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Linear Model
Parameter estimate	Adjusted Mean Difference
Point estimate	0.245
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.147
upper limit	0.342

Secondary: CHF1535 (BDP/FF) vs. Placebo - Change from baseline in IC at isotime after 3 weeks of treatment

End point title	CHF1535 (BDP/FF) vs. Placebo - Change from baseline in IC at isotime after 3 weeks of treatment

End point description:

Key-secondary variables were analysed using a linear model including treatment and period as fixed effects, baseline value of the current treatment period and baseline value averaged across all the treatment periods as covariates, and subject as a random effect.

End point type	Secondary

End point timeframe:

The baseline IC value was collected at isotime at the beginning of each treatment period [V2, V4 and V6].

End point values	BDP/FF	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	95[7]	92[8]		
Units: score				
arithmetic mean (standard deviation)	0.126 (± 0.560)	-0.027 (± 0.435)		

Notes:

[7] - Number of subjects with available data/Number of subjects in the ITT set: 95/99

[8] - Number of subjects with available data/Number of subjects in the ITT set: 92/105

Statistical analyses

Statistical analysis title	Change from baseline in IC at isotime at week 3

Statistical analysis description:

An unstructured covariance matrix was assumed, and the Kenward-Roger adjustment was used for the degrees of freedom.
Data are presented as adjusted mean differences with their 95% two-sided Confidence Intervals, and p value.

Comparison groups	BDP/FF v Placebo

Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.053
Method	Linear Model
Parameter estimate	Adjusted Mean Difference
Point estimate	0.096
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.001
upper limit	0.193

Secondary: CHF5993 (BDP/FF/G) vs. Placebo - Change from baseline in 2h post-dose EET after 3 weeks of treatment

End point title	CHF5993 (BDP/FF/G) vs. Placebo - Change from baseline in 2h post-dose EET after 3 weeks of treatment

End point description:

Key-secondary variables were analysed using a linear model including treatment and period as fixed effects, baseline value of the current treatment period and baseline value averaged across all the treatment periods as covariates, and subject as a random effect.

End point type	Secondary

End point timeframe:

The baseline EET value was collected at the beginning of each treatment period [V2, V4 and V6].

End point values	BDP/FF/G	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	95[9]	95[10]		
Units: seconds				
arithmetic mean (standard deviation)	67.0 (± 184.7)	0.3 (± 149.6)		

Notes:

[9] - Number of subjects with available data/Number of subjects in the ITT set: 95/99

[10] - Number of subjects with available data/Number of subjects in the ITT set: 95/105

Statistical analyses

Statistical analysis title	Change from baseline in 2h post-dose EET at week 3

Statistical analysis description:

An unstructured covariance matrix was assumed, and the Kenward-Roger adjustment was used for the degrees of freedom.
Data are presented as adjusted mean differences with their 95% two-sided Confidence Intervals, and p value.

Comparison groups	BDP/FF/G v Placebo

Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Linear Model
Parameter estimate	Adjusted Mean Difference
Point estimate	69.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	32.88
upper limit	105.51

Secondary: CHF1535 (BDP/FF) vs. Placebo - Change from baseline in 2h post-dose EET after 3 weeks of treatment

End point title	CHF1535 (BDP/FF) vs. Placebo - Change from baseline in 2h post-dose EET after 3 weeks of treatment

End point description:

Key-secondary variables were analysed using a linear model including treatment and period as fixed effects, baseline value of the current treatment period and baseline value averaged across all the treatment periods as covariates, and subject as a random effect.

End point type	Secondary

End point timeframe:

The baseline EET value was collected at the beginning of each treatment period [V2, V4 and V6].

End point values	BDP/FF	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	96[11]	95[12]		
Units: seconds				
arithmetic mean (standard deviation)	46.4 (± 149.5)	0.3 (± 149.6)		

Notes:

[11] - Number of subjects with available data/Number of subjects in the ITT set: 96/99

[12] - Number of subjects with available data/Number of subjects in the ITT set: 95/105

Statistical analyses

Statistical analysis title	Change from baseline in 2h post-dose EET at week 3

Statistical analysis description:

An unstructured covariance matrix was assumed, and the Kenward-Roger adjustment was used for the degrees of freedom.
Data are presented as adjusted mean differences with their 95% two-sided Confidence Intervals, and p value.

Comparison groups	BDP/FF v Placebo

Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Linear Model
Parameter estimate	Adjusted Mean Difference
Point estimate	70.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	33.57
upper limit	106.56

Other pre-specified: CHF5993 (BDP/FF/G) vs. Placebo - Change from baseline in pre-dose morning FEV1 after 3 weeks of treatment

End point title	CHF5993 (BDP/FF/G) vs. Placebo - Change from baseline in pre-dose morning FEV1 after 3 weeks of treatment

End point description:

The exploratory variable was analysed on the ITT population using a linear mixed model similar as the one used for the primary efficacy analysis, including the FEV1
baseline value of the current treatment period and baseline value averaged across all the treatment periods as covariates.

End point type	Other pre-specified

End point timeframe:

Baseline value was defined as the FEV1 value collected at the beginning of each treatment period.

End point values	BDP/FF/G	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98[13]	102[14]		
Units: L				
arithmetic mean (standard deviation)	0.178 (± 0.199)	-0.058 (± 0.206)		

Notes:

[13] - Number of subjects with available data/Number of subjects in the ITT set: 98/99

[14] - Number of subjects with available data/Number of subjects in the ITT set: 102/105

Statistical analyses

Statistical analysis title	Change from baseline in pre-dose FEV1 at week 3

Statistical analysis description:

Data are presented as adjusted mean differences with their 95% two-sided Confidence Intervals, and p value.

Comparison groups	BDP/FF/G v Placebo

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Adjusted Mean Difference
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.25

Other pre-specified: CHF1535 (BDP/FF) vs. Placebo - Change from baseline in pre-dose morning FEV1 after 3 weeks of treatment

End point title	CHF1535 (BDP/FF) vs. Placebo - Change from baseline in pre-dose morning FEV1 after 3 weeks of treatment

End point description:

The exploratory variable was analysed on the ITT population using a linear mixed model similar as the one used for the primary efficacy analysis, including the FEV1
baseline value of the current treatment period and baseline value averaged across all the treatment periods as covariates.

End point type	Other pre-specified

End point timeframe:

Baseline value was defined as the FEV1 value collected at the beginning of each treatment period.

End point values	BDP/FF	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98[15]	102[16]		
Units: L				
arithmetic mean (standard deviation)	0.047 (± 0.188)	-0.085 (± 0.206)		

Notes:

[15] - Number of subjects with available data/Number of subjects in the ITT set: 98/99

[16] - Number of subjects with available data/Number of subjects in the ITT set: 102/105

Statistical analyses

Statistical analysis title	Change from baseline in pre-dose FEV1 at week 3

Statistical analysis description:

Data are presented as adjusted mean differences with their 95% two-sided Confidence Intervals, and p value.

Comparison groups	Placebo v BDP/FF

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Adjusted Mean Difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.15

Other pre-specified: CHF5993 (BDP/FF/G) vs. CHF1535 (BDP/FF) - Change from baseline in pre-dose morning FEV1 after 3 weeks of treatment

End point title	CHF5993 (BDP/FF/G) vs. CHF1535 (BDP/FF) - Change from baseline in pre-dose morning FEV1 after 3 weeks of treatment

End point description:

The exploratory variable was analysed on the ITT population using a linear mixed model similar as the one used for the primary efficacy analysis, including the FEV1
baseline value of the current treatment period and baseline value averaged across all the treatment periods as covariates.

End point type	Other pre-specified

End point timeframe:

Baseline value was defined as the FEV1 value collected at the beginning of each treatment period.

End point values	BDP/FF/G	BDP/FF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98[17]	98[18]		
Units: L				
arithmetic mean (standard deviation)	0.178 (± 0.199)	0.047 (± 0.188)		

Notes:

[17] - Number of subjects with available data/Number of subjects in the ITT set: 98/99

[18] - Number of subjects with available data/Number of subjects in the ITT set: 98/99

Statistical analyses

Statistical analysis title	Change from baseline in pre-dose FEV1 at week 3

Statistical analysis description:

Data are presented as adjusted mean differences with their 95% two-sided Confidence Intervals, and p value.

Comparison groups	BDP/FF/G v BDP/FF

Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Adjusted Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.14

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety analyses were conducted in the Safety population that included 106 subjects overall. Treatment-emergent adverse events (TEAE), defined as AEs starting on or after time of first study drug intake, were displayed.

Adverse event reporting additional description:

All AEs are reported by System Organ Class and Preferred Term and are coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 24.0.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	BDP/FF/G

Reporting group description:

CHF5993 (BDP/FF/G pMDI 100/6/10 µg), 2 inhalations BID via pMDI (in the morning and in the evening).

Reporting group title	BDP/FF

Reporting group description:

CHF1535 (BDP/FF pMDI 100/6 µg) 2 inhalations BID via pMDI (in the morning and in the evening).

Reporting group title	Placebo

Reporting group description:

CHF5993 Placebo, 2 inhalations BID via pMDI.

Serious adverse events	BDP/FF/G	BDP/FF	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 99 (0.00%)	0 / 99 (0.00%)	0 / 105 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

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

Non-serious adverse events	BDP/FF/G	BDP/FF	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 99 (27.27%)	25 / 99 (25.25%)	20 / 105 (19.05%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Oral haemangioma			
subjects affected / exposed	1 / 99 (1.01%)	0 / 99 (0.00%)	0 / 105 (0.00%)
occurrences (all)	1	0	0

Vascular disorders			
Blood pressure fluctuation			
subjects affected / exposed	1 / 99 (1.01%)	0 / 99 (0.00%)	0 / 105 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	1 / 99 (1.01%)	1 / 99 (1.01%)	0 / 105 (0.00%)
occurrences (all)	1	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 99 (1.01%)	0 / 99 (0.00%)	0 / 105 (0.00%)
occurrences (all)	1	0	0
Sensation of foreign body			
subjects affected / exposed	0 / 99 (0.00%)	1 / 99 (1.01%)	0 / 105 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 99 (0.00%)	0 / 99 (0.00%)	4 / 105 (3.81%)
occurrences (all)	0	0	4
Cough			
subjects affected / exposed	1 / 99 (1.01%)	1 / 99 (1.01%)	0 / 105 (0.00%)
occurrences (all)	1	1	0
Dysphonia			
subjects affected / exposed	1 / 99 (1.01%)	3 / 99 (3.03%)	0 / 105 (0.00%)
occurrences (all)	1	3	0
Dyspnoea			
subjects affected / exposed	0 / 99 (0.00%)	0 / 99 (0.00%)	2 / 105 (1.90%)
occurrences (all)	0	0	2
Oropharyngeal pain			
subjects affected / exposed	1 / 99 (1.01%)	2 / 99 (2.02%)	0 / 105 (0.00%)
occurrences (all)	1	2	0
Productive cough			
subjects affected / exposed	0 / 99 (0.00%)	0 / 99 (0.00%)	1 / 105 (0.95%)
occurrences (all)	0	0	1
Rhinorrhoea			

subjects affected / exposed	1 / 99 (1.01%)	0 / 99 (0.00%)	0 / 105 (0.00%)
occurrences (all)	1	0	0
Sputum increased			
subjects affected / exposed	0 / 99 (0.00%)	1 / 99 (1.01%)	0 / 105 (0.00%)
occurrences (all)	0	1	0
Throat irritation			
subjects affected / exposed	1 / 99 (1.01%)	1 / 99 (1.01%)	0 / 105 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Middle insomnia			
subjects affected / exposed	0 / 99 (0.00%)	1 / 99 (1.01%)	0 / 105 (0.00%)
occurrences (all)	0	1	0
Investigations			
White blood cell count increased			
subjects affected / exposed	1 / 99 (1.01%)	0 / 99 (0.00%)	0 / 105 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 99 (1.01%)	0 / 99 (0.00%)	0 / 105 (0.00%)
occurrences (all)	1	0	0
Foot fracture			
subjects affected / exposed	0 / 99 (0.00%)	1 / 99 (1.01%)	0 / 105 (0.00%)
occurrences (all)	0	1	0
Sternal fracture			
subjects affected / exposed	0 / 99 (0.00%)	1 / 99 (1.01%)	0 / 105 (0.00%)
occurrences (all)	0	1	0
Vaccination complication			
subjects affected / exposed	0 / 99 (0.00%)	0 / 99 (0.00%)	1 / 105 (0.95%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 99 (2.02%)	0 / 99 (0.00%)	1 / 105 (0.95%)
occurrences (all)	2	0	1
Ear and labyrinth disorders			
Ear pain			

subjects affected / exposed	1 / 99 (1.01%)	0 / 99 (0.00%)	0 / 105 (0.00%)
occurrences (all)	1	0	0
Vertigo			
subjects affected / exposed	0 / 99 (0.00%)	0 / 99 (0.00%)	1 / 105 (0.95%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 99 (1.01%)	0 / 99 (0.00%)	0 / 105 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	0 / 99 (0.00%)	1 / 99 (1.01%)	0 / 105 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	1 / 99 (1.01%)	2 / 99 (2.02%)	2 / 105 (1.90%)
occurrences (all)	1	2	2
Dyspepsia			
subjects affected / exposed	1 / 99 (1.01%)	0 / 99 (0.00%)	0 / 105 (0.00%)
occurrences (all)	1	0	0
Food poisoning			
subjects affected / exposed	0 / 99 (0.00%)	1 / 99 (1.01%)	0 / 105 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 99 (0.00%)	2 / 99 (2.02%)	1 / 105 (0.95%)
occurrences (all)	0	2	1
Toothache			
subjects affected / exposed	0 / 99 (0.00%)	0 / 99 (0.00%)	1 / 105 (0.95%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	1 / 99 (1.01%)	0 / 99 (0.00%)	0 / 105 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 99 (1.01%)	0 / 99 (0.00%)	0 / 105 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			

Erythema			
subjects affected / exposed	1 / 99 (1.01%)	0 / 99 (0.00%)	0 / 105 (0.00%)
occurrences (all)	1	0	0
Hand dermatitis			
subjects affected / exposed	0 / 99 (0.00%)	1 / 99 (1.01%)	0 / 105 (0.00%)
occurrences (all)	0	1	0
Skin irritation			
subjects affected / exposed	1 / 99 (1.01%)	0 / 99 (0.00%)	0 / 105 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 99 (2.02%)	2 / 99 (2.02%)	2 / 105 (1.90%)
occurrences (all)	2	2	2
Back pain			
subjects affected / exposed	0 / 99 (0.00%)	1 / 99 (1.01%)	1 / 105 (0.95%)
occurrences (all)	0	1	1
Haemarthrosis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 99 (0.00%)	1 / 105 (0.95%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 99 (0.00%)	1 / 99 (1.01%)	0 / 105 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 99 (1.01%)	0 / 99 (0.00%)	0 / 105 (0.00%)
occurrences (all)	1	0	0
COVID-19			
subjects affected / exposed	0 / 99 (0.00%)	3 / 99 (3.03%)	4 / 105 (3.81%)
occurrences (all)	0	3	4
Conjunctivitis			
subjects affected / exposed	0 / 99 (0.00%)	1 / 99 (1.01%)	0 / 105 (0.00%)
occurrences (all)	0	1	0
Cystitis			
subjects affected / exposed	2 / 99 (2.02%)	0 / 99 (0.00%)	0 / 105 (0.00%)
occurrences (all)	2	0	0
Fungal skin infection			

subjects affected / exposed	0 / 99 (0.00%)	1 / 99 (1.01%)	1 / 105 (0.95%)
occurrences (all)	0	1	1
Furuncle			
subjects affected / exposed	0 / 99 (0.00%)	0 / 99 (0.00%)	1 / 105 (0.95%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	4 / 99 (4.04%)	3 / 99 (3.03%)	3 / 105 (2.86%)
occurrences (all)	4	3	3
Oral candidiasis			
subjects affected / exposed	0 / 99 (0.00%)	1 / 99 (1.01%)	0 / 105 (0.00%)
occurrences (all)	0	1	0
Paronychia			
subjects affected / exposed	0 / 99 (0.00%)	0 / 99 (0.00%)	1 / 105 (0.95%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	0 / 99 (0.00%)	1 / 99 (1.01%)	0 / 105 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 99 (1.01%)	0 / 99 (0.00%)	0 / 105 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 99 (1.01%)	0 / 99 (0.00%)	0 / 105 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported