Clinical trial results:
A Phase 3 Randomized, Double-Blind, Placebo- Controlled Study to Evaluate the Efficacy and Safety of Ensifentrine over 24 Weeks (With a 48-Week Safety Subset) in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease.

Summary

EudraCT number	2020-002086-34
Trial protocol	CZ DE SK HU BG GR RO
Global end of trial date	02 December 2022

Results information

Result version number	v1 (current)
This version publication date	15 September 2023
First version publication date	15 September 2023

Trial information

Trial identification

Sponsor protocol code	RPL554-CO-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04535986
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Verona Pharma plc
Sponsor organisation address	3 More London Riverside, London, United Kingdom, SE1 2RE
Public contact	Chief Medical Officer, Verona Pharma plc, info@veronapharma.com
Scientific contact	Chief Medical Officer, Verona Pharma plc, info@veronapharma.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	02 December 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of ensifentrine on lung function compared to placebo over a 12-hour dosing interval in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

Protection of trial subjects:

The study was conducted in accordance with the protocol, the ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonisation Good Clinical Practice and other Guidelines, and applicable laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 September 2020
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	Bulgaria: 45
Country: Number of subjects enrolled	Czechia: 106
Country: Number of subjects enrolled	Germany: 190
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Hungary: 39
Country: Number of subjects enrolled	Korea, Republic of: 23
Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Romania: 39
Country: Number of subjects enrolled	Russian Federation: 104
Country: Number of subjects enrolled	Slovakia: 41
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	United States: 145
Worldwide total number of subjects	763
EEA total number of subjects	479

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)	353
From 65 to 84 years	410
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This Phase 3, randomized, double-blind, placebo-controlled study was conducted in patients with moderate to severe COPD at 120 study centers. Patients were randomized in a 5:3 ratio overall (1:1 over 24 weeks and 3:1 over 48 weeks), stratified by duration, smoking status and background medication use, to receive either ensifentrine or placebo.

Pre-assignment

Screening details:

Patients were screened for eligibility before entering a 28-day run in period to ensure a stable COPD treatment regimen and to collect baseline information on symptoms and rescue medication use.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ensifentrine

Arm description:

3 milligram (mg) twice daily via standard jet nebulizer.

Arm type	Experimental
Investigational medicinal product name	Ensifentrine
Investigational medicinal product code	RPL554
Other name	
Pharmaceutical forms	Nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:

Ensifentrine 3 mg inhaled by jet nebulizer twice daily (morning and evening) for 24 weeks or 48 weeks.

Arm title	Placebo

Arm description:

Twice daily via standard jet nebulizer.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:

Ensifentrine placebo inhaled by jet nebulizer twice daily (morning and evening) for 24 weeks or 48 weeks.

Number of subjects in period 1	Ensifentrine	Placebo
Started	479	284
Received Treatment	477	283
Completed	400	245
Not completed	79	39
COPD exacerbation withdrawal criteria	7	5
Consent withdrawn by subject	32	14
Adverse event, non-fatal	10	1
Death	4	5
Unspecified	7	3
Investigator discretion	3	-
Lost to follow-up	5	3
Coronavirus disease 2019 (COVID-19)	8	6
Lack of efficacy	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Ensifentrine
Reporting group description: 3 milligram (mg) twice daily via standard jet nebulizer.	
Reporting group title	Placebo
Reporting group description: Twice daily via standard jet nebulizer.	

Reporting group values	Ensifentrine	Placebo	Total
Number of subjects	479	284	763
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	65.1	64.9	
standard deviation	± 7.12	± 7.73	-
Gender categorical Units: Subjects			
Female	204	117	321
Male	275	167	442
Race Units: Subjects			
Asian	13	11	24
Black or African American	16	9	25
White	437	251	688
Other	0	1	1
Not Reported	13	12	25
Ethnicity Units: Subjects			
Hispanic or Latino	15	6	21
Not Hispanic or Latino	464	278	742

End points

End points reporting groups

Reporting group title	Ensifentrine
Reporting group description:	
3 milligram (mg) twice daily via standard jet nebulizer.	
Reporting group title	Placebo
Reporting group description:	
Twice daily via standard jet nebulizer.	

Primary: Least Square (LS) Mean Change From Baseline in Average Forced Expiratory Volume in 1 Second (FEV1) Area Under the Curve Over 12 Hours (AUC0-12h) at Week 12

End point title	Least Square (LS) Mean Change From Baseline in Average Forced Expiratory Volume in 1 Second (FEV1) Area Under the Curve Over 12 Hours (AUC0-12h) at Week 12
End point description:	
Forced spirometry maneuvers including the FEV1 were used to assess pulmonary function. Average FEV1 AUC0-12h was defined as AUC over 12 hours of the FEV1, divided by 12 hours. Baseline FEV1 is the mean of the 2 measurements taken before study medication on the day of first dosing, that is, <=40 minutes pre-dose on Day 1. Spirometry assessments were performed in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines. The modified Intent-to-Treat (mITT) population set included all patients in the randomized set who received at least 1 dose (or partial dose) of study medication, and patients were classified according to randomized treatment. 1 patient was missing a baseline FEV1 assessment.	
End point type	Primary
End point timeframe:	
Baseline (pre-dose on Day 1) and Week 12	

End point values	Ensifentrine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	477	282		
Units: liters				
least squares mean (standard error)	0.0611 (± 0.01825)	-0.0256 (± 0.0195)		

Statistical analyses

Statistical analysis title	Treatment difference in average FEV1 AUC0-12h
Comparison groups	Ensifentrine v Placebo

Number of subjects included in analysis	759
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.0868
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0551
upper limit	0.1185
Variability estimate	Standard error of the mean
Dispersion value	0.0162

Notes:

[1] - The analysis of covariance (ANCOVA) model was used to model the change from baseline FEV1 to average FEV1 AUC0-12h with treatment, region, background medication strata and smoking strata as fixed effects and baseline FEV1 as covariate.

Secondary: LS Mean Change From Baseline FEV1 to Peak FEV1 at Day 1 and Weeks 6, 12 and 24

End point title	LS Mean Change From Baseline FEV1 to Peak FEV1 at Day 1 and Weeks 6, 12 and 24

End point description:

Forced spirometry maneuvers including the FEV1 were used to assess pulmonary function. Peak FEV1 is the maximum value in the 4 hours after dosing. Baseline FEV1 is the mean of the 2 measurements taken before study medication on the day of first dosing, that is, <=40 minutes pre-dose on Day 1. Spirometry assessments were performed in accordance with ATS/ERS guidelines. The mITT population set included all patients in the randomized set who received at least 1 dose (or partial dose) of study medication, and patients were classified according to randomized treatment.

End point type	Secondary

End point timeframe:

Baseline (pre-dose on Day 1), post-dose on Day 1, Weeks 6, 12, and 24

End point values	Ensifentrine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	477	282		
Units: liters				
least squares mean (standard error)				
Day 1 (Post-dose)	0.2274 (± 0.0130)	0.0755 (± 0.0138)		
Week 6	0.2038 (± 0.0193)	0.0677 (± 0.0207)		
Week 12	0.2042 (± 0.0201)	0.0570 (± 0.0217)		
Week 24	0.1623 (± 0.0217)	0.0462 (± 0.0234)		

Statistical analyses

No statistical analyses for this end point

Secondary: LS Mean Change From Baseline to the Mean Weekly Evaluating-Respiratory Symptoms (E-RS) Total Score at Weeks 6, 12 and 24

End point title	LS Mean Change From Baseline to the Mean Weekly Evaluating-Respiratory Symptoms (E-RS) Total Score at Weeks 6, 12 and 24

End point description:

The E-RS scale consists of 11 questions, with 3 sub-domains of: breathlessness, cough and sputum, and chest symptoms. The E-RS sub-domain score was calculated as the sum from the relevant questions. The E-RS total score was derived as the sum of the raw scores of the 11 items ranging from 0 to 40. Higher scores indicates severe respiratory symptoms. The E-RS was collected daily by electronic diary (e-diary). Baseline is the mean over the 7 days prior to the first intake of study medication, using only days where data was recorded. The mITT population set included all patients in the randomized set who received at least 1 dose (or partial dose) of study medication, and patients were classified according to randomized treatment.

End point type	Secondary

End point timeframe:

Baseline (pre-dose on Day 1) and Weeks 6, 12, and 24

End point values	Ensifentrine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	475	281		
Units: units on a scale				
least squares mean (standard error)				
Week 6	-1.944 (± 0.3581)	-1.157 (± 0.3831)		
Week 12	-2.498 (± 0.3897)	-1.127 (± 0.4176)		
Week 24	-2.249 (± 0.4247)	-1.298 (± 0.4573)		

Statistical analyses

No statistical analyses for this end point

Secondary: LS Mean Change From Baseline in the St. George's Respiratory Questionnaire (SGRQ) Total Score at Weeks 6, 12 and 24

End point title	LS Mean Change From Baseline in the St. George's Respiratory Questionnaire (SGRQ) Total Score at Weeks 6, 12 and 24

End point description:

The SGRQ questionnaire consists of 17 questions, split into 2 parts. Part 1 consisted of the first 8 questions and was related to the symptoms subdomain. The remaining 9 questions were in Part 2, which were related to the activity and impacts subdomains. The total score was calculated by dividing the summed weights by the maximum possible weight for all items in the questionnaire and expressing the result as a percentage. Score ranging from 0 to 100 and higher scores indicated a worse outcome. Baseline is the score calculated on Day 1 prior to 4 hour post-dose spirometry. The mITT population set included all patients in the randomized set who received at least 1 dose (or partial dose) of study medication, and patients were classified according to randomized treatment.

End point type	Secondary

End point timeframe:

Baseline (pre-dose on Day 1) and Weeks 6, 12, and 24

End point values	Ensifentrine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	474	281		
Units: units on a scale				
least squares mean (standard error)				
Week 6	-6.184 (± 0.9838)	-3.965 (± 1.0511)		
Week 12	-5.665 (± 1.0163)	-2.652 (± 1.0859)		
Week 24	-6.167 (± 1.1405)	-3.868 (± 1.2178)		

Statistical analyses

No statistical analyses for this end point

Secondary: LS Mean Change From Baseline FEV1 to Morning Trough FEV1 at Weeks 6, 12 and 24

End point title	LS Mean Change From Baseline FEV1 to Morning Trough FEV1 at Weeks 6, 12 and 24

End point description:

Forced spirometry maneuvers including the FEV1 were used to assess pulmonary function. Morning trough FEV1 was the last value collected prior to the morning dose. Baseline FEV1 is the mean of the two measurements taken before study medication on the day of first dosing, that is, <=40 minutes pre-dose on day 1. Spirometry assessments were performed in accordance with ATS/ERS guidelines. The mITT population set included all patients in the randomized set who received at least 1 dose (or partial dose) of study medication, and patients were classified according to randomized treatment.

End point type	Secondary

End point timeframe:

Baseline (pre-dose on Day 1) and Weeks 6, 12, and 24

End point values	Ensifentrine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	477	282		
Units: liters				
least squares mean (standard error)				
Week 6	0.0112 (± 0.0181)	-0.0259 (± 0.0193)		
Week 12	0.0076 (± 0.0190)	-0.0272 (± 0.0204)		
Week 24	-0.0236 (± 0.0205)	-0.0369 (± 0.0219)		

Statistical analyses

No statistical analyses for this end point

Secondary: LS Mean Change From Baseline in Average FEV1 Area Under the Curve Over 4 Hours (AUC0-4h) at Day 1 and Weeks 6, 12 and 24

End point title	LS Mean Change From Baseline in Average FEV1 Area Under the Curve Over 4 Hours (AUC0-4h) at Day 1 and Weeks 6, 12 and 24

End point description:

Forced spirometry maneuvers including the FEV1 were used to assess pulmonary function. Average FEV1 AUC0-4h was defined as area under the curve over 4 hours of the FEV1, divided by 4 hours. Baseline FEV1 is the mean of the 2 measurements taken before study medication on the day of first dosing, that is, <=40 minutes pre-dose on Day 1. Spirometry assessments were performed in accordance with ATS/ERS guidelines. The mITT population set included all patients in the randomized set who received at least 1 dose (or partial dose) of study medication, and patients were classified according to randomized treatment.

End point type	Secondary

End point timeframe:

Baseline (pre-dose on Day 1), post-dose on Day 1, Weeks 6, 12, and 24

End point values	Ensifentrine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	477	282		
Units: liters				
least squares mean (standard error)				
Day 1 (Post-dose)	0.1495 (± 0.0108)	0.0099 (± 0.0115)		
Week 6	0.1259 (± 0.0184)	-0.0044 (± 0.0196)		
Week 12	0.1243 (± 0.0191)	-0.0149 (± 0.0203)		
Week 24	0.0875 (± 0.0206)	-0.0139 (± 0.0220)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of SGRQ Responders at Weeks 6, 12 and 24

End point title	Percentage of SGRQ Responders at Weeks 6, 12 and 24

End point description:

The SGRQ questionnaire consists of 17 questions, split into 2 parts. Part 1 consisted of the first 8 questions and was related to the symptoms subdomain. The remaining 9 questions were in Part 2, which were related to the activity and impacts subdomains. The total score was calculated by dividing the summed weights by the maximum possible weight for all items in the questionnaire and expressing the result as a percentage. Responder was a patient with an improvement from baseline in SGRQ total score of 4 or more. Percentage of SGRQ responders are reported. The mITT population set included all patients in the randomized set who received at least 1 dose (or partial dose) of study medication, and patients were classified according to randomized treatment.

End point type	Secondary

End point timeframe:

Weeks 6, 12 and 24

End point values	Ensifentrine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	474	281		
Units: percentage of patients				
number (not applicable)				
Week 6	50.8	40.6		
Week 12	52.5	37.0		
Week 24	58.2	45.9		

Statistical analyses

No statistical analyses for this end point

Secondary: LS Mean Change From Baseline to the Mean Weekly Rescue Medication Use at Weeks 6, 12 and 24

End point title	LS Mean Change From Baseline to the Mean Weekly Rescue Medication Use at Weeks 6, 12 and 24

End point description:

Use of rescue medication (albuterol/salbutamol) per week was calculated as the LS mean use daily over 7 days. Daily rescue medication use was collected in an e-diary throughout the study. Baseline is the mean over the 7 days prior to the first intake of study medication, calculated as the sum of puffs taken, divided by number of days data has been recorded. The mITT population set included all patients in the randomized set who received at least 1 dose (or partial dose) of study medication, and patients were classified according to randomized treatment.

End point type	Secondary

End point timeframe:

Baseline (pre-dose on Day 1) and Weeks 6, 12, and 24

End point values	Ensifentrine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	475	281		
Units: rescue medication puffs per week				
least squares mean (standard error)				
Week 6	-0.442 (± 0.1065)	-0.306 (± 0.1139)		
Week 12	-0.469 (± 0.1155)	-0.182 (± 0.1234)		
Week 24	-0.506 (± 0.1448)	-0.052 (± 0.1554)		

Statistical analyses

No statistical analyses for this end point

Secondary: LS Mean Transition Dyspnea Index (TDI) Questionnaire Total Score at Weeks 6, 12 and 24

End point title	LS Mean Transition Dyspnea Index (TDI) Questionnaire Total Score at Weeks 6, 12 and 24

End point description:

The TDI is a questionnaire that focused on 3 sub-domains: functional impairment, magnitude of task and magnitude of effort. Sub-domain score was calculated as the sum from the related questions. Total score was calculated as the sum of the sub-domain scores. The TDI measures the change in dyspnea severity from the baseline as measured by the baseline dyspnea index. It was rated by 7 grades ranging from -3 (major deterioration) to +3 (major improvement). Higher scores indicate better outcome. Change from baseline was assessed with the Baseline Dyspnea Index. The mITT population set included all patients in the randomized set who received at least 1 dose (or partial dose) of study medication, and patients were classified according to randomized treatment.

End point type	Secondary

End point timeframe:

Weeks 6, 12 and 24

End point values	Ensifentrine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	471	277		
Units: units on a scale				
least squares mean (standard error)				
Week 6	1.3 (± 0.19)	0.6 (± 0.21)		
Week 12	1.6 (± 0.21)	0.4 (± 0.23)		
Week 24	1.9 (± 0.24)	0.8 (± 0.27)		

Statistical analyses

No statistical analyses for this end point

Secondary: LS Mean Change From Baseline FEV1 to Evening Trough FEV1 at Week 12

End point title	LS Mean Change From Baseline FEV1 to Evening Trough FEV1 at Week 12

End point description:

Forced spirometry maneuvers including the FEV1 were used to assess pulmonary function. Evening trough FEV1 was the value collected at 12 hours post-morning dose and prior to the evening dose. Baseline FEV1 is the mean of the 2 measurements taken before study medication on the day of first dosing, that is, <=40 minutes pre-dose on day 1. Spirometry assessments were performed in accordance with ATS/ERS guidelines. The mITT population set included all patients in the randomized set who received at least 1 dose (or partial dose) of study medication, and patients were classified according to randomized treatment.

End point type	Secondary

End point timeframe:

Baseline (pre-dose on Day 1) and Week 12

End point values	Ensifentrine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	477	282		
Units: liters				
least squares mean (standard error)	-0.0117 (± 0.0203)	-0.0697 (± 0.0214)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events were collected from first dose of study treatment up to 10 days after final study visit at Week 24, approximately 25 weeks, and for 48-week subset, up to 10 days after final study visit at Week 48, approximately 49 weeks.

Adverse event reporting additional description:

The safety analysis set included all patients in the randomized set who received at least 1 dose (or partial dose) of study medication, and patients were classified according to treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Up to Week 24: Ensifentrine

Reporting group description:

3 mg twice daily via standard jet nebulizer.

Reporting group title	Up to Week 24: Placebo

Reporting group description:

Twice daily via standard jet nebulizer.

Reporting group title	From Week 24 to Week 48: Ensifentrine

Reporting group description:

3 mg twice daily via standard jet nebulizer (patients that had at least 1 dose after Week 24 visit).

Reporting group title	From Week 24 to Week 48: Placebo

Reporting group description:

Twice daily via standard jet nebulizer (patients that had at least 1 dose after Week 24 visit).

Serious adverse events	Up to Week 24: Ensifentrine	Up to Week 24: Placebo	From Week 24 to Week 48: Ensifentrine
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 477 (6.71%)	19 / 283 (6.71%)	11 / 228 (4.82%)
number of deaths (all causes)	2	4	2
number of deaths resulting from adverse events	2	4	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma metastatic			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cholangiocarcinoma			

subjects affected / exposed	0 / 477 (0.00%)	1 / 283 (0.35%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Laryngeal cancer			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 477 (0.00%)	1 / 283 (0.35%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer stage I			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell lung cancer metastatic			

subjects affected / exposed	0 / 477 (0.00%)	1 / 283 (0.35%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 477 (0.00%)	1 / 283 (0.35%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	1 / 477 (0.21%)	1 / 283 (0.35%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Uterine prolapse			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	7 / 477 (1.47%)	6 / 283 (2.12%)	2 / 228 (0.88%)
occurrences causally related to treatment / all	0 / 7	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	0 / 477 (0.00%)	1 / 283 (0.35%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal injury			
subjects affected / exposed	0 / 477 (0.00%)	1 / 283 (0.35%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular pseudoaneurysm			

subjects affected / exposed	0 / 477 (0.00%)	1 / 283 (0.35%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 477 (0.00%)	1 / 283 (0.35%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress cardiomyopathy			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral microangiopathy			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 477 (0.00%)	1 / 283 (0.35%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 477 (0.00%)	1 / 283 (0.35%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 477 (0.00%)	1 / 283 (0.35%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular disorder			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary dyskinesia			

subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy toxic			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 477 (0.42%)	2 / 283 (0.71%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
COVID-19 pneumonia			
subjects affected / exposed	3 / 477 (0.63%)	1 / 283 (0.35%)	1 / 228 (0.44%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lung abscess			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Myocarditis bacterial			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 477 (0.63%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 477 (0.00%)	1 / 283 (0.35%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia chlamydial			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 477 (0.21%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 477 (0.00%)	1 / 283 (0.35%)	0 / 228 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	From Week 24 to Week 48: Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 70 (7.14%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma metastatic			

subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholangiocarcinoma				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laryngeal cancer				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung adenocarcinoma				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung neoplasm malignant				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malignant melanoma				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-small cell lung cancer stage I				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma				
subjects affected / exposed	1 / 70 (1.43%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma metastatic				

subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small cell lung cancer metastatic			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transitional cell carcinoma			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Shock haemorrhagic			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			

Benign prostatic hyperplasia				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Uterine prolapse				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Chronic obstructive pulmonary disease				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Femur fracture				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ligament sprain				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pharyngeal injury				

subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular pseudoaneurysm				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stress cardiomyopathy				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebral microangiopathy				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				

subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vestibular disorder			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stone			

subjects affected / exposed	1 / 70 (1.43%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Biliary dyskinesia				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nephropathy toxic				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Lumbar spinal stenosis				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
COVID-19				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COVID-19 pneumonia				
subjects affected / exposed	0 / 70 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Lung abscess			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocarditis bacterial			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia chlamydial			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Urosepsis			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Up to Week 24: Ensifentrine	Up to Week 24: Placebo	From Week 24 to Week 48: Ensifentrine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	90 / 477 (18.87%)	58 / 283 (20.49%)	16 / 228 (7.02%)
Investigations			
Prostatic specific antigen increased			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Essential hypertension			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	11 / 477 (2.31%)	4 / 283 (1.41%)	0 / 228 (0.00%)
occurrences (all)	12	4	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	5 / 477 (1.05%)	1 / 283 (0.35%)	0 / 228 (0.00%)
occurrences (all)	5	3	0
Supraventricular extrasystoles			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	3 / 477 (0.63%)	4 / 283 (1.41%)	0 / 228 (0.00%)
occurrences (all)	3	4	0
Headache			
subjects affected / exposed	16 / 477 (3.35%)	12 / 283 (4.24%)	4 / 228 (1.75%)
occurrences (all)	16	13	4
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	1 / 228 (0.44%)
occurrences (all)	0	0	1
Chest pain			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Food poisoning			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	6 / 477 (1.26%)	2 / 283 (0.71%)	0 / 228 (0.00%)
occurrences (all)	6	2	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 477 (0.63%)	4 / 283 (1.41%)	0 / 228 (0.00%)
occurrences (all)	3	4	0
Epistaxis			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences (all)	0	0	0
Pulmonary mass			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences (all)	0	0	0
Throat irritation			
subjects affected / exposed	1 / 477 (0.21%)	3 / 283 (1.06%)	0 / 228 (0.00%)
occurrences (all)	1	3	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 477 (1.05%)	3 / 283 (1.06%)	0 / 228 (0.00%)
occurrences (all)	5	3	0
Back pain			
subjects affected / exposed	10 / 477 (2.10%)	1 / 283 (0.35%)	0 / 228 (0.00%)
occurrences (all)	10	1	0
Haemarthrosis			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences (all)	0	0	0

Spinal pain			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences (all)	0	0	0
COVID-19			
subjects affected / exposed	16 / 477 (3.35%)	9 / 283 (3.18%)	2 / 228 (0.88%)
occurrences (all)	16	9	2
Cellulitis			
subjects affected / exposed	0 / 477 (0.00%)	3 / 283 (1.06%)	0 / 228 (0.00%)
occurrences (all)	0	3	0
Conjunctivitis			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	1 / 228 (0.44%)
occurrences (all)	0	0	1
Helicobacter infection			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	13 / 477 (2.73%)	16 / 283 (5.65%)	6 / 228 (2.63%)
occurrences (all)	16	18	6
Oral fungal infection			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences (all)	0	0	0
Pulpitis dental			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	6 / 477 (1.26%)	5 / 283 (1.77%)	4 / 228 (1.75%)
occurrences (all)	6	5	4
Urinary tract infection			

subjects affected / exposed	5 / 477 (1.05%)	1 / 283 (0.35%)	0 / 228 (0.00%)
occurrences (all)	5	1	0
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 477 (0.00%)	0 / 283 (0.00%)	0 / 228 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	From Week 24 to Week 48: Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 70 (24.29%)		
Investigations			
Prostatic specific antigen increased			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Vascular disorders			
Essential hypertension			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences (all)	0		
Supraventricular extrasystoles			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences (all)	0		
Headache			

subjects affected / exposed	2 / 70 (2.86%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Gastrointestinal disorders			
Food poisoning			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Pulmonary mass			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Throat irritation			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences (all)	0		
Haemarthrosis			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Spinal pain			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
COVID-19			
subjects affected / exposed	2 / 70 (2.86%)		
occurrences (all)	2		
Cellulitis			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Gastroenteritis viral			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Helicobacter infection			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences (all)	0		
Oral fungal infection			

subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Pulpitis dental			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 70 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 70 (1.43%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2020	The protocol was amended to address minor administrative items, clarifications, and substantial changes to add an electrocardiogram exclusion criterion, spirometry at Week 24, optional rather than mandatory COVID-19 testing, and adding a section on "Treatment After the End of Study".
26 June 2020	The protocol was amended to remove the requirement for pregnancy testing in all women and to only perform pregnancy testing on women of childbearing potential.
17 July 2020	The protocol was amended to reorder the secondary endpoint testing hierarchy, to remove an evening dosing requirement at early termination visits with 12-hour spirometry, to revise 'Events Meeting the Adverse Events Definition', to clarify COVID-19 testing as optional, to correct a minor document formatting issue, and to clarify the protocol version and amendment numbers.
30 April 2021	The protocol was amended to allow some patients with stable use of inhaled corticosteroids, reorder the secondary endpoint testing hierarchy and add additional endpoints, to update the handling of missing data in the statistical analysis, to incorporate contents of protocol clarification letters dated 29 September 2020 and 05 November 2020, to revise exclusion criteria relating to hepatitis B and C, and to revise and clarify prohibited medication requirements regarding chronic use of antibiotics and beta-blockers, and to update and clarify requirements for stable use of maintenance therapy in inclusion criteria.
18 February 2022	This amendment was a minor clarification to the protocol to allow flexibility to enroll approximately 50% of patients on stable background therapy, rather than to cap enrollment of patients on background therapy precisely at 50%. This clarification to the protocol had no impact on the safety of trial patients, as patients on background therapy were already being enrolled into the trial. Additionally, allowing slightly more than 50% of patients on background bronchodilator therapy had no significant impact on the robustness of the trial data or the scientific value of the clinical trial, as the protocol requirement that patients withhold background bronchodilators for a 24 to 48 hour washout period prior to all spirometry visits ensured the planned powering assumptions for the study would not be impacted. Medical Monitor contact information was updated according to administrative letter dated 29 November 2021.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported