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

Summary

EudraCT number	2020-002069-32
Trial protocol	SK BE DK HU BG
Global end of trial date	06 July 2022

Results information

Result version number	v1 (current)
This version publication date	23 July 2023
First version publication date	23 July 2023

Trial information

Trial identification

Sponsor protocol code	RPL554-CO-302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04542057
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	06 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 July 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 Organizations 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	22 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	Belgium: 5
Country: Number of subjects enrolled	Bulgaria: 131
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	Estonia: 20
Country: Number of subjects enrolled	Hungary: 52
Country: Number of subjects enrolled	Poland: 58
Country: Number of subjects enrolled	Slovakia: 18
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	United States: 455
Worldwide total number of subjects	790
EEA total number of subjects	322

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)	348
From 65 to 84 years	442
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 130 study centers. Patients were randomized in a 5:3 ratio, stratified by smoking status and background medication use, manner to receive either ensifentrine or placebo. A total of 790 patients were randomized in this study.

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.

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 solution
Routes of administration	Inhalation use

Dosage and administration details:

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

Number of subjects in period 1	Ensifentrine	Placebo
Started	499	291
Received Treatment	498	291
Completed	393	218
Not completed	106	73
COPD exacerbation withdrawal criteria	5	6
Consent withdrawn by subject	52	30
Adverse event, non-fatal	15	6
Death	3	1
Study terminated by sponsor	1	-
Unspecified	2	2
COVID-19 adverse event	6	4
Investigator discretion	2	1
Lost to follow-up	8	11
Coronavirus disease 2019 (COVID-19)	10	7
Lack of efficacy	2	5

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	499	291	790
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	65.0	65.3	
standard deviation	± 7.38	± 7.30	-
Gender categorical Units: Subjects			
Female	254	153	407
Male	245	138	383
Race Units: Subjects			
American Indian or Alaska native	1	0	1
Asian	1	1	2
Black or African American	24	11	35
White	472	276	748
Other	1	3	4
Ethnicity Units: Subjects			
Hispanic or Latino	26	14	40
Not Hispanic or Latino	473	277	750

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.	
End point type	Primary
End point timeframe:	
Baseline (40 minutes before first administration on Day 1) and Week 12	

End point values	Ensifentrine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	498	291		
Units: liters				
least squares mean (standard error)	0.0480 (± 0.00941)	-0.0462 (± 0.01236)		

Statistical analyses

Statistical analysis title	Treatment difference in average FEV1 AUC0-12h
Comparison groups	Placebo v Ensifentrine
Number of subjects included in analysis	789
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.0941

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0647
upper limit	0.1236
Variability estimate	Standard error of the mean
Dispersion value	0.01501

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 (40 minutes before first administration 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	498	291		
Units: liters				
least squares mean (standard error)				
Day 1 (Post-dose)	0.2369 (± 0.00601)	0.0801 (± 0.00784)		
Week 6	0.2158 (± 0.00969)	0.0636 (± 0.01276)		
Week 12	0.1945 (± 0.01012)	0.0482 (± 0.01349)		
Week 24	0.1957 (± 0.01099)	0.0434 (± 0.01475)		

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 (average of 7 days before first administration 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	492	291		
Units: units on a scale				
least squares mean (standard error)				
Week 6	-1.938 (± 0.2086)	-0.614 (± 0.2763)		
Week 12	-2.051 (± 0.2245)	-1.161 (± 0.2963)		
Week 24	-2.146 (± 0.2557)	-1.529 (± 0.3365)		

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 4h 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 (40 minutes before first administration 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	489	286		
Units: units on a scale				
least squares mean (standard error)				
Week 6	-3.602 (± 0.5902)	-1.890 (± 0.7692)		
Week 12	-4.019 (± 0.6171)	-2.942 (± 0.8168)		
Week 24	-4.532 (± 0.6840)	-4.054 (± 0.9084)		

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 (40 minutes before first administration 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	498	291		
Units: liters				
least squares mean (standard error)				
Week 6	0.0177 (± 0.00899)	-0.0261 (± 0.01181)		
Week 12	0.0057 (± 0.00957)	-0.0435 (± 0.01266)		
Week 24	-0.0066 (± 0.01006)	-0.0318 (± 0.01323)		

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 (40 minutes before first administration 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	498	291		
Units: liters				
least squares mean (standard error)				
Day 1 (Post-dose)	0.1556 (± 0.00527)	0.0063 (± 0.00686)		
Week 6	0.1357 (± 0.00932)	-0.0082 (± 0.01209)		
Week 12	0.1148 (± 0.00943)	-0.0209 (± 0.01260)		
Week 24	0.1148 (± 0.01036)	-0.0248 (± 0.01381)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Responder was a patient with an improvement from baseline in SGRQ total score of 4 or more. Percentage of patients with 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	489	286		
Units: percentage of patients				
number (not applicable)				
Week 6	44.0	39.5		
Week 12	45.2	43.0		
Week 24	45.4	50.3		

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 (average of 7 days before first administration 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	492	291		
Units: number of rescue medication puffs				
least squares mean (standard error)				
Week 6	-0.530 (± 0.0883)	-0.191 (± 0.1165)		
Week 12	-0.573 (± 0.0745)	-0.288 (± 0.0976)		
Week 24	-0.485 (± 0.0871)	-0.346 (± 0.1143)		

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. 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	484	286		
Units: units on a scale				
least squares mean (standard error)				
Week 6	1.6 (± 0.12)	0.9 (± 0.16)		
Week 12	1.8 (± 0.13)	1.2 (± 0.18)		
Week 24	2.2 (± 0.15)	1.3 (± 0.20)		

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 (40 minutes before first administration on Day 1) and Week 12

End point values	Ensifentrine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	498	291		
Units: liters				
least squares mean (standard error)	-0.0246 (± 0.01079)	-0.0783 (± 0.01358)		

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 the first dose of study treatment up to 10 days after the final study visit at Week 24, approximately 25 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	Ensifentrine

Reporting group description:

3 mg twice daily via standard jet nebulizer.

Reporting group title	Placebo

Reporting group description:

Twice daily via standard jet nebulizer.

Serious adverse events	Ensifentrine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 498 (5.62%)	17 / 291 (5.84%)	
number of deaths (all causes)	4	1	
number of deaths resulting from adverse events	4	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 498 (0.20%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 498 (0.20%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer stage II			
subjects affected / exposed	1 / 498 (0.20%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lung adenocarcinoma			
subjects affected / exposed	1 / 498 (0.20%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 498 (0.20%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophageal neoplasm			
subjects affected / exposed	0 / 498 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 498 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 498 (0.20%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 498 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 498 (0.20%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 498 (0.20%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Cardiac disorders			
Acute left ventricular failure			
subjects affected / exposed	1 / 498 (0.20%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 498 (0.20%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 498 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 498 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hemiparesis			
subjects affected / exposed	1 / 498 (0.20%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	1 / 498 (0.20%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 498 (0.20%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			

subjects affected / exposed	1 / 498 (0.20%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure	Additional description: These adverse events were secondary to: adverse events of COVID-19 pneumonia, acute diastolic congestive heart failure, and toxicity to various agents.		
subjects affected / exposed	3 / 498 (0.60%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	0 / 498 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	10 / 498 (2.01%)	5 / 291 (1.72%)	
occurrences causally related to treatment / all	1 / 10	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 498 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 498 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 498 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			

subjects affected / exposed	1 / 498 (0.20%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	2 / 498 (0.40%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 498 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Colonic abscess			
subjects affected / exposed	1 / 498 (0.20%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 498 (0.20%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 498 (0.40%)	4 / 291 (1.37%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 498 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinusitis			
subjects affected / exposed	1 / 498 (0.20%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 498 (0.20%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ensifentrine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 498 (13.65%)	46 / 291 (15.81%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 498 (1.00%)	1 / 291 (0.34%)	
occurrences (all)	5	1	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 498 (0.20%)	4 / 291 (1.37%)	
occurrences (all)	1	4	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 498 (2.01%)	7 / 291 (2.41%)	
occurrences (all)	10	8	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 498 (0.20%)	3 / 291 (1.03%)	
occurrences (all)	1	3	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	8 / 498 (1.61%)	2 / 291 (0.69%)	
occurrences (all)	8	2	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 498 (0.40%)	3 / 291 (1.03%)	
occurrences (all)	2	3	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	3 / 498 (0.60%)	4 / 291 (1.37%)	
occurrences (all)	3	4	
Musculoskeletal and connective tissue			

disorders			
Back pain			
subjects affected / exposed	8 / 498 (1.61%)	5 / 291 (1.72%)	
occurrences (all)	8	5	
Infections and infestations			
COVID-19			
subjects affected / exposed	16 / 498 (3.21%)	10 / 291 (3.44%)	
occurrences (all)	16	10	
Nasopharyngitis			
subjects affected / exposed	9 / 498 (1.81%)	3 / 291 (1.03%)	
occurrences (all)	10	3	
Sinusitis			
subjects affected / exposed	5 / 498 (1.00%)	0 / 291 (0.00%)	
occurrences (all)	5	0	
Urinary tract infection			
subjects affected / exposed	7 / 498 (1.41%)	5 / 291 (1.72%)	
occurrences (all)	7	5	
Tooth Abcess			
subjects affected / exposed	0 / 498 (0.00%)	4 / 291 (1.37%)	
occurrences (all)	0	4	

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 criteria, 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 make minor clarifications to the pharmacokinetic section, 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported