Clinical trial results:
A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Two-Treatment, Two-Period Crossover Efficacy and Safety Study in Idiopathic Pulmonary Fibrosis With Nalbuphine ER Tablets for the Treatment of Cough

Summary

EudraCT number	2018-004744-31
Trial protocol	GB
Global end of trial date	27 May 2022

Results information

Result version number	v1 (current)
This version publication date	29 May 2025
First version publication date	29 May 2025

Trial information

Trial identification

Sponsor protocol code	TR12

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04030026
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Trevi Therapeutics
Sponsor organisation address	195 Church St, 14th Floor, New Haven, United States, 06510
Public contact	VP Clinical Operations, Trevi Therapeutics, Inc., +1 203 304 2499,
Scientific contact	VP Clinical Operations, Trevi Therapeutics, Inc., +1 203 304 2499,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 May 2022
Global end of trial reached?	Yes
Global end of trial date	27 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of nalbuphine ER tablets in the study population and to evaluate the effect of NAL ER tablets on the mean daytime cough frequency (coughs per hour) at Day 22 (dose 162 mg BID) as compared to placebo tablets.

Protection of trial subjects:

Subjects were included with a level of respiratory and general health, per the inclusion/exclusion criteria.
Drugs with potential interactions with the study drug were restricted, per the inclusion/exclusion criteria.
Subjects were allowed to continue the anti-fibrotic treatment for IPF on a stable dose throughout the study, per the inclusion/exclusion criteria.
An independent Data Safety Monitoring Board (DSMB) periodically reviewed safety data.
Subjects were closely monitored for safety. AEs were continuously evaluated throughout the study. Vital signs, locally reviewed and central cardiac core laboratory-read ECGs, physical examinations, spirometry and clinical laboratory testing were conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 October 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 42
Worldwide total number of subjects	42
EEA total number of subjects	0

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)	4
From 65 to 84 years	37
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 11 sites in the United Kingdom from 29 October 2019 to 27 May 2022.

Pre-assignment

Screening details:

A total of 56 subjects were screened from whom 42 subjects were enrolled and randomized to receive treatment in this study.

Period 1

Period 1 title	Treatment Period 1 (22 Days)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Subject, Assessor

Blinding implementation details:

This study utilized a cross-over design with all subjects planned to receive both placebo and active study treatment during the study. The treatments the subjects received, and the order of those treatments were double-blinded (blinding performed via Interactive Web Response System). Under normal circumstances, the blind was not broken. In the event of a medical emergency, when management of a subject's condition required knowledge of the treatment assignment, the blind could have been broken.

Arms

Are arms mutually exclusive?	Yes
Arm title	First NAL ER then Placebo

Arm description:

Subjects received NAL ER in treatment period 1 at dose 27 mg once daily (QD) to 54 mg twice daily (BID) over a 5-day period and then maintained at 54 mg BID for 4 days. Dose was increased to 108 mg BID for 1 week then to 162 mg BID for 6 days, followed by placebo for 3 weeks in treatment period 2. Both the treatment periods were separated by 2 weeks of washout period.

Arm type	Experimental
Investigational medicinal product name	Nalbuphine
Investigational medicinal product code	NAL ER
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received NAL ER 27 mg QD, 27 mg BID, 54 mg BID, 108 mg BID, and 162 mg BID for 3 weeks in treatment period 1.

Arm title	First Placebo then NAL ER

Arm description:

Subjects received placebo for 3 weeks in treatment period 1 followed by NAL ER in treatment period 2 at dose 27 mg QD to 54 mg BID over a 5-day period and then maintained at 54 mg BID for 4 days. Dose was increased to 108 mg BID for 1 week then to 162 mg BID for 6 days. Both the treatment periods were separated by 2 weeks of washout period.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo for 3 weeks, in treatment period 1.

Number of subjects in period 1	First NAL ER then Placebo	First Placebo then NAL ER
Started	21	21
Safety Analysis Set	20	21
Completed	19	19
Not completed	2	2
Physician decision	1	-
COVID-19 pandemic restrictions	-	1
Withdrawal by subject	1	-
Protocol deviation	-	1

Period 2

Period 2 title	Treatment Period 2 (22 Days)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Blinding implementation details:

This study utilized a cross-over design with all subjects planned to receive both placebo and active study treatment during the study. The treatments the subjects received, and the order of those treatments were double-blinded (blinding performed via Interactive Web Response System). Under normal circumstances, the blind was not broken. In the event of a medical emergency, when management of a subject's condition required knowledge of the treatment assignment, the blind could have been broken.

Arms

Are arms mutually exclusive?	Yes
Arm title	First NAL ER then Placebo

Arm description:

Subjects received NAL ER in treatment period 1 at dose 27 mg QD to 54 mg BID over a 5-day period and then maintained at 54 mg BID for 4 days. Dose was increased to 108 mg BID for 1 week then to 162 mg BID for 6 days, followed by placebo for 3 weeks in treatment period 2. Both the treatment periods were separated by 2 weeks of washout period.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo for 3 weeks in treatment period 2.

Arm title	First Placebo then NAL ER

Arm description:

Subjects received placebo for 3 weeks in treatment period 2 followed by NAL ER in treatment period 1 at dose 27 mg QD to 54 mg BID over a 5-day period and then maintained at 54 mg BID for 4 days. Dose was increased to 108 mg BID for 1 week then to 162 mg BID for 6 days. Both the treatment periods

were separated by 2 weeks of washout period.

Arm type	Experimental
Investigational medicinal product name	Nalbuphine
Investigational medicinal product code	NAL ER
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received NAL ER 27 mg QD, 27 mg BID, 54 mg BID, 108 mg BID, 162 mg BID for 3 weeks in treatment period 2.

Number of subjects in period 2	First NAL ER then Placebo	First Placebo then NAL ER
Started	19	19
Completed	18	10
Not completed	1	9
Adverse event	-	6
COVID-19 pandemic restrictions	1	1
Withdrawal by subject	-	2

Baseline characteristics

Reporting groups

Reporting group title	First NAL ER then Placebo

Reporting group description:

Subjects received NAL ER in treatment period 1 at dose 27 mg once daily (QD) to 54 mg twice daily (BID) over a 5-day period and then maintained at 54 mg BID for 4 days. Dose was increased to 108 mg BID for 1 week then to 162 mg BID for 6 days, followed by placebo for 3 weeks in treatment period 2. Both the treatment periods were separated by 2 weeks of washout period.

Reporting group title	First Placebo then NAL ER

Reporting group description:

Subjects received placebo for 3 weeks in treatment period 1 followed by NAL ER in treatment period 2 at dose 27 mg QD to 54 mg BID over a 5-day period and then maintained at 54 mg BID for 4 days. Dose was increased to 108 mg BID for 1 week then to 162 mg BID for 6 days. Both the treatment periods were separated by 2 weeks of washout period.

Reporting group values	First NAL ER then Placebo	First Placebo then NAL ER	Total
Number of subjects	21	21	42
Age categorical Units: Subjects			
18-64 years	3	1	4
65-84 years	18	19	37
85 years and above	0	1	1
Gender categorical Units: Subjects			
Female	2	4	6
Male	19	17	36
Race Units: Subjects			
Asian	1	3	4
White	20	18	38
Ethnicity Units: Subjects			
Not Hispanic or Latino	20	20	40
Not reported	1	1	2
Daytime Cough Frequency Units: coughs per hour arithmetic mean standard deviation	±	±	-

Subject analysis sets

Subject analysis set title	NAL ER
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received NAL ER 27 mg QD to 54 mg BID over a 5-day period, and then maintained at 54 mg BID for 4 days. Dose was increased to 108 mg BID for 1 week followed by162 mg, BID for 6 days in treatment period 1 or 2 of the study.

Subject analysis set title	Placebo
Subject analysis set type	Full analysis

Subject analysis set description:
Subjects received placebo for 3 weeks through treatment period 1 or 2 of the study.

Reporting group values	NAL ER	Placebo	
Number of subjects	38	38	
Age categorical Units: Subjects			
18-64 years 65-84 years 85 years and above			
Gender categorical Units: Subjects			
Female Male			
Race Units: Subjects			
Asian White			
Ethnicity Units: Subjects			
Not Hispanic or Latino Not reported			
Daytime Cough Frequency Units: coughs per hour			
arithmetic mean	27.99	27.99	
standard deviation	± 23.704	± 23.704	

End points

End points reporting groups

Reporting group title	First NAL ER then Placebo

Reporting group description:

Subjects received NAL ER in treatment period 1 at dose 27 mg once daily (QD) to 54 mg twice daily (BID) over a 5-day period and then maintained at 54 mg BID for 4 days. Dose was increased to 108 mg BID for 1 week then to 162 mg BID for 6 days, followed by placebo for 3 weeks in treatment period 2. Both the treatment periods were separated by 2 weeks of washout period.

Reporting group title	First Placebo then NAL ER

Reporting group description:

Subjects received placebo for 3 weeks in treatment period 1 followed by NAL ER in treatment period 2 at dose 27 mg QD to 54 mg BID over a 5-day period and then maintained at 54 mg BID for 4 days. Dose was increased to 108 mg BID for 1 week then to 162 mg BID for 6 days. Both the treatment periods were separated by 2 weeks of washout period.

Reporting group title	First NAL ER then Placebo

Reporting group description:

Subjects received NAL ER in treatment period 1 at dose 27 mg QD to 54 mg BID over a 5-day period and then maintained at 54 mg BID for 4 days. Dose was increased to 108 mg BID for 1 week then to 162 mg BID for 6 days, followed by placebo for 3 weeks in treatment period 2. Both the treatment periods were separated by 2 weeks of washout period.

Reporting group title	First Placebo then NAL ER

Reporting group description:

Subjects received placebo for 3 weeks in treatment period 2 followed by NAL ER in treatment period 1 at dose 27 mg QD to 54 mg BID over a 5-day period and then maintained at 54 mg BID for 4 days. Dose was increased to 108 mg BID for 1 week then to 162 mg BID for 6 days. Both the treatment periods were separated by 2 weeks of washout period.

Subject analysis set title	NAL ER
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received NAL ER 27 mg QD to 54 mg BID over a 5-day period, and then maintained at 54 mg BID for 4 days. Dose was increased to 108 mg BID for 1 week followed by162 mg, BID for 6 days in treatment period 1 or 2 of the study.

Subject analysis set title	Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects received placebo for 3 weeks through treatment period 1 or 2 of the study.

Primary: Number of Subjects Who Experienced at Least one Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Subjects Who Experienced at Least one Treatment Emergent Adverse Events (TEAEs)[1]

End point description:

AE was defined as untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with treatment.AE can be any unfavorable, unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to medicinal product. TEAE was defined as any AE that occurs after first dose of study drug. TEAEs included both serious and non-serious TEAEs. Safety analysis set (SAS) included all randomized subjects who had received at least 1 dose of IP. 3 subjects did not receive at least one dose of NAL ER but received placebo and 1 subject did not receive at least one dose of placebo but received NAL ER treatment. Data was summarized under actual treatment received (NAL ER or placebo) independently whether this was received in Treatment Period 1 or 2 (subjects who received both treatments are counted in both arms.

End point type	Primary

End point timeframe:

Up to Day 72

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned to be performed for this endpoint.

End point values	NAL ER	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	40		
Units: subjects	35	26		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Abnormalities in Laboratory Parameters

End point title	Number of Subjects With Clinically Significant Abnormalities in Laboratory Parameters[2]

End point description:

The clinical laboratory parameters included the urinalysis, hematology, serum chemistry, coagulation and liver function parameters. Clinical significance was determined by the investigator. SAS included all randomized subjects who had received at least 1 dose of IP. 3 subjects did not receive at least one dose of NAL ER but received placebo and 1 subject did not receive at least one dose of placebo but received NAL ER treatment. Data was summarized under actual treatment received (NAL ER or placebo) independently whether this was received in Treatment Period 1 or 2 (subjects who received both treatments are counted in both arms.

End point type	Primary

End point timeframe:

Up to Day 72

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned to be performed for this endpoint.

End point values	NAL ER	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	40		
Units: subjects				
Urinalysis	0	0		
Hematology	1	0		
Serum Chemistry	1	1		
Coagulation	0	1		
Liver Function Parameters	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Changes in Vital Sign

Parameters

End point title	Number of Subjects With Clinically Significant Changes in Vital Sign Parameters[3]

End point description:

Vital signs measurements included blood pressure, heart rate, and respiration rate, body temperature, pulse oximetry, and weight. Clinical significance was determined by the investigator. SAS included all randomized subjects who had received at least 1 dose of IP. 3 subjects did not receive at least one dose of NAL ER but received placebo and 1 subject did not receive at least one dose of placebo but received NAL ER treatment. Data was summarized under actual treatment received (NAL ER or placebo) independently whether this was received in Treatment Period 1 or 2 (subjects who received both treatments are counted in both arms.

End point type	Primary

End point timeframe:

Up to Day 72

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned to be performed for this endpoint.

End point values	NAL ER	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	40		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Changes in Physical Examination Parameters

End point title	Number of Subjects With Clinically Significant Changes in Physical Examination Parameters[4]

End point description:

Physical examination included examination of the following body systems: general appearance, eyes, ears, nose, throat, head and neck, chest and lungs, cardiovascular, abdomen, musculoskeletal, lymphatic, dermatological, neurological, and extremities. Clinical significance was determined by the investigator. SAS included all randomized subjects who had received at least 1 dose of IP. 3 subjects did not receive at least one dose of NAL ER but received placebo and 1 subject did not receive at least one dose of placebo but received NAL ER treatment. Data was summarized under actual treatment received (NAL ER or placebo) independently whether this was received in Treatment Period 1 or 2 (subjects who received both treatments are counted in both arms.

End point type	Primary

End point timeframe:

Up to Day 72

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned to be performed for this endpoint.

End point values	NAL ER	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	40		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Abnormalities in 12-Lead Electrocardiogram (ECG)

End point title	Number of Subjects With Clinically Significant Abnormalities in 12-Lead Electrocardiogram (ECG)[5]

End point description:

Changes in ECG data such as heart rate, rhythm, and other clinically significant abnormalities (left ventricular hypertrophy, pathological Q-waves) were measured. Clinical significance was determined by the investigator. SAS included all randomized subjects who had received at least 1 dose of IP. 3 subjects did not receive at least one dose of NAL ER but received placebo and 1 subject did not receive at least one dose of placebo but received NAL ER treatment. Data was summarized under actual treatment received (NAL ER or placebo) independently whether this was received in Treatment Period 1 or 2 (subjects who received both treatments are counted in both arms.

End point type	Primary

End point timeframe:

Up to Day 72

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned to be performed for this endpoint.

End point values	NAL ER	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	40		
Units: subjects	1	1		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Forced Vital Capacity (FVC) at Day 21

End point title	Change From Baseline in Forced Vital Capacity (FVC) at Day

End point description:

Spirometry was used to assess FVC. It was used to assess pulmonary breathing mechanics. Subjects in SAS were analyzed. 3 subjects did not receive at least 1 dose of NAL ER but received placebo and 1 subject did not receive at least 1 dose of placebo but received NAL ER treatment. Data was summarized under actual treatment received (NAL ER or placebo) independently whether in Treatment Period 1 or 2 (subjects who received both treatments are counted in both NAL ER and placebo columns). Overall number of subjects analyzed'=subjects who were evaluable for the OM.

End point type	Primary

End point timeframe:

Baseline, Day 21

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned to be performed for this endpoint.

End point values	NAL ER	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	28	35		
Units: litre(s)				
arithmetic mean (standard deviation)	-2.3 (± 5.58)	-1.0 (± 5.56)		

Statistical analyses

No statistical analyses for this end point

Primary: Subjective Opiate Withdrawal (SOWS) Total Raw Score

End point title	Subjective Opiate Withdrawal (SOWS) Total Raw Score[7]

End point description:

The SOWS is a self-administered scale for grading opioid withdrawal symptoms and was collected via the study issued e-diary. It consisted of 16 symptoms related to how the subject felt. Each symptom was scored between 0 to 4. The total score ranges between 0 to 64, higher score indicates more severe symptoms. Subjects in SAS were analyzed. 3 subjects did not receive at least 1 dose of NAL ER but received placebo and 1 subject did not receive at least 1 dose of placebo but received NAL ER treatment. Data was summarized under actual treatment received (NAL ER or placebo) independently whether in Treatment Period 1 or 2 (subjects who received both treatments are counted in both NAL ER and placebo columns). Overall number of subjects analyzed'=subjects who were evaluable for the OM.

End point type	Primary

End point timeframe:

Up to Day 72

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was planned to be performed for this endpoint.

End point values	NAL ER	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	38		
Units: score on a scale				
arithmetic mean (standard deviation)	4.7055 (± 5.0019)	2.4082 (± 3.5561)		

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change From Baseline in Daytime Cough Frequency at Day 22

End point title	Percent Change From Baseline in Daytime Cough Frequency at

	Day 22

End point description:

Daytime cough was defined as cough that occurs between the time that the subject is a wake in the 24 hours after the digital cough monitor was applied for use. Assessment was done using objective digital cough monitoring. Percent change in cough frequency (coughs per hour) from baseline was assessed. Baseline was defined as the last available assessment prior to the first Treatment Period 1 IP intake. Full Analysis Set (FAS) included all randomized subjects who had received at least single dose of the study medication and provided study baseline and at least one post -baseline primary efficacy variable assessment during the treatment Period. 'Number of subjects analysed' included those subjects who were evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Day 22

End point values	NAL ER	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29	37		
Units: percent change				
geometric mean (confidence interval 95%)	-75.11 (-82.655 to -67.567)	-22.62 (-42.531 to -2.715)		

Statistical analyses

Statistical analysis title	NAL ER vs Placebo
Comparison groups	NAL ER v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	Mixed-effects model
Parameter estimate	Geometric Mean Ratio
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.208
upper limit	0.431

Notes:

[8] - Mixed-effects model: unstructured, heterogeneous toeplitz and autoregressive covariance matrices. Dependent variable: change from baseline in log-transformed scale of Daytime Cough Frequency. Fixed effects: sequence (arm), period and treatment.

Secondary: Change From Baseline in Daytime Cough Frequency at Day 22

End point title	Change From Baseline in Daytime Cough Frequency at Day 22

End point description:

Daytime cough was defined as cough that occurs between the time that the subject wakes up and the time that the subject goes to bed. Assessment was done using objective digital cough monitoring. The change in daytime cough frequency (coughs per hour) from baseline was assessed. Baseline was defined as the last available assessment prior to the first Treatment Period 1 IP intake. FAS included all

randomized subjects who had received at least single dose of the study medication and provided study baseline and at least one post -baseline primary efficacy variable assessment during the treatment Period. 'Number of subjects analysed' included those subjects who were evaluable for this endpoint.

End point type	Secondary
End point timeframe:	
Baseline, Day 22	

End point values	NAL ER	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29	37		
Units: Coughs Per Hour				
arithmetic mean (standard deviation)	-19.386 (± 19.5688)	-6.264 (± 12.4006)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in 24-Hour Cough Frequency at Day 22

End point title	Percent Change From Baseline in 24-Hour Cough Frequency at Day 22
End point description:	
Percent change in 24-hour (combined daytime and nighttime) cough frequency (coughs per hour) from baseline was assessed. Assessment was done using objective digital cough monitoring. Baseline was defined as the last available assessment prior to the first Treatment Period 1 IP intake. FAS included all randomized subjects who had received at least single dose of the study medication and provided study baseline and at least one post -baseline primary efficacy variable assessment during the treatment Period. 'Number of subjects analysed' included those subjects who were evaluable for this endpoint.	
End point type	Secondary
End point timeframe:	
Baseline, Day 22	

End point values	NAL ER	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29	37		
Units: percent change				
geometric mean (confidence interval 95%)	-76.10 (-83.133 to -69.075)	-25.29 (-43.894 to -6.690)		

Statistical analyses

Statistical analysis title	NAL ER vs Placebo
Comparison groups	NAL ER v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [9]
Method	Mixed-effects model
Parameter estimate	Geometric Mean Ratio
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.208
upper limit	0.431

Notes:

[9] - Mixed-effects model: unstructured, heterogeneous toeplitz and autoregressive covariance matrices. Dependent variable: change from baseline in log-transformed scale of Daytime Cough Frequency. Fixed effects: sequence (arm), period and treatment.

Secondary: Percent Change From Baseline in Nighttime Cough Frequency at Day 22

End point title	Percent Change From Baseline in Nighttime Cough Frequency at Day 22

End point description:

Nighttime cough frequency was intended as the average coughs per hour while the subject was flagged as being asleep. Assessment was done using objective digital cough monitoring. Percent change in cough frequency (coughs per hour) from baseline was assessed. Baseline was defined as the last available assessment prior to the first Treatment Period 1 IP intake. FAS included all randomized subjects who had received at least single dose of the study medication and provided study baseline and at least one post -baseline primary efficacy variable assessment during the treatment Period. 'Number of subjects analysed' included those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 22

End point values	NAL ER	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29	37		
Units: percent change				
geometric mean (confidence interval 95%)	-62.27 (-79.588 to -44.957)	-20.30 (-51.391 to 10.783)		

Statistical analyses

Statistical analysis title	NAL ER vs Placebo
Comparison groups	Placebo v NAL ER

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0087 [10]
Method	Mixed-effects model
Parameter estimate	Geometric Mean Ratio
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	0.717

Notes:

[10] - Mixed-effects model: unstructured, heterogeneous toeplitz and autoregressive covariance matrices. Dependent variable: change from baseline in log-transformed scale of Daytime Cough Frequency. Fixed effects: sequence (arm), period and treatment.

Secondary: Mean Change From Baseline in the Evaluating Respiratory Symptoms (E-RS) Diary Cough Subscale at Days 9, 16, and 22

End point title	Mean Change From Baseline in the Evaluating Respiratory Symptoms (E-RS) Diary Cough Subscale at Days 9, 16, and 22

End point description:

E-RS daily diary instrument has four separate respiratory symptom domain scales which is a valid, reliable and sensitive measure of four distinct respiratory symptoms. The four domain scales that included cough [E-RS item 2- How often did you cough today?;score range 0 (not at all)-4 (almost constantly)], and other items such as breathlessness, sputum, and chest symptoms. The raw totals for the E-RS for each subscales were converted to a scale range of 0 to 100 (least symptomatic to most symptomatic). Higher score =more severe grade to the symptom. Negative score=improvement in symptoms. Baseline was defined as the last available assessment prior to the first Treatment Period 1 IP intake. FAS =randomized subjects who received at least single dose of the study medication and provided study baseline and one post -baseline primary efficacy assessment. 'Number analyzed'= data available for analysis at the specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Days 9, 16, and 22

End point values	NAL ER	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	38		
Units: score on scale				
arithmetic mean (standard deviation)				
Change at Day 9 (n=32, 38)	-0.7 (± 0.77)	-0.1 (± 0.70)		
Change at Day 16 (n=30, 38)	-0.9 (± 0.82)	-0.2 (± 0.59)		
Change at Day 22 (n=27, 32)	-1.0 (± 0.94)	-0.2 (± 0.85)		

Statistical analyses

Statistical analysis title	NAL ER vs Placebo

Statistical analysis description:

Change from baseline at Day 9

Comparison groups	Placebo v NAL ER
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0014 [11]
Method	Student's T-test

Notes:

[11] - Student's T-test was used to evaluate if the difference in mean change from baseline is different between planned treatments (NAL ER vs placebo).

Statistical analysis title	NAL ER vs Placebo

Statistical analysis description:

Change from baseline at Day 16

Comparison groups	Placebo v NAL ER
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [12]
Method	Student's T-test

Notes:

[12] - Student's T-test was used to evaluate if the difference in mean change from baseline is different between planned treatments (NAL ER vs placebo).

Statistical analysis title	NAL ER vs Placebo

Statistical analysis description:

Change from baseline at Day 22

Comparison groups	NAL ER v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [13]
Method	Student's T-test

Notes:

[13] - Student's T-test was used to evaluate if the difference in mean change from baseline is different between planned treatments (NAL ER vs placebo).

Secondary: Mean Change from Baseline in E-RS Breathlessness Score at Days 9, 16, and 22

End point title	Mean Change from Baseline in E-RS Breathlessness Score at Days 9, 16, and 22

End point description:

E-RS daily diary instrument has four separate respiratory symptom domain scales which is a valid,reliable and sensitive measure of four distinct respiratory symptoms.Four domain scales included breathlessness [E-RS items 7 (were you breathless today),8(how breathless were you today),9(breathlessness doing personal care activities),10 (breathlessness doing indoor activities)& 11 (breathlessness doing outdoor activities);score =0:not at all)-23:almost constantly].Raw totals for the E-RS subscales were converted to a scale of 0 to 100 (least to most symptoms).Higher score=more severe grade to the symptom.Negative score=improvement in symptoms.Baseline=last available assessment prior to the first Treatment Period 1 investigational product intake.FAS=randomized subjects who received at least single dose of the study medication and provided study baseline and one post - baseline primary efficacy assessment. 'Number analyzed'= data available for analysis at the specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Days 9, 16 and 22

End point values	NAL ER	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	38		
Units: score on scale				
arithmetic mean (standard deviation)				
Change at Day 9 (n=32, 38)	-0.5 (± 2.68)	1.1 (± 2.74)		
Change at Day 16 (n=30, 38)	0.0 (± 2.30)	1.2 (± 2.26)		
Change at Day 22 (n=27, 32)	0.1 (± 2.45)	0.8 (± 2.43)		

Statistical analyses

Statistical analysis title	NAL ER vs Placebo
Statistical analysis description: Change from baseline at Day 9	
Comparison groups	NAL ER v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0198 [14]
Method	Student's T-test

Notes:

[14] - Student's T-test was used to evaluate if the difference in mean change from baseline is different between planned treatments (NAL ER vs placebo).

Statistical analysis title	NAL ER vs Placebo
Statistical analysis description: Change from baseline at Day 16	
Comparison groups	NAL ER v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0374 [15]
Method	Student's T-test

Notes:

[15] - Student's T-test was used to evaluate if the difference in mean change from baseline is different between planned treatments (NAL ER vs placebo).

Statistical analysis title	NAL ER vs Placebo
Statistical analysis description: Change from baseline at Day 22	
Comparison groups	Placebo v NAL ER

Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2982 [16]
Method	Student's T-test

Notes:

[16] - Student's T-test was used to evaluate if the difference in mean change from baseline is different between planned treatments (NAL ER vs placebo).

Secondary: Mean Change From Baseline in the Cough Severity Numerical Rating Scale at Days 8, 15, and 21

End point title	Mean Change From Baseline in the Cough Severity Numerical Rating Scale at Days 8, 15, and 21

End point description:

The Cough Severity NRS instrument is a single-dimension 11-point Likert scale ranging from 0 (no cough) to 10 (worst possible cough). Subjects completed the cough numerical severity rating via the study specific e-diary. The mean change from baseline in the Cough Severity Numerical Rating Scale was assessed. Baseline was defined as the last available assessment prior to the first Treatment Period 1 IP intake. FAS included all randomized subjects who had received at least single dose of the study medication and provided study baseline and at least one post -baseline primary efficacy variable assessment during the treatment Period. Here, 'n' signifies number of subjects analysed for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Days 8, 15, and 21

End point values	NAL ER	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	38		
Units: score on scale				
arithmetic mean (standard deviation)				
Change at Day 8 (n=27, 38)	-1.7 (± 1.98)	-0.4 (± 1.54)		
Change at Day 15 (n=29, 37)	-2.7 (± 1.75)	-0.6 (± 1.74)		
Change at Day 21 (n=27, 33)	-2.5 (± 2.19)	-0.3 (± 1.85)		

Statistical analyses

Statistical analysis title	NAL ER vs Placebo

Statistical analysis description:

Change from baseline at Day 8

Comparison groups	NAL ER v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0054 [17]
Method	Student's T-test

Notes:

[17] - Student's T-test was used to evaluate if the difference in mean change from baseline is different between planned treatments (NAL ER vs placebo)

Statistical analysis title	NAL ER vs Placebo
Statistical analysis description: Change from baseline at Day 15	
Comparison groups	NAL ER v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	Student's T-test

Notes:

[18] - Student's T-test was used to evaluate if the difference in mean change from baseline is different between planned treatments (NAL ER vs placebo).

Statistical analysis title	NAL ER vs Placebo
Statistical analysis description: Change from baseline at Day 21	
Comparison groups	NAL ER v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [19]
Method	Student's T-test

Notes:

[19] - Student's T-test was used to evaluate if the difference in mean change from baseline is different between planned treatments (NAL ER vs placebo).

Secondary: Mean Change From Baseline in the 14-item EXAcerbation of Chronic Pulmonary Disease Tool (EXACT) v1.1 e-Diary Tool Total Score at Days 9, 16, and 22

End point title	Mean Change From Baseline in the 14-item EXAcerbation of Chronic Pulmonary Disease Tool (EXACT) v1.1 e-Diary Tool Total Score at Days 9, 16, and 22

End point description:

EXACT tool is a 14-item Daily Diary Tool Patient-reported outcome (PRO) instrument developed to quantify and measure exacerbations of COPD. It provides a total score and subscale scores for breathlessness, cough and sputum, and chest symptoms. The 14 items have interval-level scale ranging between 0 to 100. Total score of each domain of breathlessness, cough and sputum, and chest symptoms ranges from 0 to 100. Higher score indicated a more severe condition. Negative score=improvement. Baseline was defined as the last available assessment prior to the first Treatment Period 1 IP intake.FAS included all randomized subjects who had received at least single dose of the study medication and provided study baseline and at least one post -baseline primary efficacy variable assessment during the treatment Period.Here,'n' signifies number of subjects analysed for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Days 9, 16, and 22

End point values	NAL ER	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	38		
Units: score on scale				
arithmetic mean (standard deviation)				
Change at Day 9 (n=32, 38)	-2.0 (± 5.63)	1.6 (± 5.55)		
Change at Day 16 (n=30, 38)	-1.8 (± 4.89)	1.9 (± 5.46)		
Change at Day 22 (n=27, 32)	-1.6 (± 5.92)	0.6 (± 5.76)		

Statistical analyses

Statistical analysis title	NAL ER vs Placebo
Statistical analysis description: Change from baseline at Day 9	
Comparison groups	NAL ER v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0107 [20]
Method	Student's T-test

Notes:

[20] - Student's T-test was used to evaluate if the difference in mean change from baseline is different between planned treatments (NAL ER vs placebo).

Statistical analysis title	NAL ER vs Placebo
Statistical analysis description: Change for baseline at Day 16	
Comparison groups	NAL ER v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0051 [21]
Method	Student's T-test

Notes:

[21] - Student's T-test was used to evaluate if the difference in mean change from baseline is different between planned treatments (NAL ER vs placebo).

Statistical analysis title	NAL ER vs Placebo
Statistical analysis description: Change from baseline at Day 22	
Comparison groups	NAL ER v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1513 [22]
Method	Student's T-test

Notes:

[22] - Student's T-test was used to evaluate if the difference in mean change from baseline is different between planned treatments (NAL ER vs placebo).

Secondary: Mean Change From Baseline in the Patient Reported Outcomes Measurement Information System (PROMIS) Item Bank v1.0 Fatigue Short Form 7a scale Total Score at Day 21

End point title	Mean Change From Baseline in the Patient Reported Outcomes Measurement Information System (PROMIS) Item Bank v1.0 Fatigue Short Form 7a scale Total Score at Day 21

End point description:

The PROMIS Fatigue Short Form 7a is a self-administered Likert-type rating 5-point scale of 7 questions that assess tiredness, exhaustion, energy, fatigue limit, tiredness to think, tiredness impact on hygiene and impact on ability to exercise strenuously over the past 7 days. It consisted of 7 items with each item was scored between 1 to 5. The total score could range between 1 to 35, higher score indicates more severe symptoms. FAS included all randomized subjects who had received at least single dose of the study medication and provided study baseline and at least one post -baseline primary efficacy variable assessment during the treatment Period. Baseline was defined as the last available assessment prior to the first Treatment Period 1 IP intake. 'Number of subjects analysed' included those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 21

End point values	NAL ER	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	30		
Units: score on scale				
arithmetic mean (standard deviation)	0.9 (± 3.98)	0.0 (± 2.98)		

Statistical analyses

Statistical analysis title	NAL ER vs Placebo
Comparison groups	NAL ER v Placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3601 [23]
Method	Student's T-test

Notes:

[23] - Student's T-test was used to evaluate if the difference in mean change from baseline is different between planned treatments (NAL ER vs placebo).

Secondary: Clinical Global Impression of Change (CGI-C) Over Time Measured at Day 21

End point title	Clinical Global Impression of Change (CGI-C) Over Time Measured at Day 21

End point description:

The CGI-C is a one-item measure evaluating change from the initiation of treatment on a 7-point scale. It provides an overall clinician-determined summary measure that takes into account all available information, including knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function. The total score ranges between 0 (very much improved) to 7 (very much worse). The lower scores indicate an improvement in respiratory symptoms. FAS included all randomized subjects who had received at least single dose of the study medication and provided study baseline and at least one post -baseline primary efficacy variable assessment during the treatment Period. 'Number of subjects analysed' included those subjects who

were evaluable for this endpoint.

End point type	Secondary

End point timeframe:
At Day 21

End point values	NAL ER	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29	36		
Units: score on scale				
arithmetic mean (standard deviation)	3.0 (± 1.50)	3.9 (± 0.91)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 72

Adverse event reporting additional description:

All-cause mortality: All randomized subjects. AEs: SAS included all randomized subjects who received ≥1 dose of IP. 3 received only placebo, 1 only NAL ER. Data summarized by actual treatment received (NAL ER/placebo), regardless of period; subjects receiving both counted in both.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	NAL ER

Reporting group description:

Subjects received NAL ER 27 mg QD to 54 mg BID over a 5-day period, and then maintained at 54 mg BID for 4 days. Dose was increased to 108 mg BID for 1 week followed by 162 mg, BID for 6 days in treatment period 1 or 2 of the study.

Reporting group title	Placebo

Reporting group description:

Subjects received placebo for 3 weeks through treatment period 1 or 2 of the study.

Serious adverse events	NAL ER	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 38 (2.63%)	1 / 40 (2.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Urosepsis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 40 (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	0 / 38 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	NAL ER	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 38 (92.11%)	26 / 40 (65.00%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 38 (26.32%)	0 / 40 (0.00%)	
occurrences (all)	10	0	
Somnolence			
subjects affected / exposed	9 / 38 (23.68%)	1 / 40 (2.50%)	
occurrences (all)	9	1	
Headache			
subjects affected / exposed	5 / 38 (13.16%)	5 / 40 (12.50%)	
occurrences (all)	5	5	
Lethargy			
subjects affected / exposed	3 / 38 (7.89%)	2 / 40 (5.00%)	
occurrences (all)	3	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	12 / 38 (31.58%)	3 / 40 (7.50%)	
occurrences (all)	12	3	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	16 / 38 (42.11%)	0 / 40 (0.00%)	
occurrences (all)	16	0	
Constipation			
subjects affected / exposed	11 / 38 (28.95%)	2 / 40 (5.00%)	
occurrences (all)	11	2	
Vomiting			
subjects affected / exposed	7 / 38 (18.42%)	5 / 40 (12.50%)	
occurrences (all)	7	5	
Dry Mouth			
subjects affected / exposed	5 / 38 (13.16%)	1 / 40 (2.50%)	
occurrences (all)	5	1	
Diarrhoea			
subjects affected / exposed	3 / 38 (7.89%)	6 / 40 (15.00%)	
occurrences (all)	3	6	
Respiratory, thoracic and mediastinal			

disorders Dyspnea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	 6 / 38 (15.79%) 6 3 / 38 (7.89%) 3	 2 / 40 (5.00%) 2 6 / 40 (15.00%) 6	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	 5 / 38 (13.16%) 5	 0 / 40 (0.00%) 0	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 4 / 38 (10.53%) 4	 3 / 40 (7.50%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2019	Incorporated MHRA feedback: • Added exclusion for patients taking medications which may induce serotonin syndrome. • Added exclusion for patients taking benzodiazepines, alcohol, and other CNS depressants. • Deleted the following sentence from Section 9.3 ("Procedures for Breaking the Randomization Code"), "Investigators contemplating unblinding a subject should make every effort to contact the Medical Monitor prior to unblinding." Unblinding of treatment assignments is at the discretion of the site medical personnel.
13 June 2019	Incorporated suggestions in from the overall study team/Investigators based on the experiences with practical implementations of the protocol. • Modified the primary objectives to update the definition of 'daytime' wherein the digital cough monitor was the tool used to obtain cough frequency. The text related to the primary efficacy endpoint was updated to be consistent with the primary objective. • Modified the secondary objective based on the discussions with the scientific team and the cough monitor experts. The text related to secondary endpoint was also updated to be consistent with the secondary objective. • Increased the number of sites from 10 sites to approximately 15. • Updated the study procedures related to: - inclusion of triplicate ECG runs, - use of e-diary, - administration of certain scales in the study that will use the e-diary, - use and restrictions of opioid medication, - corrections of previous SOWS document, - administration of the Cough Severity Numerical Rating Scale during the study, - removal of cough monitor in relation to dosing and procedure to return it. • Corrected the administrative issues and other minor errors.

15 November 2019	Incorporated suggestions from the overall investigative sites; based on their experiences with practical implementation of the protocol. • Updated the exclusion criteria related to: - ECG assessments where the ECG assessments had to be performed in triplicate within the 3-5 minute period and if any of the 3 tracings were out of range, the subject had to be excluded, - length of time and modality constituting the continuous oxygen therapy, - limitation of alcohol consumption instead of prohibition during the study treatment due to potential CNS effects • Clarified the study procedures related to: - the timeframe (29 days) for randomization with relation to the Screening period - clinical laboratory tests where subjects had to be in a fasting state at the time of the laboratory assessments unless contraindicated due to clinical reasons - inclusion of rescreening at the discretion of the medical monitor and written permission from the Sponsor - spirometry - swallow test - safety monitoring and assessments regarding clarification that ECGs had to be locally reviewed at the site level (for safety) in addition to the central cardiac laboratory-read. • Corrected minor administrative errors for clarity and consistency of suggested order of procedures.
17 July 2020	Updated study procedures as part of the mitigation strategies due to COVID-19 pandemic: - extended the overall study timelines due to enrollment challenges and to provide greater flexibility to sites for scheduling subject visits - added potential countries to the study - reduced the number and frequency of the interpersonal (face-to-face) contact between subject population and the site personnel for the efficacy and safety assessments to reduce exposure of this high-risk subject population - increased the enrollment of subjects to allow for the possibility that COVID-19 related disruption could result in the premature discontinuation of subjects - allowed for utilization of the telemedicine in order to decrease face-to-face contact and reduce exposure of high risk subject population - provided greater flexibility to sites for scheduling subject visits and facilitate adherence to protocol requirements - provided administrative clarification throughout the protocol including for rescreening subjects - provided administrative changes throughout the protocol for clarity. • Clarified the statistical analysis methodology for data analysis using continuous-based methods • Clarified the wording and rationale for use of the e-diary instrument to capture data from EXACT 14-item e-diary Tool and E-RS Diary Cough and Breathlessness Scales

11 June 2021	Clarified the QTcF values in exclusion criteria #30 and 31 to prevent exclusion of subjects who were presented with Right Bundle Branch block. • Modified the withdrawal criteria related to QTcF to accurately reflect the electrophysiologically meaningful change on ECG parameters that would be used as the basis for excluding subjects from the study. • Deleted text related to QTcF>500 ms was deleted in sections related to ECG assessments as QTcF clarifications and appropriate actions to be taken are provided in the withdrawal criteria section. • Modified text in sections related to ECG assessments to clarify that local ECG read was for safety purposes and central ECG read was related to subject inclusion/withdrawal. • Corrected minor administrative errors.
14 December 2021	Modified text related to sample size and power to allow for a potential statistical update when a minimum of 12 subjects had completed the study periods for the purposes of determining whether POC could be established prior to complete enrollment of the study. • Updated the Sponsor contact information was updated. • Other administrative updates were done as needed for consistency with the above changes (additions to abbreviations list, updated document date and version number).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
25 March 2020	Enrollment was paused in the study on 25 March 2020 due to COVID-19 restrictions imposed in the United Kingdom, including movement restrictions and shielding of vulnerable populations. Subjects in screening were not randomized, and no further subjects were invited for screening. Screening and enrollment into the study recommenced from October 2020, only after the study protocol was amended and received relevant ethics and regulatory approvals, and in compliance with local COVID-19 restrictions.	01 October 2020

Notes:

Limitations and caveats

None reported