Clinical trial results:
A DOUBLE-BLIND, RANDOMISED, PLACEBO CONTROLLED, TWO PERIOD CROSS-OVER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ORVEPITANT IN CHRONIC COUGH IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

Summary

EudraCT number	2021-006278-22
Trial protocol	NL
Global end of trial date	19 June 2024

Results information

Result version number	v1 (current)
This version publication date	07 August 2025
First version publication date	07 August 2025

Trial information

Trial identification

Sponsor protocol code	ORV-PF-01

Additional study identifiers

ISRCTN number	ISRCTN12372820
ClinicalTrials.gov id (NCT number)	NCT05185089
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NeRRe Therapeutics Ltd
Sponsor organisation address	SBC, Incubator Building, Gunnels Wood Road, Stevenage, United Kingdom, SG1 2FX
Public contact	Susan Seymore, NeRRe Therapeutics Ltd, info@nerretherapeutics.com
Scientific contact	Dr. Steve Pawsey, NeRRe Therapeutics Ltd, info@nerretherapeutics.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	16 July 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 June 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Main objective of the trial:
• To evaluate the effect of orvepitant once daily on cough severity, as perceived by patients, with IPF

• To evaluate the safety of orvepitant once daily in patients with IPF

Protection of trial subjects:

Trial selection criteria excluded subjects that could not participate safely in the study and medications with potential interactions with the study drug were restricted or prohibited. Subject safety was closely monitored by regular safety assessments (vital signs, spirometry, physical exams, ECGs and blood & urine tests) and AEs were continuously monitored. The safety of the study drug also monitored by an independent Data Safety Monitoring Board.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2022
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	Netherlands: 5
Country: Number of subjects enrolled	United Kingdom: 54
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	80
EEA total number of subjects	5

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	12
From 65 to 84 years	66
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted between 01 August 2022 and 19 June 2024 at 37 sites in the USA, UK and NL (of which 32 sites screened at least one subject and 28 randomised at least one subject. A total of 123 subjects were screened, of whom 80 (65.0%) completed Screening and were randomised.

Pre-assignment

Screening details:

Subjects who satisfied all criteria and in whom no clinically relevant laboratory abnormalities were anticipated, were provided with an eDiary and trained on its use. The diary was then completed throughout the screening period before the subject returned for the baseline visit.

Period 1

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

Blinding implementation details:

The study was conducted in a double-blind manner, with the subjects, Investigators and Sponsor’s study management team (and including CROs) all blinded to the treatment allocated.
Both orvepitant (10 and 30 mg) and placebo were presented as white tablets, identical in size and shape.

Arms

Are arms mutually exclusive?	No
Arm title	Placebo (10 mg Cohort)

Arm description:

Placebo once-daily for 4 weeks in either Period A or Period B (subjects assigned to orvepitant 10mg cohort).

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

Dosage and administration details:

One placebo tablet (oral) once-daily for 4 weeks

Arm title	Orvepitant 10mg

Arm description:

Orvepitant 10 mg once-daily for 4 weeks in either Period A or Period B.

Arm type	Experimental
Investigational medicinal product name	Orvepitant 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One 10 mg orvepitant tablet (oral) once-daily for 4 weeks

Arm title	Placebo (30 mg Cohort)

Arm description:

Placebo once-daily for 4 weeks in either Period A or Period B (subjects assigned to orvepitant 30mg

cohort).

Arm type	Placebo
Investigational medicinal product name	Placebo 30 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One placebo tablet (oral) once-daily for 4 weeks

Arm title	Orvepitant 30mg

Arm description:

Orvepitant 30 mg once-daily for 4 weeks in either Period A or Period B.

Arm type	Experimental
Investigational medicinal product name	Orvepitant 30mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One 30 mg orvepitant tablet (oral) once-daily for 4 weeks

Number of subjects in period 1	Placebo (10 mg Cohort)	Orvepitant 10mg	Placebo (30 mg Cohort)
Started	40	40	39
Completed	39	39	39
Not completed	1	1	0
Adverse event, serious fatal	1	-	-
Adverse event, non-fatal	-	1	-

Number of subjects in period 1	Orvepitant 30mg
Started	40
Completed	39
Not completed	1
Adverse event, serious fatal	-
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups

Reporting group title	Treatment Period A+B

Reporting group description: -

Reporting group values	Treatment Period A+B	Total	
Number of subjects	80	80	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	12	12	
From 65-84 years	66	66	
85 years and over	2	2	
Age continuous Units: years			
arithmetic mean	71.9		
standard deviation	± 7.17	-	
Gender categorical Units: Subjects			
Female	21	21	
Male	59	59	

End points

End points reporting groups

Reporting group title	Placebo (10 mg Cohort)
Reporting group description:	
Placebo once-daily for 4 weeks in either Period A or Period B (subjects assigned to orvepitant 10mg cohort).	
Reporting group title	Orvepitant 10mg
Reporting group description:	
Orvepitant 10 mg once-daily for 4 weeks in either Period A or Period B.	
Reporting group title	Placebo (30 mg Cohort)
Reporting group description:	
Placebo once-daily for 4 weeks in either Period A or Period B (subjects assigned to orvepitant 30mg cohort).	
Reporting group title	Orvepitant 30mg
Reporting group description:	
Orvepitant 30 mg once-daily for 4 weeks in either Period A or Period B.	

Primary: Mean Change from Baseline to Week 4 in Weekly Average of the Daily IPF Coughing Severity Scale

End point title	Mean Change from Baseline to Week 4 in Weekly Average of the Daily IPF Coughing Severity Scale
End point description:	
Note, there was a significant (p=0.048) treatment by period interaction for the 30 mg cohort.	
End point type	Primary
End point timeframe:	
Baseline to Week 4	

End point values	Placebo (10 mg Cohort)	Orvepitant 10mg	Placebo (30 mg Cohort)	Orvepitant 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	39	39	39
Units: Units on a scale				
least squares mean (standard error)	-0.6 (± 0.219)	-0.66 (± 0.219)	-0.26 (± 0.207)	-0.84 (± 0.207)

Statistical analyses

Statistical analysis title	Difference versus placebo at Week 4 (10mg)
Comparison groups	Orvepitant 10mg v Placebo (10 mg Cohort)

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.989
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	0.63
Variability estimate	Standard error of the mean
Dispersion value	0.305

Statistical analysis title	Difference versus placebo at Week 4 (30mg)
Comparison groups	Orvepitant 30mg v Placebo (30 mg Cohort)
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.16
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.293

Secondary: Mean Change from Baseline to Week 4 in Weekly Average of the Urge to Cough Scale Score

End point title	Mean Change from Baseline to Week 4 in Weekly Average of the Urge to Cough Scale Score

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 4

End point values	Placebo (10 mg Cohort)	Orvepitant 10mg	Placebo (30 mg Cohort)	Orvepitant 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	39	39	39
Units: Units on a scale				
least squares mean (standard error)	-0.47 (± 0.213)	-0.61 (± 0.212)	-0.30 (± 0.191)	-0.76 (± 0.191)

Statistical analyses

Statistical analysis title	Difference versus placebo at Week 4 (10mg)
Comparison groups	Placebo (10 mg Cohort) v Orvepitant 10mg
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.639
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	0.45
Variability estimate	Standard error of the mean
Dispersion value	0.291

Statistical analysis title	Difference versus placebo at Week 4 (30mg)
Comparison groups	Placebo (30 mg Cohort) v Orvepitant 30mg
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.092
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.08
Variability estimate	Standard error of the mean
Dispersion value	0.271

Secondary: Mean Change from Baseline to Week 4 in Weekly Average of the Cough

Frequency Scale Score	
End point title	Mean Change from Baseline to Week 4 in Weekly Average of the Cough Frequency Scale Score

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 4

End point values	Placebo (10 mg Cohort)	Orvepitant 10mg	Placebo (30 mg Cohort)	Orvepitant 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	39	39	39
Units: units on a scale				
least squares mean (standard error)	-0.19 (± 0.083)	-0.15 (± 0.083)	-0.05 (± 0.067)	-0.29 (± 0.067)

Statistical analyses

Statistical analysis title	Difference versus placebo at Week 4 (10mg)
Comparison groups	Placebo (10 mg Cohort) v Orvepitant 10mg
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.65
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.26
Variability estimate	Standard error of the mean
Dispersion value	0.104

Statistical analysis title	Difference versus placebo at Week 4 (30mg)
Comparison groups	Placebo (30 mg Cohort) v Orvepitant 30mg

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	-0.06
Variability estimate	Standard error of the mean
Dispersion value	0.085

Secondary: Mean Change from Baseline in Week 4 of the Dyspnoea Scale Score

End point title	Mean Change from Baseline in Week 4 of the Dyspnoea Scale Score
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to Week 4	

End point values	Placebo (10 mg Cohort)	Orvepitant 10mg	Placebo (30 mg Cohort)	Orvepitant 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	39	39	39
Units: Units on a scale				
least squares mean (standard error)	-0.26 (± 0.172)	-0.21 (± 0.172)	0.01 (± 0.148)	-0.44 (± 0.148)

Statistical analyses

Statistical analysis title	Difference versus placebo at Week 4 (10mg)
Comparison groups	Placebo (10 mg Cohort) v Orvepitant 10mg
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.856
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	0.53
Variability estimate	Standard error of the mean
Dispersion value	0.24

Statistical analysis title	Difference versus placebo at Week 4 (30mg)
Comparison groups	Placebo (30 mg Cohort) v Orvepitant 30mg
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.036
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	-0.03
Variability estimate	Standard error of the mean
Dispersion value	0.21

Secondary: Mean Change from Baseline to Week 4 in LCQ Total Scores

End point title	Mean Change from Baseline to Week 4 in LCQ Total Scores
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to Week 4	

End point values	Placebo (10 mg Cohort)	Orvepitant 10mg	Placebo (30 mg Cohort)	Orvepitant 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	39	39	39	39
Units: Units on a scale				
least squares mean (standard error)	1.06 (± 0.326)	1.25 (± 0.326)	0.24 (± 0.387)	1.48 (± 0.388)

Statistical analyses

Statistical analysis title	Difference versus placebo at Week 4 (10mg)
Comparison groups	Placebo (10 mg Cohort) v Orvepitant 10mg
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.678
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	1.11
Variability estimate	Standard error of the mean
Dispersion value	0.462

Statistical analysis title	Difference versus placebo at Week 4 (30mg)
Comparison groups	Placebo (30 mg Cohort) v Orvepitant 30mg
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	2.31
Variability estimate	Standard error of the mean
Dispersion value	0.525

Secondary: Mean Change from Baseline to Week 4 in 24-hour Cough Frequency (Number of Coughs per Hour)

End point title	Mean Change from Baseline to Week 4 in 24-hour Cough Frequency (Number of Coughs per Hour)
End point description:	
Mean change from Baseline to Week 4 in 24-hour cough frequency	
End point type	Secondary
End point timeframe:	
Baseline to Week 4 in 24-hour cough frequency	

End point values	Placebo (10 mg Cohort)	Orvepitant 10mg	Placebo (30 mg Cohort)	Orvepitant 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	31	32	32
Units: Coughs per hour (ratio vs baseline)				
least squares mean (standard error)	0.93 (± 1.114)	1.00 (± 1.115)	0.84 (± 1.113)	0.87 (± 1.112)

Statistical analyses

Statistical analysis title	Difference versus placebo at Week 4 (10mg)
Comparison groups	Placebo (10 mg Cohort) v Orvepitant 10mg
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.438
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.33
Variability estimate	Standard error of the mean
Dispersion value	1.105

Statistical analysis title	Difference versus placebo at Week 4 (30mg)
Comparison groups	Placebo (30 mg Cohort) v Orvepitant 30mg
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.761
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.31
Variability estimate	Standard error of the mean
Dispersion value	1.222

Secondary: Mean Change from Baseline to Week 4 in 24-hour Cough Frequency

(Number of Bouts per Hour)	
End point title	Mean Change from Baseline to Week 4 in 24-hour Cough Frequency (Number of Bouts per Hour)
End point description:	

End point type	Secondary
End point timeframe:	
Baseline to Week 4	

End point values	Placebo (10 mg Cohort)	Orvepitant 10mg	Placebo (30 mg Cohort)	Orvepitant 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	31	32	32
Units: Bouts per hour (ratio vs baseline)				
least squares mean (standard error)	0.91 (± 1.089)	1.00 (± 1.090)	0.82 (± 1.087)	0.88 (± 1.087)

Statistical analyses

Statistical analysis title	Difference versus placebo at Week 4 (10mg)
Comparison groups	Placebo (10 mg Cohort) v Orvepitant 10mg
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.287
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.29
Variability estimate	Standard error of the mean
Dispersion value	1.084

Statistical analysis title	Difference versus placebo at Week 4 (30mg)
Comparison groups	Placebo (30 mg Cohort) v Orvepitant 30mg
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.42
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.08

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.29
Variability estimate	Standard error of the mean
Dispersion value	1.092

Secondary: Mean Change from Baseline to Week 4 in 24-hour Cough Frequency (Number of Coughs per Bout)

End point title	Mean Change from Baseline to Week 4 in 24-hour Cough Frequency (Number of Coughs per Bout)
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to Week 4	

End point values	Placebo (10 mg Cohort)	Orvepitant 10mg	Placebo (30 mg Cohort)	Orvepitant 30mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	30	32	32
Units: Coughs per bout (ratio vs baseline)				
least squares mean (standard error)	0.91 (± 1.027)	0.92 (± 1.027)	0.98 (± 1.028)	0.89 (± 1.028)

Statistical analyses

Statistical analysis title	Difference versus placebo at Week 4 (10mg)
Comparison groups	Placebo (10 mg Cohort) v Orvepitant 10mg
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.765
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.05
Variability estimate	Standard error of the mean
Dispersion value	1.022

Statistical analysis title	Difference versus placebo at Week 4 (30mg)
Comparison groups	Placebo (30 mg Cohort) v Orvepitant 30mg
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	0.97
Variability estimate	Standard error of the mean
Dispersion value	1.033

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout the study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups	
Reporting group title	Placebo (10 mg Cohort)
Reporting group description:	
AEs started during placebo treatment in a subject in the Orvepitant 10 mg cohort.	
Reporting group title	Orvepitant 10 mg
Reporting group description:	
AEs started during treatment with orvepitant 10 mg.	
Reporting group title	Placebo (30 mg Cohort)
Reporting group description:	
AEs started during placebo treatment in a subject in the Orvepitant 30 mg cohort.	
Reporting group title	Orvepitant 30 mg
Reporting group description:	
AEs started during treatment with orvepitant 30 mg	

Serious adverse events	Placebo (10 mg Cohort)	Orvepitant 10 mg	Placebo (30 mg Cohort)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 40 (5.00%)	1 / 40 (2.50%)	3 / 38 (7.89%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	0 / 40 (0.00%)	0 / 40 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	0 / 38 (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
Angina pectoris			

subjects affected / exposed	0 / 40 (0.00%)	0 / 40 (0.00%)	0 / 38 (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			
Obstructive pancreatitis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 40 (0.00%)	0 / 38 (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
Respiratory, thoracic and mediastinal disorders			
Idiopathic pulmonary fibrosis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 40 (2.50%)	0 / 38 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 40 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 40 (2.50%)	0 / 40 (0.00%)	0 / 38 (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
COVID-19			
subjects affected / exposed	0 / 40 (0.00%)	0 / 40 (0.00%)	1 / 38 (2.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Orvepitant 30 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 39 (2.56%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Oxygen saturation decreased			

subjects affected / exposed	0 / 39 (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	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Obstructive pancreatitis			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Idiopathic pulmonary fibrosis			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
COVID-19			

subjects affected / exposed	0 / 39 (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: 5 %

Non-serious adverse events	Placebo (10 mg Cohort)	Orvepitant 10 mg	Placebo (30 mg Cohort)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 40 (45.00%)	30 / 40 (75.00%)	17 / 38 (44.74%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 40 (2.50%)	2 / 40 (5.00%)	2 / 38 (5.26%)
occurrences (all)	1	2	2
Headache			
subjects affected / exposed	3 / 40 (7.50%)	1 / 40 (2.50%)	1 / 38 (2.63%)
occurrences (all)	3	1	1
Lethargy			
subjects affected / exposed	0 / 40 (0.00%)	2 / 40 (5.00%)	0 / 38 (0.00%)
occurrences (all)	0	2	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 40 (7.50%)	3 / 40 (7.50%)	1 / 38 (2.63%)
occurrences (all)	3	3	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 40 (5.00%)	4 / 40 (10.00%)	1 / 38 (2.63%)
occurrences (all)	2	4	1
Abdominal pain upper			
subjects affected / exposed	0 / 40 (0.00%)	2 / 40 (5.00%)	0 / 38 (0.00%)
occurrences (all)	0	2	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 40 (2.50%)	2 / 40 (5.00%)	1 / 38 (2.63%)
occurrences (all)	1	2	1
Dyspnoea			

subjects affected / exposed	2 / 40 (5.00%)	0 / 40 (0.00%)	2 / 38 (5.26%)
occurrences (all)	2	0	2
Sputum increased			
subjects affected / exposed	0 / 40 (0.00%)	0 / 40 (0.00%)	1 / 38 (2.63%)
occurrences (all)	0	0	1
Haemoptysis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 40 (0.00%)	2 / 38 (5.26%)
occurrences (all)	0	0	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 40 (5.00%)	0 / 40 (0.00%)	0 / 38 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 40 (2.50%)	2 / 40 (5.00%)	0 / 38 (0.00%)
occurrences (all)	1	2	0
Myalgia			
subjects affected / exposed	1 / 40 (2.50%)	3 / 40 (7.50%)	0 / 38 (0.00%)
occurrences (all)	1	3	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 40 (2.50%)	3 / 40 (7.50%)	4 / 38 (10.53%)
occurrences (all)	1	3	4
Lower respiratory tract infection			
subjects affected / exposed	0 / 40 (0.00%)	3 / 40 (7.50%)	2 / 38 (5.26%)
occurrences (all)	0	3	3
COVID-19			
subjects affected / exposed	1 / 40 (2.50%)	1 / 40 (2.50%)	1 / 38 (2.63%)
occurrences (all)	1	1	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 40 (0.00%)	3 / 40 (7.50%)	0 / 38 (0.00%)
occurrences (all)	0	3	0

Non-serious adverse events	Orvepitant 30 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 39 (51.28%)		

Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Lethargy			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Sputum increased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Haemoptysis			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			

Insomnia			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Lower respiratory tract infection			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
COVID-19			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2022	Protocol version 2.0 (Amendment 1) •Revisions to patient reported outcomes made in response to FDA feedback on protocol. •This was the first version of the protocol implemented in the study (version 1.0 never implemented). •A country specific version was implemented in the Netherlands (Version 2.1 NL 05 Jul 2022) to incorporate additional NL-specific changes, requested by the ethics committee, namely to reflect the 2013 version of the Declaration of Helsinki, add a section addressing post-trial access to IMP, and clarify that subjects would be randomised to cohort and treatment order using a single, blocked randomisation list.
05 April 2023	Protocol version 3.0 (Amendment 2) was a non-substantial amendment: • Small changes were made to several of the selection criteria but without meaningfully changing the overall nature of the recruited study population. •Clarified the use of concomitant respiratory medications. •Clarified the requirements with respect to PFTs. •Removed the limitation on reducing the sample size if the sample size re-estimate showed the study was likely to be over-powered. •Clarified the concomitant use of CYP3A4 inhibitors and inducers and P-glycoprotein inhibitors. Country-specific versions were implemented in the UK & NL: •The UK version (Version 3.1 UK 05April2023) incorporated allowance for the collection of additional blood samples for analysis of more biomarkers. •The NL version (Version 3.1 NL 05April2023) included the previous NL-specific changes.
16 May 2024	Protocol version 4.0 (Amendment 3) was a non-substantial amendment implemented in US only to correct some typographical errors in the sample size section and fully align statistical text in the protocol with the equivalent text in the SAP, at the request of the FDA.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported