Clinical trial results:
A DOUBLE-BLIND, RANDOMIZED, PLACEBO CONTROLLED STUDY OF THE EFFICACY AND SAFETY OF THREE DOSES OF ORVEPITANT IN SUBJECTS WITH CHRONIC REFRACTORY COUGH

Summary

EudraCT number	2016-004979-49
Trial protocol	GB
Global end of trial date	05 February 2019

Results information

Result version number	v1 (current)
This version publication date	06 February 2022
First version publication date	06 February 2022

Trial information

Trial identification

Sponsor protocol code	VOLCANO-2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02993822
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NeRRe Therapeutics Ltd
Sponsor organisation address	Gunnels Wood Road, Stevenage, United Kingdom, SG1 2FX
Public contact	Elizabeth Ballantyne, NeRRe Therapeutics Ltd., +44 (0) 1438906960, Elizabeth.Ballantyne@nerretherapeutics.com
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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	24 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 January 2019
Global end of trial reached?	Yes
Global end of trial date	05 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of once daily doses of 10 mg, 20 mg, and 30 mg orvepitant versus placebo in reducing awake objective cough frequency

Protection of trial subjects:

No specific measures required.

Background therapy:

None

Evidence for comparator:

Placebo was used as the reference agent in the study to allow comparisons of the effects of orvepitant on both safety and efficacy, and was considered justifiable in relation to the duration of the study and the nature of the disorder being evaluated. Placebo has been used commonly as the reference agent in similar trials.

Actual start date of recruitment	02 May 2017
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	United Kingdom: 113
Country: Number of subjects enrolled	United States: 199
Country: Number of subjects enrolled	Canada: 3
Worldwide total number of subjects	315
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)	183
From 65 to 84 years	129
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

USA recruitment from 31-May-2017 to 28-Sep-2018
UK recruitment from 26-Sep-2017 to 28-Sep-2018
Canada recruitment from 29-Jun-2018 to 28-Sep-2018

Pre-assignment

Screening details:

488 subjects were screened, of whom 315 (64.5%) completed screening and were randomised. Screening failures occurred due to not meeting inclusion criteria (74 subjects [15.2%]) or exclusion criteria (79 subjects [16.2%]), withdrawal of consent (nine [1.8%] subjects) and AEs (2 [0.4%] subjects). All other reasons reported in individual subjects.

Period 1

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

Blinding implementation details:

The study was conducted in a double blind manner, with the subjects, Investigators and Sponsor all blinded to the treatment allocated. Both orvepitant and placebo were presented as white tablets, identical in size, colour and shape.

Arms

Are arms mutually exclusive?	Yes
Arm title	Orvepitant 10mg

Arm description:

Subjects receive orvepitant 10 mg

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

Dosage and administration details:

Orvepitant 10mg tablet administered orally once daily for 12 weeks

Arm title	Orvepitant 20mg

Arm description:

Subjects receive orvepitant 20mg

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

Dosage and administration details:

Orvepitant 20mg tablet administered orally once daily for 12 weeks

Arm title	Orvepitant 30mg

Arm description:	
Subjects receive orvepitant 30mg	
Arm type	Experimental
Investigational medicinal product name	Orvepitant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Orvepitant 30mg tablet administered orally once daily for 12 weeks	

Arm title	Reference
Arm description:	
Subjects receive placebo	
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:	
Placebo tablet administered orally once daily for 12 weeks	

Number of subjects in period 1	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg
Started	79	78	79
Completed	69	74	69
Not completed	10	4	10
Consent withdrawn by subject	4	2	2
Adverse event, non-fatal	3	1	7
Unable to attend follow-up due to illness	-	-	-
Lost to follow-up	1	-	1
Protocol deviation	1	-	-
Lack of efficacy	1	-	-
Lack of efficacy	-	1	-

Number of subjects in period 1	Reference
Started	79
Completed	75
Not completed	4
Consent withdrawn by subject	3
Adverse event, non-fatal	-
Unable to attend follow-up due to illness	1
Lost to follow-up	-

Protocol deviation	-
Lack of efficacy	-
Lack of efficacy	-

Baseline characteristics

Reporting groups	
Reporting group title	Orvepitant 10mg
Reporting group description: Subjects receive orvepitant 10 mg	
Reporting group title	Orvepitant 20mg
Reporting group description: Subjects receive orvepitant 20mg	
Reporting group title	Orvepitant 30mg
Reporting group description: Subjects receive orvepitant 30mg	
Reporting group title	Reference
Reporting group description: Subjects receive placebo	

Reporting group values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg
Number of subjects	79	78	79
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	46	44	56
From 65-84 years	32	33	22
85 years and over	1	1	1
Age continuous Units: years			
arithmetic mean	62.29	59.86	59.47
standard deviation	± 9.850	± 13.173	± 10.020
Gender categorical Units: Subjects			
Female	65	69	60
Male	14	9	19

Reporting group values	Reference	Total	
Number of subjects	79	315	
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)	37	183	
From 65-84 years	42	129	
85 years and over	0	3	
Age continuous			
Units: years			
arithmetic mean	62.24		
standard deviation	± 11.815	-	
Gender categorical			
Units: Subjects			
Female	59	253	
Male	20	62	

End points

End points reporting groups	
Reporting group title	Orvepitant 10mg
Reporting group description: Subjects receive orvepitant 10 mg	
Reporting group title	Orvepitant 20mg
Reporting group description: Subjects receive orvepitant 20mg	
Reporting group title	Orvepitant 30mg
Reporting group description: Subjects receive orvepitant 30mg	
Reporting group title	Reference
Reporting group description: Subjects receive placebo	

Primary: Change from baseline to Week 12 in awake objective cough frequency	
End point title	Change from baseline to Week 12 in awake objective cough frequency
End point description: The change from Baseline to Week 12 in awake objective cough frequency measured with an automated cough monitor (ACM) and analysed after taking logs (to base 10).	
End point type	Primary
End point timeframe: Change from baseline to Week 12	

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	72	67	70
Units: coughs/hour (log transformed)				
arithmetic mean (standard deviation)	-0.185 (± 0.3258)	-0.912 (± 0.3405)	-0.271 (± 0.4055)	-0.243 (± 0.3225)

Statistical analyses

Statistical analysis title	Primary variable (10 mg)
Statistical analysis description: Change from baseline to each visit (Week 2, Week 4 and Week 12) in log transformed awake objective cough frequency was analysed using a mixed model for repeated measures (MMRM) with restricted maximum likelihood (REML) estimation. The treatment effect at Week 12 was estimated using the ratio of geometric means (i.e. the difference between the treatments least squares means [adjusted means] on the log scale, back transformed to the original scale).	
Comparison groups	Reference v Orvepitant 10mg

Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.324
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.49
Variability estimate	Standard deviation

Notes:

[1] - This study was designed to test for superiority. The null hypothesis for the treatment comparison was that there is no difference between orvepitant treatment group and placebo in mean change in log transformed (to base 10) awake objective cough frequency at Week 12 compared to Baseline. The alternative hypothesis was that there is a difference. Two-sided tests with alpha=0.05 were used to test this hypothesis.

Statistical analysis title	Primary variable (20 mg)

Statistical analysis description:

Change from baseline to each visit (Week 2, Week 4 and Week 12) in log transformed awake objective cough frequency was analysed using a mixed model for repeated measures (MMRM) with restricted maximum likelihood (REML) estimation. The treatment effect at Week 12 was estimated using the ratio of geometric means (i.e. the difference between the treatments least squares means [adjusted means] on the log scale, back transformed to the original scale).

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.332
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.48
Variability estimate	Standard deviation

Notes:

[2] - This study was designed to test for superiority. The null hypothesis for the treatment comparison was that there is no difference between orvepitant treatment group and placebo in mean change in log transformed (to base 10) awake objective cough frequency at Week 12 compared to Baseline. The alternative hypothesis was that there is a difference. Two-sided tests with alpha=0.05 were used to test this hypothesis.

Statistical analysis title	Primary variable (30 mg)

Statistical analysis description:

Change from baseline to each visit (Week 2, Week 4 and Week 12) in log transformed awake objective cough frequency was analysed using a mixed model for repeated measures (MMRM) with restricted maximum likelihood (REML) estimation. The treatment effect at Week 12 was estimated using the ratio of geometric means (i.e. the difference between the treatments least squares means [adjusted means] on the log scale, back transformed to the original scale).

Comparison groups	Reference v Orvepitant 30mg

Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.531
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.2
Variability estimate	Standard deviation

Notes:

[3] - This study was designed to test for superiority. The null hypothesis for the treatment comparison was that there is no difference between orvepitant treatment group and placebo in mean change in log transformed (to base 10) awake objective cough frequency at Week 12 compared to Baseline. The alternative hypothesis was that there is a difference. Two-sided tests with alpha=0.05 were used to test this hypothesis.

Secondary: Change in awake objective cough frequency at Week 2 compared to baseline

End point title	Change in awake objective cough frequency at Week 2 compared to baseline

End point description:

The change from Baseline to Week 2 in awake objective cough frequency measured with an automated cough monitor (ACM) and analysed after taking logs (to base 10).

End point type	Secondary

End point timeframe:

Change from Baseline to Week 2

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73	74	75	73
Units: coughs/hour (log transformed)				
arithmetic mean (standard deviation)	-0.180 (± 0.2791)	-0.181 (± 0.3142)	-0.215 (± 0.2515)	-0.139 (± 0.2892)

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

Change from baseline to each visit (Week 2, Week 4 and Week 12) in log transformed awake objective cough frequency was analysed using a mixed model for repeated measures (MMRM) with restricted maximum likelihood (REML) estimation. The treatment effect at Week 2 was estimated using the ratio of geometric means (i.e. the difference between the treatments least squares means [adjusted means] on the log scale, back transformed to the original scale).

Comparison groups	Orvepitant 10mg v Reference

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.482
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.15
Variability estimate	Standard deviation

Notes:

[4] - This study was designed to test for superiority. The null hypothesis for the treatment comparison was that there is no difference between orvepitant treatment group and placebo in mean change in log transformed (to base 10) awake objective cough frequency at Week 2 compared to Baseline. The alternative hypothesis was that there is a difference. Two-sided tests with alpha=0.05 were used to test this hypothesis.

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

Change from baseline to each visit (Week 2, Week 4 and Week 12) in log transformed awake objective cough frequency was analysed using a mixed model for repeated measures (MMRM) with restricted maximum likelihood (REML) estimation. The treatment effect at Week 2 was estimated using the ratio of geometric means (i.e. the difference between the treatments least squares means [adjusted means] on the log scale, back transformed to the original scale).

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.46
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.14
Variability estimate	Standard deviation

Notes:

[5] - This study was designed to test for superiority. The null hypothesis for the treatment comparison was that there is no difference between orvepitant treatment group and placebo in mean change in log transformed (to base 10) awake objective cough frequency at Week 2 compared to Baseline. The alternative hypothesis was that there is a difference. Two-sided tests with alpha=0.05 were used to test this hypothesis.

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

Change from baseline to each visit (Week 2, Week 4 and Week 12) in log transformed awake objective cough frequency was analysed using a mixed model for repeated measures (MMRM) with restricted maximum likelihood (REML) estimation. The treatment effect at Week 2 was estimated using the ratio of geometric means (i.e. the difference between the treatments least squares means [adjusted means] on the log scale, back transformed to the original scale).

Comparison groups	Reference v Orvepitant 30mg

Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.144
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.06
Variability estimate	Standard deviation

Notes:

[6] - This study was designed to test for superiority. The null hypothesis for the treatment comparison was that there is no difference between orvepitant treatment group and placebo in mean change in log transformed (to base 10) awake objective cough frequency at Week 2 compared to Baseline. The alternative hypothesis was that there is a difference. Two-sided tests with alpha=0.05 were used to test this hypothesis.

Secondary: Change in awake objective cough frequency at Week 4 compared to baseline

End point title	Change in awake objective cough frequency at Week 4 compared to baseline

End point description:

The change from Baseline to Week 4 in awake objective cough frequency measured with an automated cough monitor (ACM) and analyzed after taking logs (to base 10).

End point type	Secondary

End point timeframe:

Change from Baseline to Week 4

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	77	75	72
Units: coughs/hour (log transformed)				
arithmetic mean (standard deviation)	-0.188 (± 0.3292)	-0.231 (± 0.3665)	-0.211 (± 0.2994)	-0.169 (± 0.2699)

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

Change from baseline to each visit (Week 2, Week 4 and Week 12) in log transformed awake objective cough frequency was analysed using a mixed model for repeated measures (MMRM) with restricted maximum likelihood (REML) estimation. The treatment effect at Week 4 was estimated using the ratio of geometric means (i.e. the difference between the treatments least squares means [adjusted means] on the log scale, back transformed to the original scale).

Comparison groups	Orvepitant 10mg v Reference

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.992
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.27
Variability estimate	Standard deviation

Notes:

[7] - This study was designed to test for superiority. The null hypothesis for the treatment comparison was that there is no difference between orvepitant treatment group and placebo in mean change in log transformed (to base 10) awake objective cough frequency at Week 4 compared to Baseline. The alternative hypothesis was that there is a difference. Two-sided tests with alpha=0.05 were used to test this hypothesis.

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

Change from baseline to each visit (Week 2, Week 4 and Week 12) in log transformed awake objective cough frequency was analysed using a mixed model for repeated measures (MMRM) with restricted maximum likelihood (REML) estimation. The treatment effect at Week 4 was estimated using the ratio of geometric means (i.e. the difference between the treatments least squares means [adjusted means] on the log scale, back transformed to the original scale).

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.387
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.14
Variability estimate	Standard deviation

Notes:

[8] - This study was designed to test for superiority. The null hypothesis for the treatment comparison was that there is no difference between orvepitant treatment group and placebo in mean change in log transformed (to base 10) awake objective cough frequency at Week 4 compared to Baseline. The alternative hypothesis was that there is a difference. Two-sided tests with alpha=0.05 were used to test this hypothesis.

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

Change from baseline to each visit (Week 2, Week 4 and Week 12) in log transformed awake objective cough frequency was analysed using a mixed model for repeated measures (MMRM) with restricted maximum likelihood (REML) estimation. The treatment effect at Week 4 was estimated using the ratio of geometric means (i.e. the difference between the treatments least squares means [adjusted means] on the log scale, back transformed to the original scale).

Comparison groups	Reference v Orvepitant 30mg

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.6
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.19
Variability estimate	Standard deviation

Notes:

[9] - This study was designed to test for superiority. The null hypothesis for the treatment comparison was that there is no difference between orvepitant treatment group and placebo in mean change in log transformed (to base 10) awake objective cough frequency at Week 4 compared to Baseline. The alternative hypothesis was that there is a difference. Two-sided tests with alpha=0.05 were used to test this hypothesis.

Secondary: Change in the Leicester Cough Questionnaire (LCQ) at Week 2 compared to baseline

End point title	Change in the Leicester Cough Questionnaire (LCQ) at Week 2 compared to baseline

End point description:

The LCQ is a 19 item questionnaire that assessed cough related quality of life. It has three domains (physical, psychological and social) and subjects were asked to complete it based on their experience in a recall period of 2 weeks. The total score range is 3 to 21 and domain scores each range from 1 to 7; a higher score indicated a better quality of life.
Subjects completed the LCQ whilst in the clinic at baseline/Day 1 (pre dose) and at Weeks 2, 4, 8, and 12.

End point type	Secondary

End point timeframe:

Change from Baseline to Week 2

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72	77	75	75
Units: Total score				
arithmetic mean (standard deviation)	2.41 (± 3.309)	2.37 (± 3.252)	2.93 (± 3.010)	1.24 (± 2.714)

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

The change from baseline in LCQ total score and the three domain scores was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline.
The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in LCQ total score and the three domain scores was analysed using a MMRM with

REML estimation.

Comparison groups	Orvepitant 10mg v Reference
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.042
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	2
Variability estimate	Standard deviation

Notes:

[10] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups are presented.

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

The change from baseline in LCQ total score and the three domain scores was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline.
The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in LCQ total score and the three domain scores was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.026
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	2
Variability estimate	Standard deviation

Notes:

[11] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups are presented.

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

The change from baseline in LCQ total score and the three domain scores was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline.
The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in LCQ total score and the three domain scores was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 30mg

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.003
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	2.4
Variability estimate	Standard deviation

Notes:

[12] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups are presented.

Secondary: Change in the Leicester Cough Questionnaire (LCQ) at Week 4 compared to baseline

End point title	Change in the Leicester Cough Questionnaire (LCQ) at Week 4 compared to baseline

End point description:

The LCQ is a 19 item questionnaire that assessed cough related quality of life. It has three domains (physical, psychological and social) and subjects were asked to complete it based on their experience in a recall period of 4 weeks. The total score range is 3 to 21 and domain scores each range from 1 to 7; a higher score indicated a better quality of life.
Subjects completed the LCQ whilst in the clinic at baseline/Day 1 (pre dose) and at Weeks 2, 4, 8, and 12

End point type	Secondary

End point timeframe:

Change from Baseline to Week 4

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	77	74	76
Units: Total score				
arithmetic mean (standard deviation)	2.50 (± 3.416)	2.15 (± 3.490)	2.98 (± 3.163)	1.61 (± 3.132)

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

The change from baseline in LCQ total score and the three domain scores was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline.
The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in LCQ total score and the three domain scores was analysed using a MMRM with REML estimation.

Comparison groups	Orvepitant 10mg v Reference

Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.25
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.7
Variability estimate	Standard deviation

Notes:

[13] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups are presented.

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

The change from baseline in LCQ total score and the three domain scores was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline.
The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in LCQ total score and the three domain scores was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.325
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	1.5
Variability estimate	Standard deviation

Notes:

[14] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups are presented.

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

The change from baseline in LCQ total score and the three domain scores was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline.
The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in LCQ total score and the three domain scores was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 30mg

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.029
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	2.2
Variability estimate	Standard deviation

Notes:

[15] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups are presented.

Secondary: Change in the Leicester Cough Questionnaire (LCQ) at Week 8 compared to baseline

End point title	Change in the Leicester Cough Questionnaire (LCQ) at Week 8 compared to baseline

End point description:

The LCQ is a 19 item questionnaire that assessed cough related quality of life. It has three domains (physical, psychological and social) and subjects were asked to complete it based on their experience in a recall period of 8 weeks. The total score range is 3 to 21 and domain scores each range from 1 to 7; a higher score indicated a better quality of life.
Subjects completed the LCQ whilst in the clinic at baseline/Day 1 (pre dose) and at Weeks 2, 4, 8, and 12

End point type	Secondary

End point timeframe:

Change from Baseline to Week 8

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	76	70	75
Units: Total score				
arithmetic mean (standard deviation)	2.78 (± 3.535)	2.19 (± 3.602)	2.82 (± 3.960)	1.34 (± 3.222)

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

The change from baseline in LCQ total score and the three domain scores was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline.
The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in LCQ total score and the three domain scores was analysed using a MMRM with REML estimation.

Comparison groups	Orvepitant 10mg v Reference

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.038
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	2.3
Variability estimate	Standard deviation

Notes:

[16] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups are presented.

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

The change from baseline in LCQ total score and the three domain scores was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline.
The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in LCQ total score and the three domain scores was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.118
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	2
Variability estimate	Standard deviation

Notes:

[17] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups are presented.

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

The change from baseline in LCQ total score and the three domain scores was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline.
The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in LCQ total score and the three domain scores was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 30mg

Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.025
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	2.4
Variability estimate	Standard deviation

Notes:

[18] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups are presented.

Secondary: Change in the Leicester Cough Questionnaire (LCQ) at Week 12 compared to baseline

End point title	Change in the Leicester Cough Questionnaire (LCQ) at Week 12 compared to baseline

End point description:

The LCQ is a 19 item questionnaire that assessed cough related quality of life. It has three domains (physical, psychological and social) and subjects were asked to complete it based on their experience in a recall period of 12 weeks. The total score range is 3 to 21 and domain scores each range from 1 to 7; a higher score indicated a better quality of life.
Subjects completed the LCQ whilst in the clinic at baseline/Day 1 (pre dose) and at Weeks 2, 4, 8, and 12

End point type	Secondary

End point timeframe:

Change from Baseline to Week 12

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	74	67	74
Units: Total score				
arithmetic mean (standard deviation)	2.38 (± 3.609)	2.09 (± 3.736)	3.23 (± 4.007)	1.50 (± 3.586)

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

The change from baseline in LCQ total score and the three domain scores was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline.
The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in LCQ total score and the three domain scores was analysed using a MMRM with REML estimation.

Comparison groups	Orvepitant 10mg v Reference

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.258
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	1.9
Variability estimate	Standard deviation

Notes:

[19] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups are presented.

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

The change from baseline in LCQ total score and the three domain scores was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline.
The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in LCQ total score and the three domain scores was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.243
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	1.8
Variability estimate	Standard deviation

Notes:

[20] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups are presented.

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

The change from baseline in LCQ total score and the three domain scores was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline.
The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in LCQ total score and the three domain scores was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 30mg

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.009
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	2.8
Variability estimate	Standard deviation

Notes:

[21] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups are presented.

Secondary: Change in the cough severity visual analogue scale (VAS) at Week 2 compared to baseline - Day-time

End point title	Change in the cough severity visual analogue scale (VAS) at Week 2 compared to baseline - Day-time

End point description:

The cough VAS is a 100 mm scale on which subjects indicated their severity of cough over the previous 24 hours, both during the day-time and during night time separately. The VAS ranged from "no cough" (0 mm) on the left to "worst cough" (100 mm) on the right.
Subjects completed the cough severity VAS at baseline/Day 1 (pre dose) and at Weeks 2, 4, 8, and 12.

End point type	Secondary

End point timeframe:

Change from Baseline to Week 2

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	77	75	75
Units: Score				
arithmetic mean (standard deviation)	-17.7 (± 26.06)	-10.5 (± 27.78)	-13.5 (± 22.93)	-6.3 (± 19.24)

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Orvepitant 10mg v Reference

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.008
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-9.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.6
upper limit	-2.5
Variability estimate	Standard deviation

Notes:

[22] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.198
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.4
upper limit	2.4
Variability estimate	Standard deviation

Notes:

[23] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 30mg

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.055
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.7
upper limit	0.1
Variability estimate	Standard deviation

Notes:

[24] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Secondary: Change in the cough severity visual analogue scale (VAS) at Week 4 compared to baseline - Day-time

End point title	Change in the cough severity visual analogue scale (VAS) at Week 4 compared to baseline - Day-time

End point description:

The cough VAS is a 100 mm scale on which subjects indicated their severity of cough over the previous 24 hours, both during the day-time and during night time separately. The VAS ranged from "no cough" (0 mm) on the left to "worst cough" (100 mm) on the right.
Subjects completed the cough severity VAS at baseline/Day 1 (pre dose) and at Weeks 2, 4, 8, and 12.

End point type	Secondary

End point timeframe:

Change from Baseline to Week 4

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	77	75	76
Units: Score				
arithmetic mean (standard deviation)	-17.9 (± 27.11)	-9.4 (± 26.76)	-15.9 (± 25.02)	-7.8 (± 22.36)

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Orvepitant 10mg v Reference

Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.026
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-8.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.3
upper limit	-1.1
Variability estimate	Standard deviation

Notes:

[25] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	= 0.571
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.6
upper limit	5.3
Variability estimate	Standard deviation

Notes:

[26] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 30mg

Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	= 0.043
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-7.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.2
upper limit	-0.3
Variability estimate	Standard deviation

Notes:

[27] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Secondary: Change in the cough severity visual analogue scale (VAS) at Week 8 compared to baseline - Day-time

End point title	Change in the cough severity visual analogue scale (VAS) at Week 8 compared to baseline - Day-time

End point description:

The cough VAS is a 100 mm scale on which subjects indicated their severity of cough over the previous 24 hours, both during the day-time and during night time separately. The VAS ranged from "no cough" (0 mm) on the left to "worst cough" (100 mm) on the right.
Subjects completed the cough severity VAS at baseline/Day 1 (pre dose) and at Weeks 2, 4, 8, and 12.

End point type	Secondary

End point timeframe:

Change from Baseline to Week 8

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	76	72	75
Units: Score				
arithmetic mean (standard deviation)	-21.0 (± 30.37)	-9.9 (± 29.57)	-18.6 (± 27.24)	-8.2 (± 23.58)

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Orvepitant 10mg v Reference

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.006
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-11.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.7
upper limit	-3.3
Variability estimate	Standard deviation

Notes:

[28] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.435
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.1
upper limit	4.8
Variability estimate	Standard deviation

Notes:

[29] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 30mg

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	= 0.022
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-9.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.4
upper limit	-1.4
Variability estimate	Standard deviation

Notes:

[30] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Secondary: Change in the cough severity visual analogue scale (VAS) at Week 12 compared to baseline - Day-time

End point title	Change in the cough severity visual analogue scale (VAS) at Week 12 compared to baseline - Day-time

End point description:

The cough VAS is a 100 mm scale on which subjects indicated their severity of cough over the previous 24 hours, both during the day-time and during night time separately. The VAS ranged from "no cough" (0 mm) on the left to "worst cough" (100 mm) on the right.
Subjects completed the cough severity VAS at baseline/Day 1 (pre dose) and at Weeks 2, 4, 8, and 12.

End point type	Secondary

End point timeframe:

Change from Baseline to Week 12

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	74	68	73
Units: Score				
arithmetic mean (standard deviation)	-18.8 (± 31.27)	-11.6 (± 27.33)	-20.1 (± 29.33)	-10.6 (± 24.46)

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Orvepitant 10mg v Reference

Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.103
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.3
upper limit	1.4
Variability estimate	Standard deviation

Notes:

[31] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority[32]
P-value	= 0.546
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.6
upper limit	5.6
Variability estimate	Standard deviation

Notes:

[32] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 30mg

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.034
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.2
upper limit	-0.7
Variability estimate	Standard deviation

Notes:

[33] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Secondary: Change in the cough severity visual analogue scale (VAS) at Week 2 compared to baseline - Night-time

End point title	Change in the cough severity visual analogue scale (VAS) at Week 2 compared to baseline - Night-time

End point description:

The cough VAS is a 100 mm scale on which subjects indicated their severity of cough over the previous 24 hours, both during the day-time and during night time separately. The VAS ranged from "no cough" (0 mm) on the left to "worst cough" (100 mm) on the right.
Subjects completed the cough severity VAS at baseline/Day 1 (pre dose) and at Weeks 2, 4, 8, and 12.

End point type	Secondary

End point timeframe:

Change from baseline to Week 2

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	77	75	75
Units: Score				
arithmetic mean (standard deviation)	-12.8 (± 28.96)	-7.8 (± 26.76)	-6.2 (± 24.97)	-3.9 (± 27.62)

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Orvepitant 10mg v Reference

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	= 0.004
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-11.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.8
upper limit	-3.6
Variability estimate	Standard deviation

Notes:

[34] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	= 0.282
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.5
upper limit	3.4
Variability estimate	Standard deviation

Notes:

[35] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 30mg

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	= 0.398
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.7
upper limit	4.3
Variability estimate	Standard deviation

Notes:

[36] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Secondary: Change in the cough severity visual analogue scale (VAS) at Week 4 compared to baseline - Night-time

End point title	Change in the cough severity visual analogue scale (VAS) at Week 4 compared to baseline - Night-time

End point description:

The cough VAS is a 100 mm scale on which subjects indicated their severity of cough over the previous 24 hours, both during the day-time and during night time separately. The VAS ranged from "no cough" (0 mm) on the left to "worst cough" (100 mm) on the right.
Subjects completed the cough severity VAS at baseline/Day 1 (pre dose) and at Weeks 2, 4, 8, and 12.

End point type	Secondary

End point timeframe:

Change from Baseline to Week 4

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	77	75	76
Units: Score				
arithmetic mean (standard deviation)	-10.1 (± 32.87)	-7.9 (± 27.52)	-5.8 (± 27.96)	-2.7 (± 27.99)

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Orvepitant 10mg v Reference

Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	= 0.019
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-10
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.3
upper limit	-1.7
Variability estimate	Standard deviation

Notes:

[37] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	= 0.17
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.7
upper limit	2.4
Variability estimate	Standard deviation

Notes:

[38] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 30mg

Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	= 0.384
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.7
upper limit	4.5
Variability estimate	Standard deviation

Notes:

[39] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Secondary: Change in the cough severity visual analogue scale (VAS) at Week 8 compared to baseline - Night-time

End point title	Change in the cough severity visual analogue scale (VAS) at Week 8 compared to baseline - Night-time

End point description:

The cough VAS is a 100 mm scale on which subjects indicated their severity of cough over the previous 24 hours, both during the day-time and during night time separately. The VAS ranged from "no cough" (0 mm) on the left to "worst cough" (100 mm) on the right.
Subjects completed the cough severity VAS at baseline/Day 1 (pre dose) and at Weeks 2, 4, 8, and 12.

End point type	Secondary

End point timeframe:

Change from Baseline to Week 8

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	76	72	75
Units: Score				
arithmetic mean (standard deviation)	-11.5 (± 32.65)	-6.8 (± 29.07)	-9.8 (± 28.73)	-2.2 (± 28.95)

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Orvepitant 10mg v Reference

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority[40]
P-value	= 0.006
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-11.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20
upper limit	-3.3
Variability estimate	Standard deviation

Notes:

[40] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	= 0.222
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13
upper limit	3
Variability estimate	Standard deviation

Notes:

[41] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 30mg

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority[42]
P-value	= 0.058
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16
upper limit	0.3
Variability estimate	Standard deviation

Notes:

[42] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Secondary: Change in the cough severity visual analogue scale (VAS) at Week 12 compared to baseline - Night-time

End point title	Change in the cough severity visual analogue scale (VAS) at Week 12 compared to baseline - Night-time

End point description:

The cough VAS is a 100 mm scale on which subjects indicated their severity of cough over the previous 24 hours, both during the day-time and during night time separately. The VAS ranged from "no cough" (0 mm) on the left to "worst cough" (100 mm) on the right.
Subjects completed the cough severity VAS at baseline/Day 1 (pre dose) and at Weeks 2, 4, 8, and 12.

End point type	Secondary

End point timeframe:

Change from Baseline to Week 12

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	74	68	73
Units: Score				
arithmetic mean (standard deviation)	-8.9 (± 35.99)	-7.1 (± 26.88)	-9.6 (± 30.24)	-1.5 (± 33.74)

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Orvepitant 10mg v Reference

Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	= 0.027
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-10
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.9
upper limit	-1.2
Variability estimate	Standard deviation

Notes:

[43] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority[44]
P-value	= 0.147
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.9
upper limit	2.2
Variability estimate	Standard deviation

Notes:

[44] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

Change in the Cough Severity VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in Cough Severity VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 30mg

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority[45]
P-value	= 0.046
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-8.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.6
upper limit	-0.1
Variability estimate	Standard deviation

Notes:

[45] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Secondary: Change in the urge-to-cough visual analogue scale (VAS) at Week 2 compared to baseline

End point title	Change in the urge-to-cough visual analogue scale (VAS) at Week 2 compared to baseline

End point description:

The urge-to-cough VAS was a 100 mm scale on which subjects indicated their urge to cough over the previous 24 hours (day/awake time and night time combined). The VAS ranged from "no urge to cough" (0 mm) on the left to "severe urge to cough" (100 mm) on the right.
Subjects completed the urge to cough VAS at baseline/Day 1 (pre dose) and at Weeks 2, 4, 8, and 12.

End point type	Secondary

End point timeframe:

Change from Baseline to Week 2

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72	77	75	74
Units: Score				
arithmetic mean (standard deviation)	-20.8 (± 24.59)	-12.0 (± 25.09)	-13.8 (± 22.03)	-7.0 (± 20.35)

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

Change in the urge-to-cough VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in urge-to cough VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 10mg

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority[46]
P-value	< 0.001
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-12.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.5
upper limit	-5.5
Variability estimate	Standard deviation

Notes:

[46] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

Change in the urge-to-cough VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in urge-to cough VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority[47]
P-value	= 0.114
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.4
upper limit	1.3
Variability estimate	Standard deviation

Notes:

[47] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

Change in the urge-to-cough VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in urge-to cough VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 30mg

Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority[48]
P-value	= 0.056
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.7
upper limit	0.2
Variability estimate	Standard deviation

Notes:

[48] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Secondary: Change in the urge-to-cough visual analogue scale (VAS) at Week 4 compared to baseline

End point title	Change in the urge-to-cough visual analogue scale (VAS) at Week 4 compared to baseline

End point description:

The urge-to-cough VAS was a 100 mm scale on which subjects indicated their urge to cough over the previous 24 hours (day/awake time and night time combined). The VAS ranged from "no urge to cough" (0 mm) on the left to "severe urge to cough" (100 mm) on the right.
Subjects completed the urge to cough VAS at baseline/Day 1 (pre dose) and at Weeks 2, 4, 8, and 12.

End point type	Secondary

End point timeframe:

Change from Baseline to Week 4

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	68	77	75	76
Units: Score				
arithmetic mean (standard deviation)	-19.0 (± 26.93)	-12.0 (± 26.67)	-17.3 (± 24.73)	-8.8 (± 24.26)

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

Change in the urge-to-cough VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in urge-to cough VAS was analysed using a MMRM with REML estimation.

Comparison groups	Orvepitant 10mg v Reference

Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority[49]
P-value	= 0.027
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-8.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.8
upper limit	-1
Variability estimate	Standard deviation

Notes:

[49] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

Change in the urge-to-cough VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in urge-to cough VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority[50]
P-value	= 0.357
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.3
upper limit	4.1
Variability estimate	Standard deviation

Notes:

[50] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

Change in the urge-to-cough VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in urge-to cough VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 30mg

Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority[51]
P-value	= 0.031
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-8.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.2
upper limit	-0.8
Variability estimate	Standard deviation

Notes:

[51] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Secondary: Change in the urge-to-cough visual analogue scale (VAS) at Week 8 compared to baseline

End point title	Change in the urge-to-cough visual analogue scale (VAS) at Week 8 compared to baseline

End point description:

The urge-to-cough VAS was a 100 mm scale on which subjects indicated their urge to cough over the previous 24 hours (day/awake time and night time combined). The VAS ranged from "no urge to cough" (0 mm) on the left to "severe urge to cough" (100 mm) on the right.
Subjects completed the urge to cough VAS at baseline/Day 1 (pre dose) and at Weeks 2, 4, 8, and 12.

End point type	Secondary

End point timeframe:

Change from Baseline to Week 8

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	76	72	75
Units: Score				
arithmetic mean (standard deviation)	-23.8 (± 28.00)	-14.5 (± 27.55)	-19.7 (± 26.80)	-11.0 (± 24.78)

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

Change in the urge-to-cough VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in urge-to cough VAS was analysed using a MMRM with REML estimation.

Comparison groups	Orvepitant 10mg v Reference

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority[52]
P-value	= 0.008
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-11.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.2
upper limit	-2.9
Variability estimate	Standard deviation

Notes:

[52] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

Change in the urge-to-cough VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in urge-to cough VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority[53]
P-value	= 0.321
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.8
upper limit	3.9
Variability estimate	Standard deviation

Notes:

[53] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

Change in the urge-to-cough VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in urge-to cough VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 30mg

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority[54]
P-value	= 0.047
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-8.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16
upper limit	-0.1
Variability estimate	Standard deviation

Notes:

[54] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Secondary: Change in the urge-to-cough visual analogue scale (VAS) at Week 12 compared to baseline

End point title	Change in the urge-to-cough visual analogue scale (VAS) at Week 12 compared to baseline

End point description:

The urge-to-cough VAS was a 100 mm scale on which subjects indicated their urge to cough over the previous 24 hours (day/awake time and night time combined). The VAS ranged from "no urge to cough" (0 mm) on the left to "severe urge to cough" (100 mm) on the right.
Subjects completed the urge to cough VAS at baseline/Day 1 (pre dose) and at Weeks 2, 4, 8, and 12.

End point type	Secondary

End point timeframe:

Change from Baseline to Week 12

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	74	68	74
Units: Score				
arithmetic mean (standard deviation)	-23.7 (± 27.30)	-12.6 (± 28.57)	-22.9 (± 28.43)	-11.8 (± 26.50)

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

Change in the urge-to-cough VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in urge-to cough VAS was analysed using a MMRM with REML estimation.

Comparison groups	Orvepitant 10mg v Reference

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority[55]
P-value	= 0.018
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-10.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.4
upper limit	-1.8
Variability estimate	Standard deviation

Notes:

[55] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

Change in the urge-to-cough VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in urge-to cough VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority[56]
P-value	= 0.682
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.8
upper limit	6.4
Variability estimate	Standard deviation

Notes:

[56] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

Change in the urge-to-cough VAS was summarised by treatment group and visit (Weeks 2, 4, 8 and 12) in terms of absolute values and changes from baseline. The effect of treatment in terms of the change from baseline to each scheduled visit (Week 2, Week 4, Week 8 and Week 12) in urge-to cough VAS was analysed using a MMRM with REML estimation.

Comparison groups	Reference v Orvepitant 30mg

Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority[57]
P-value	= 0.005
Method	Mixed model repeated measures
Parameter estimate	Mean difference (final values)
Point estimate	-11.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20
upper limit	-3.6
Variability estimate	Standard deviation

Notes:

[57] - The treatment effect was estimated using the difference between the treatments least squares means (adjusted means). The 95% confidence interval for the
difference between the treatments least squares means and the p-value from the hypothesis test of no difference between the treatment groups was presented.

Secondary: • Global Rating of Change in cough frequency at Week 2

End point title	• Global Rating of Change in cough frequency at Week 2

End point description:

In the Global Rating of Change scale, subjects indicated if there had been a change in their symptoms (cough frequency and, separately, cough severity) since starting the IMP. Subjects responded with "worse", "about the same" or "better". If subjects indicated a change (either "worse" or "better") they then indicated on a 7 point scale the degree of change ranging from 1 (almost the same, hardly any change) to 7 (a very great deal changed).
Subjects documented their Global Rating of Change in cough frequency and cough severity at Weeks 2, 4, 8, and 12.

End point type	Secondary

End point timeframe:

Change from Baseline to Week 2

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73	77	76	74
Units: Number of patients				
Worse	4	10	5	11
About the same	35	37	34	44
Better	34	30	37	19

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Orvepitant 10mg v Reference
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.134
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Reference v Orvepitant 30mg
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Secondary: Global Rating of Change in cough frequency at Week 4

End point title	Global Rating of Change in cough frequency at Week 4

End point description:

In the Global Rating of Change scale, subjects indicated if there had been a change in their symptoms (cough frequency and, separately, cough severity) since starting the IMP. Subjects responded with "worse", "about the same" or "better". If subjects indicated a change (either "worse" or "better") they then indicated on a 7 point scale the degree of change ranging from 1 (almost the same, hardly any change) to 7 (a very great deal changed).

Subjects documented their Global Rating of Change in cough frequency and cough severity at Weeks 2, 4, 8, and 12.

End point type	Secondary

End point timeframe:

Change from Baseline to Week 4

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	76	74	76
Units: Number of patients				
Worse	9	8	6	12
About the same	32	36	37	39
Better	28	32	31	25

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Orvepitant 10mg v Reference
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.401
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.175
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Reference v Orvepitant 30mg
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.126
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Secondary: Global Rating of Change in cough frequency at Week 8

End point title	Global Rating of Change in cough frequency at Week 8

End point description:

In the Global Rating of Change scale, subjects indicated if there had been a change in their symptoms (cough frequency and, separately, cough severity) since starting the IMP. Subjects responded with "worse", "about the same" or "better". If subjects indicated a change (either "worse" or "better") they then indicated on a 7 point scale the degree of change ranging from 1 (almost the same, hardly any change) to 7 (a very great deal changed).
Subjects documented their Global Rating of Change in cough frequency and cough severity at Weeks 2, 4, 8, and 12.

End point type	Secondary

End point timeframe:

Change from Baseline to Week 8

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	67	75	72	75
Units: Number of patients				
Worse	11	17	10	20
About the same	22	31	37	38
Better	34	27	25	17

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were

performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Reference v Orvepitant 10mg
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.144
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Reference v Orvepitant 30mg
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Secondary: Global Rating of Change in cough frequency at Week 12

End point title	Global Rating of Change in cough frequency at Week 12

End point description:

In the Global Rating of Change scale, subjects indicated if there had been a change in their symptoms (cough frequency and, separately, cough severity) since starting the IMP. Subjects responded with "worse", "about the same" or "better". If subjects indicated a change (either "worse" or "better") they then indicated on a 7 point scale the degree of change ranging from 1 (almost the same, hardly any change) to 7 (a very great deal changed).
Subjects documented their Global Rating of Change in cough frequency and cough severity at Weeks 2,

4, 8, and 12.

End point type	Secondary

End point timeframe:

Change from Baseline to Week 12

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	67	74	67	74
Units: Number of patients				
Worse	7	13	7	13
About the same	32	33	31	37
Better	28	28	29	24

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Orvepitant 10mg v Reference
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.158
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Orvepitant 20mg v Reference
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.597
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Reference v Orvepitant 30mg
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.124
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Secondary: Global Rating of Change in cough severity at Week 2

End point title	Global Rating of Change in cough severity at Week 2

End point description:

In the Global Rating of Change scale, subjects indicated if there had been a change in their symptoms (cough frequency and, separately, cough severity) since starting the IMP. Subjects responded with "worse", "about the same" or "better". If subjects indicated a change (either "worse" or "better") they then indicated on a 7 point scale the degree of change ranging from 1 (almost the same, hardly any change) to 7 (a very great deal changed).
Subjects documented their Global Rating of Change in cough frequency and cough severity at Weeks 2, 4, 8, and 12.

End point type	Secondary

End point timeframe:

Change from Baseline to Week 2

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73	77	76	74
Units: Number of patients				
Worse	7	8	4	12
About the same	33	39	35	44
Better	33	30	37	18

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Orvepitant 10mg v Reference

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Reference v Orvepitant 30mg
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Secondary: Global Rating of Change in cough severity at Week 4

End point title	Global Rating of Change in cough severity at Week 4

End point description:

In the Global Rating of Change scale, subjects indicated if there had been a change in their symptoms (cough frequency and, separately, cough severity) since starting the IMP. Subjects responded with "worse", "about the same" or "better". If subjects indicated a change (either "worse" or "better") they then indicated on a 7 point scale the degree of change ranging from 1 (almost the same, hardly any change) to 7 (a very great deal changed).
Subjects documented their Global Rating of Change in cough frequency and cough severity at Weeks 2, 4, 8, and 12.

End point type	Secondary

End point timeframe:

Change from Baseline to Week 4

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	69	76	74	76
Units: Number of patients				
Worse	9	7	7	14
About the same	32	43	31	37
Better	28	26	36	25

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Orvepitant 10mg v Reference
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.309
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.387
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Reference v Orvepitant 30mg
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Secondary: Global Rating of Change in cough severity at Week 8

End point title	Global Rating of Change in cough severity at Week 8

End point description:

In the Global Rating of Change scale, subjects indicated if there had been a change in their symptoms (cough frequency and, separately, cough severity) since starting the IMP. Subjects responded with "worse", "about the same" or "better". If subjects indicated a change (either "worse" or "better") they then indicated on a 7 point scale the degree of change ranging from 1 (almost the same, hardly any change) to 7 (a very great deal changed).
Subjects documented their Global Rating of Change in cough frequency and cough severity at Weeks 2, 4, 8, and 12.

End point type	Secondary

End point timeframe:

Change from Baseline to Week 8

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	67	75	72	75
Units: Number of patients				
Worse	8	12	6	15
About the same	26	36	35	42
Better	33	27	31	18

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Orvepitant 10mg v Reference

Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.152
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Reference v Orvepitant 30mg
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Secondary: Global Rating of Change in cough severity at Week 12

End point title	Global Rating of Change in cough severity at Week 12

End point description:

In the Global Rating of Change scale, subjects indicated if there had been a change in their symptoms (cough frequency and, separately, cough severity) since starting the IMP. Subjects responded with "worse", "about the same" or "better". If subjects indicated a change (either "worse" or "better") they then indicated on a 7 point scale the degree of change ranging from 1 (almost the same, hardly any change) to 7 (a very great deal changed).
Subjects documented their Global Rating of Change in cough frequency and cough severity at Weeks 2, 4, 8, and 12.

End point type	Secondary

End point timeframe:

Change from Baseline to Week 12

End point values	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg	Reference
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	67	74	67	74
Units: Number of patients				
Worse	5	15	8	16
About the same	38	33	30	36
Better	24	26	29	22

Statistical analyses

Statistical analysis title	Secondary variable (10 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Orvepitant 10mg v Reference
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Statistical analysis title	Secondary variable (20 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints ("worse", "about the same" and "better"). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Reference v Orvepitant 20mg
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.557
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Statistical analysis title	Secondary variable (30 mg)

Statistical analysis description:

The Global Rating of Change responses were summarised by treatment group and visit (Weeks 2, 4, 8 and 12) as categorical endpoints (“worse”, “about the same” and “better”). Pairwise comparisons were performed using the Cochran Mantel Haenszel test stratified by region using modified ridit scores (row mean scores differ).

Comparison groups	Reference v Orvepitant 30mg
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

22 May 2017 (first subject screening) to 24 January 2019 (last subject last visit)

Adverse event reporting additional description:

Adverse events that occurred from the time of consent up to the final study visit (Week 14) were recorded. Adverse events could be volunteered spontaneously by the subject, or were discovered as a result of general, non leading questioning. Note: The adverse events posted in EudraCT results are treatment-emergent adverse events.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Orvepitant 10mg
Reporting group description:	
Subjects receive orvepitant 10 mg	
Reporting group title	Orvepitant 20mg
Reporting group description:	
Subjects receive orvepitant 20mg	
Reporting group title	Orvepitant 30mg
Reporting group description:	
Subjects receive orvepitant 30mg	
Reporting group title	Placebo
Reporting group description:	
Subjects receive placebo	

Serious adverse events	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 79 (1.27%)	1 / 78 (1.28%)	3 / 79 (3.80%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 79 (1.27%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Intestinal anastomosis complication			

subjects affected / exposed	0 / 79 (0.00%)	0 / 78 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 79 (1.27%)	0 / 78 (0.00%)	0 / 79 (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
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 78 (0.00%)	0 / 79 (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
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 79 (0.00%)	0 / 78 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 79 (0.00%)	0 / 78 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 79 (0.00%)	1 / 78 (1.28%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 79 (1.27%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			

subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Intestinal anastomosis complication			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anxiety			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 79 (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	Orvepitant 10mg	Orvepitant 20mg	Orvepitant 30mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 79 (79.75%)	48 / 78 (61.54%)	53 / 79 (67.09%)
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 79 (8.86%)	10 / 78 (12.82%)	7 / 79 (8.86%)
occurrences (all)	7	19	9
Dizziness			
subjects affected / exposed	5 / 79 (6.33%)	4 / 78 (5.13%)	5 / 79 (6.33%)
occurrences (all)	5	4	6
Somnolence			
subjects affected / exposed	2 / 79 (2.53%)	4 / 78 (5.13%)	5 / 79 (6.33%)
occurrences (all)	2	4	5
Paraesthesia			
subjects affected / exposed	4 / 79 (5.06%)	0 / 78 (0.00%)	0 / 79 (0.00%)
occurrences (all)	4	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	13 / 79 (16.46%)	13 / 78 (16.67%)	11 / 79 (13.92%)
occurrences (all)	14	14	11
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 79 (2.53%)	1 / 78 (1.28%)	4 / 79 (5.06%)
occurrences (all)	2	1	4
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	5 / 79 (6.33%)	1 / 78 (1.28%)	4 / 79 (5.06%)
occurrences (all)	6	2	5
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 79 (5.06%)	1 / 78 (1.28%)	6 / 79 (7.59%)
occurrences (all)	4	1	6
Arthralgia			
subjects affected / exposed	4 / 79 (5.06%)	1 / 78 (1.28%)	1 / 79 (1.27%)
occurrences (all)	4	1	1
Infections and infestations			

Viral upper respiratory tract infection			
subjects affected / exposed	8 / 79 (10.13%)	7 / 78 (8.97%)	4 / 79 (5.06%)
occurrences (all)	9	10	4
Upper respiratory tract infection			
subjects affected / exposed	5 / 79 (6.33%)	4 / 78 (5.13%)	3 / 79 (3.80%)
occurrences (all)	6	5	3
Urinary tract infection			
subjects affected / exposed	4 / 79 (5.06%)	2 / 78 (2.56%)	3 / 79 (3.80%)
occurrences (all)	4	2	4

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 79 (50.63%)		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	6		
Dizziness			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
Somnolence			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 79 (3.80%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			

Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 79 (3.80%) 3		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all)	 0 / 79 (0.00%) 0 1 / 79 (1.27%) 1		
Infections and infestations Viral upper respiratory tract infection subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 10 / 79 (12.66%) 11 9 / 79 (11.39%) 9 4 / 79 (5.06%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 May 2017	In addition to minor typographical, formatting and administrative alterations, the following changes were made: • Removal of all reference to sampling and analysis for Substance P. • Rationalisation of prohibited concomitant cough medications. • Deletion of exclusion based on smoking pack history. • An alternative method of assessing for obstructive lung disease at screening was added. • Addition of pregnancy as a specific withdrawal criterion in Section 7.4 (Withdrawal criteria) of the protocol and modification of text in Section 10.3.9.3 (Pregnancy) of the protocol. • Correction of visit windows. • Removal of the requirement for subjects to fast for 1 hour before dosing on visit days. • Removal of references to pre dose for the Week 14 visits. • Addition of specific guidance for pregnancy reporting windows (30 days for exposed females and 90 days for partners of exposed males). • Removal of requirement to collect a PK sample in the event of an SAE. • Amendment of the criteria for inclusion in the per protocol analysis set from major deviations to relevant deviations.
08 August 2017	The following changes were made: • Number of tablets in each bottle of IMP was amended to 36. • Sentence added stating that randomisation would be stratified by region (North America and Europe).
25 September 2017	The following change was made: • Exclusion criterion #6 was amended to state that subjects were excluded if both FEV1 <80% predicted and FEV1/FVC ratio <0.7.
21 February 2018	The following changes were made: • Planned sample size was increased to 292 subjects and second sample size re estimate added. • Exclusion criterion #8 was amended to provide additional guidance for evidence of uncontrolled hypertension. • Exclusion criterion #16 was amended to remove specific examples of clinically significant abnormal laboratory tests. • Exclusion criterion #17f was amended to add two additional prohibited concomitant medications. • Clarification that for the primary efficacy analysis a mixed model for repeated measures was to be used. This also applied to analysis of selected secondary endpoints. • Clarification that AE summary by severity was for all treatment emergent adverse events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported