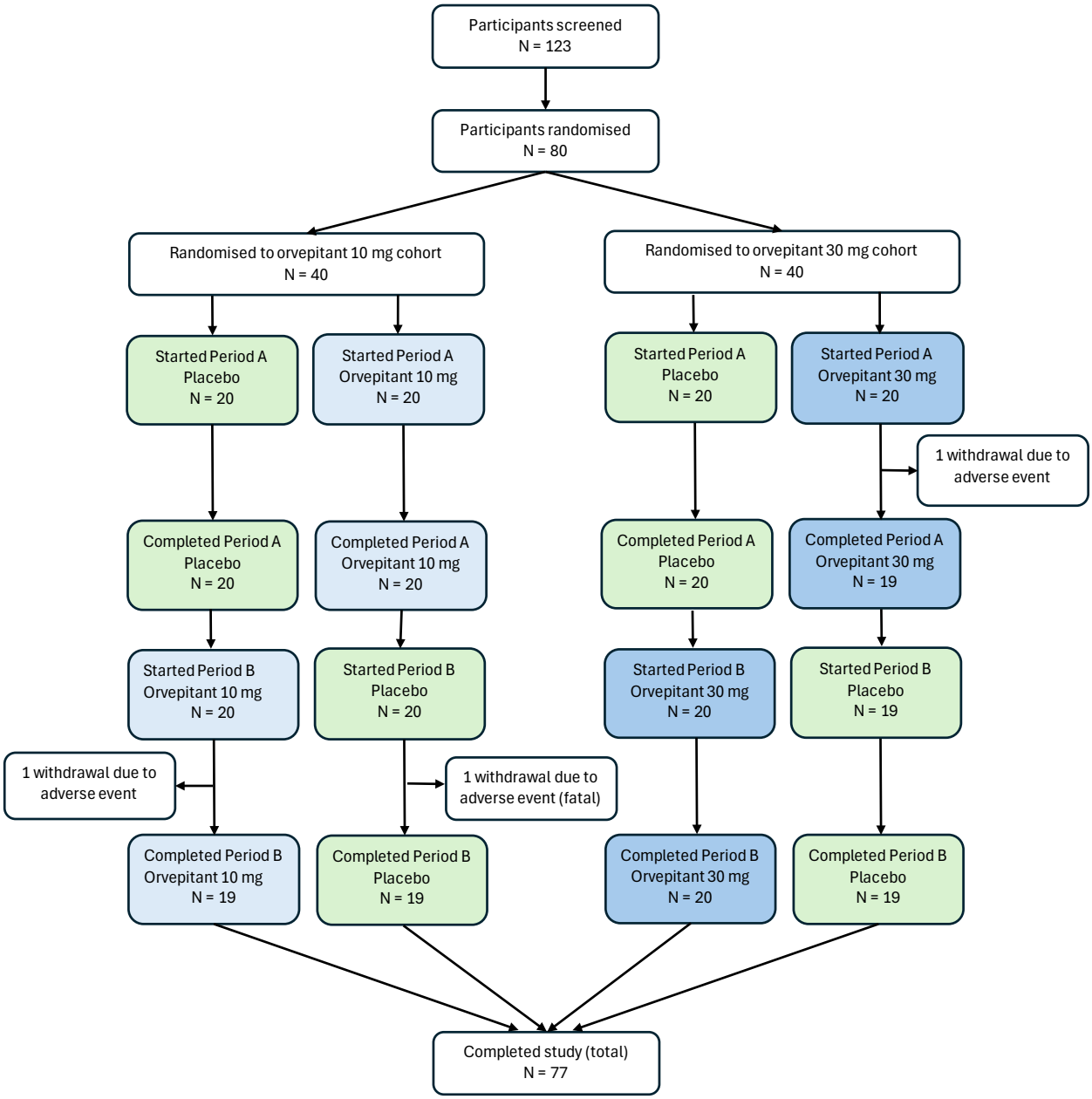
ISRCTN12372820: Results Summary

Participant Flow



Baseline Characteristics

	Parameter/ Category	Orvepitant 10 mg Cohort (N = 40)	Orvepitant 30 mg Cohort (N = 40)	Total (N = 80)
Age [years]	n	40	40	80
	Mean (SD)	71.4 (6.55)	72.4 (7.79)	71.9 (7.17)
	Median	70.5	72.0	71.5
	Range	59 to 82	54 to 90	54 to 90
Sex [n (%)]	Male	30 (75.0)	29 (72.5)	59 (73.8)
	Female	10 (25.0)	11 (27.5)	21 (26.3)
Ethnicity [n (%)]	Not Hispanic or Latino	37 (92.5)	37 (92.5)	74 (92.5)
	Not reported	2 (5.0)	2 (5.0)	4 (5.0)
	Hispanic or Latino	0	1 (2.5)	1 (1.3)
	Unknown	1 (2.5)	0	1 (1.3)
Race [n (%)]	White	40 (100)	37 (92.5)	77 (96.3)
	Asian	0	1 (2.5)	1 (1.3)
	Other	0	2 (5.0)	2 (2.5)
Weight at Baseline (kg)	n	40	40	80
	Mean (SD)	82.32 (17.712)	80.65 (15.940)	81.48 (16.763)
	Range	52.0 to 126.1	49.0 to 139.6	49.0 to 139.6
Time since IPF diagnosis (years)	n	40	40	80
	Mean (SD)	4.16 (2.914)	3.97 (2.903)	4.06 (2.892)
	Range	0.1 to 12.0	0.4 to 9.6	0.1 to 12.0
Time since onset of coughing (years)	n	38	38	76
	Mean (SD)	6.07 (4.962)	7.48 (7.114)	6.78 (6.133)
	Range	0.2 to 21.5	0.6 to 28.9	0.2 to 28.9
DLCO (%)	n	36	37	73
	Mean (SD)	49.8 (14.39)	51.4 (14.54)	50.6 (14.39)
	Range	26 to 91	27 to 95	26 to 95

DLCO = diffusion capacity for carbon monoxide; IPF = idiopathic pulmonary fibrosis; SD = standard deviation.

Outcome Measures

Primary outcome measure

Mean Change from Baseline to Week 4 in Weekly Average Score for the Daily Question in the IPF Coughing Severity Scale (CSS)

		Orvepitant 10 mg Cohort (Nc=40)		Orvepitant 30 mg Cohort (Nc=40)	
		Placebo	Orvepitant	Placebo	Orvepitant
Baseline	n	40	40	39	40
	Mean (SD)	6.78 (1.603)	6.67 (1.617)	6.76 (1.463)	6.96 (1.540)
Week 4	n	39	39	39	39
	Mean (SD)	6.05 (1.803)[a]	5.99 (1.942)	6.50 (1.724)	6.05 (1.984)
Change from Baseline to Week 4	n	39	39	39	39
	LS mean (SE)	-0.67 (0.219)	-0.66 (0.219)	-0.26 (0.207)	-0.84 (0.207)
	95% CI	-1.10, -0.23	-1.10, -0.23	-0.67, 0.15	-1.25, -0.42
Difference versus placebo at Week 4	LS mean (SE)	-	0.00 (0.305)	-	-0.58 (0.293)
	95% CI	-	-0.62, 0.63	-	-1.16, 0.01
	p-value	-	0.989	-	0.054

ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; Nc = number of subjects in cohort; SD = standard deviation; SE = standard error.

[a] A very large decrease (-6.9) in Daily IPF CSS score was observed for one subject in the orvepitant 10 mg cohort when on placebo.

Note: LS means, SE, CIs and p-values are from ANCOVA analysis for each cohort with fixed effects of treatment, Baseline score (period-specific), period and treatment by period interaction and random effect of subject.

Secondary outcome measures

Mean Change from Baseline in Weekly Average Score for the Early Morning Question in the IPF CSS

		Orvepitant 10 mg Cohort (Nc=40)		Orvepitant 30 mg Cohort (Nc=40)	
		Placebo	Orvepitant	Placebo	Orvepitant
Baseline	n	40	40	39	40
	Mean (SD)	5.69 (2.103)	5.51 (2.403)	5.44 (2.348)	5.48 (2.328)
Week 4	n	39	39	39	39
	Mean (SD)	5.04 (2.316)	4.98 (2.299)	4.94 (2.389)	4.41 (2.282)
Change from Baseline to Week 4	n	39	39	39	39
	LS mean (SE)	-0.55 (0.205)	-0.50 (0.205)	-0.49 (0.218)	-1.07 (0.218)
	95% CI	-0.96, -0.14	-0.91, -0.10	-0.92, -0.05	-1.51, -0.64
Difference versus placebo at Week 4	LS mean (SE)	-	0.05 (0.280)	-	-0.58 (0.276)

Mean Change from Baseline in Weekly Average Score for the Early Morning Question in the IPF CSS

		Orvepitant 10 mg Cohort (Nc=40)		Orvepitant 30 mg Cohort (Nc=40)	
		Placebo	Orvepitant	Placebo	Orvepitant
	95% CI	-	-0.52, 0.62	-	-1.14, -0.02
	p-value	-	0.872	-	0.041

ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; Nc = number of subjects in cohort; SE = standard error.
Note: LS means, standard errors, CIs and p-values are from ANCOVA analysis for each cohort at each time point with fixed effects of treatment, Baseline score (period-specific), period and treatment by period interaction and random effect of subject.

Mean Change from Baseline in Weekly Average Score for the Rest of the Day Question in the IPF CSS

		Orvepitant 10 mg Cohort (Nc=40)		Orvepitant 30 mg Cohort (Nc=40)	
		Placebo	Orvepitant	Placebo	Orvepitant
Baseline	n	40	40	39	40
	Mean (SD)	6.54 (1.547)	6.44 (1.520)	6.70 (1.537)	6.67 (1.602)
Week 4	n	39	39	39	39
	Mean (SD)	5.88 (1.793)	5.84 (1.858)	6.26 (1.765)	5.80 (2.115)
Change from Baseline to Week 4	n	39	39	39	39
	LS mean (SE)	-0.61 (0.214)	-0.61 (0.214)	-0.43 (0.211)	-0.80 (0.211)
	95% CI	-1.04, -0.18	-1.04, -0.19	-0.85, -0.01	-1.22, -0.38
Difference versus placebo at Week 4	LS mean (SE)	-	0.00 (0.303)	-	-0.37 (0.298)
	95% CI	-	-0.61, 0.60	-	-0.97, 0.22
	p-value	-	0.991	-	0.215

ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; SE = standard error.
Note: LS means, SE, CIs and p-values are from ANCOVA analysis for each cohort at each time point with fixed effects of treatment, Baseline score (period-specific), period and treatment by period interaction and random effect of subject.

Mean Change from Baseline in Weekly Average of the Urge to Cough Scale Score

		Orvepitant 10 mg Cohort (Nc=40)		Orvepitant 30 mg Cohort (Nc=40)	
		Placebo	**Orvepitant**	**Placebo**	**Orvepitant**
Baseline	n	40	40	39	40
	Mean (SD)	6.09 (1.799)	6.20 (1.863)	6.39 (1.550)	6.48 (1.635)
Week 4	n	39	39	39	39
	Mean (SD)	5.58 (1.949)	5.56 (2.067)	6.08 (1.632)	5.65 (1.961)
Change from Baseline to Week 4	n	39	39	39	39
	LS mean (SE)	-0.47 (0.213)	-0.61 (0.212)	-0.30 (0.191)	-0.76 (0.191)
	95% CI	-0.89, -0.05	-1.03, -0.19	-0.68, 0.08	-1.14, -0.38
Difference versus placebo at Week 4	LS mean (SE)	-	-0.14 (0.291)	-	-0.46 (0.271)
	95% CI	-	-0.73, 0.45	-	-1.00, 0.08
	p-value	-	0.639	-	0.092

ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; Nc = number of subjects in cohort; SE = standard error.
Note: LS means, standard errors, CIs and p-values are from ANCOVA analysis for each cohort at each time point with fixed effects of treatment, Baseline score (period-specific), period and treatment by period interaction and random effect of subject.

Mean Change from Baseline in Weekly Average of the Cough Frequency Scale Score

		Orvepitant 10 mg Cohort (Nc=40)		Orvepitant 30 mg Cohort (Nc=40)	
		Placebo	**Orvepitant**	**Placebo**	**Orvepitant**
Baseline	n	40	40	39	40
	Mean (SD)	2.65 (0.512)	2.64 (0.536)	2.65 (0.501)	2.67 (0.486)
Week 4	n	39	39	39	39
	Mean (SD)	2.44 (0.630)	2.49 (0.571)	2.60 (0.582)	2.37 (0.651)
Change from Baseline to Week 4	n	39	39	39	39
	LS mean (SE)	-0.19 (0.083)	-0.15 (0.083)	-0.05 (0.067)	-0.29 (0.067)
	95% CI	-0.36, -0.03	-0.31, 0.02	-0.19, 0.08	-0.42, -0.15
Difference versus placebo at Week 4	LS mean (SE)	-	0.05 (0.104)	-	-0.23 (0.085)
	95% CI	-	-0.17, 0.26	-	-0.41, -0.06
	p-value	-	0.650	-	0.010

ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; Nc = number of subjects in cohort; SE = standard error.
Note: LS means, standard errors, CIs and p-values are from ANCOVA analysis for each cohort at each time point with fixed effects of treatment, Baseline score (period-specific), period and treatment by period interaction and random effect of subject.
Note: Cough Frequency Scale score: 0=Never, 1=Rarely, 2=Sometimes, 3=Often, 4=All the time.

Mean Change from Baseline in Weekly Average of the Dyspnoea Scale Score

		Orvepitant 10 mg Cohort (Nc=40)		Orvepitant 30 mg Cohort (Nc=40)	
		Placebo	Orvepitant	Placebo	Orvepitant
Baseline	n	40	40	39	40
	Mean (SD)	5.87 (2.412)	5.84 (2.329)	5.50 (2.145)	5.61 (2.174)
Week 4	n	39	39	39	39
	Mean (SD)	5.53 (2.450)	5.59 (2.393)	5.50 (2.304)	5.14 (2.366)
Change from Baseline to Week 4	n	39	39	39	39
	LS mean (SE)	-0.26 (0.172)	-0.21 (0.172)	0.01 (0.148)	-0.44 (0.148)
	95% CI	-0.60, 0.09	-0.55, 0.13	-0.29, 0.30	-0.74, -0.15
Difference versus placebo at Week 4	LS mean (SE)	-	0.04 (0.240)	-	-0.45 (0.210)
	95% CI	-	-0.44, 0.53	-	-0.87, -0.03
	p-value	-	0.856	-	0.036

ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; Nc = number of subjects in cohort; SE = standard error.
Note: LS means, standard errors, CIs and p-values are from ANCOVA analysis for each cohort at each time point with fixed effects of treatment, Baseline score (period-specific), period and treatment by period interaction and random effect of subject.

Proportion of Subjects in Each Category of Patient Global Rating of Change for All Coughing at Week 4

		Orvepitant 10 mg Cohort (Nc=40)		Orvepitant 30 mg Cohort (Nc=40)	
		Placebo	Orvepitant	Placebo	Orvepitant
		Week 4 n (%)	Week 4 n (%)	Week 4 n (%)	Week 4 n (%)
N		39	39	39	39
Daily (all) coughing	Worsened	7 (17.9)	7 (17.9)	6 (15.4)	5 (12.8)
	No change	10 (25.6)	8 (20.5)	16 (41.0)	7 (17.9)
	Improved	22 (56.4)	24 (61.5)	17 (43.6)	27 (69.2)

Nc=number of subjects in cohort.
Note: The denominator for percent calculation is the number of subjects who completed the assessment at a given visit.

Mean Change from Baseline to Week 4 in 24-hour Cough Frequency, Bout Frequency, and Coughs per Bout (as Measured Using Leicester Cough Monitor)

		Orvepitant 10 mg Cohort (Nc=40)		Orvepitant 30 mg Cohort (Nc=40)	
		Placebo	**Orvepitant**	**Placebo**	**Orvepitant**
Average number of coughs / hour	Baseline				
	n	33	34	33	33
	Geometric Mean (SD)	20.24 (27.615)	20.06 (26.597)	25.21 (25.597)	23.83 (27.221)
	Week 4				
	n	36	34	35	36
	Geometric Mean (SD)	19.66 (22.877)	21.97 (26.124)	20.53 (21.796)	21.17 (20.157)
	Change from Baseline to Week 4				
	n	32	31	32	32
	Geometric LS mean ratio (SE)[a]	0.93 (1.114)	1.00 (1.115)	0.84 (1.113)	0.87 (1.112)
	95% CI	0.74, 1.15	0.80, 1.25	0.67, 1.04	0.70, 1.07
	Difference versus placebo at Week 4				
	Ratio of geometric LS mean ratios (SE)[b]	-	1.08 (1.105)	-	1.04 (1.122)
	95% CI	-	0.88,1.33	-	0.82, 1.31
	p-value	-	0.438	-	0.761
Average number of bouts / hour	Baseline				
	n	33	34	33	33
	Geometric Mean (SD)	4.83 (4.662)	4.74 (4.393)	5.66 (4.242)	5.39 (4.579)
	Week 4				
	n	36	34	35	36
	Geometric Mean (SD)	4.56 (4.679)	5.04 (4.691)	4.37 (3.967)	4.77 (4.340)
	Change from Baseline to Week 4				
	n	32	31	32	32
	Geometric LS mean ratio (SE)[a]	0.91 (1.089)	1.00 (1.090)	0.82 (1.087)	0.88 (1.087)
	95% CI	0.77, 1.08	0.84,1.18	0.69, 0.97	0.75, 1.04
	Difference versus placebo at Week 4				
	Ratio of geometric LS mean ratios (SE)[b]	-	1.09 (1.084)	-	1.08 (1.092)
	95% CI	-	0.93, 1.29	-	0.90, 1.29
	p-value	-	0.287	-	0.420

Mean Change from Baseline to Week 4 in 24-hour Cough Frequency, Bout Frequency, and Coughs per Bout (as Measured Using Leicester Cough Monitor)

		Orvepitant 10 mg Cohort (Nc=40)		Orvepitant 30 mg Cohort (Nc=40)	
		Placebo	**Orvepitant**	**Placebo**	**Orvepitant**
Average number of coughs / bout	Baseline				
	n	32	33	33	33
	Geometric Mean (SD)	3.40 (1.159)	3.41 (1.161)	3.52 (1.493)	3.59 (1.511)
	Week 4				
	n	35	34	35	36
	Geometric Mean (SD)	3.10 (1.116)	3.24 (1.219)	3.43 (1.412)	3.14 (0.888)
	Change from Baseline to Week 4				
	n	30	30	32	32
	Geometric LS mean ratio (SE)[a]	0.91 (1.027)	0.92 (1.027)	0.98 (1.028)	0.89 (1.028)
	95% CI	0.86, 0.96	0.87, 0.97	0.93, 1.04	0.84, 0.93
	Difference versus placebo at Week 4				
	Ratio of geometric LS mean ratios (SE)[b]	-	1.01 (1.022)	-	0.90 (1.033)
	95% CI	-	0.96, 1.05	-	0.85, 0.97
	p-value	-	0.765	-	0.004

ANCOVA=analysis of covariance; CI=confidence interval; LS=least squares; Nc=number of subjects in cohort; SE=standard error.

[a] Geometric LS mean ratio of Week 4/Baseline.

[b] Ratio of Geometric LS mean ratio of orvepitant (10 mg or 30 mg)/corresponding placebo for each cohort.

Note: Geometric LS means, SE, CIs and p-values for the Treatment Period B analysis are from ANCOVA analysis based on log transformed data for each cohort, period and time point separately including terms for treatment and Baseline score, and for the cross-over analysis are from ANCOVA analysis based on log transformed data with fixed effects of treatment, log transformed Baseline score, period and treatment by period interaction and random effect of subject. Baseline for Treatment Period A is used as Baseline in the model as there is no Baseline available for Treatment Period B. Note: Cough monitor recordings with a total duration below 120 minutes are excluded from this analysis.

Mean Change from Baseline to Week 4 in Leicester Cough Questionnaires (LCQ) Total and Domain Scores

			Orvepitant 10 mg Cohort (Nc=40)		Orvepitant 30 mg Cohort (Nc=40)	
			Placebo	Orvepitant	Placebo	Orvepitant
Total score	Baseline	n	40	40	39	40
		Mean (SD)	12.39 (3.417)	12.42 (3.020)	12.23 (3.469)	11.38 (3.031)
	Week 4	n	39	39	39	39
		Mean (SD)	13.55 (3.670)	13.81 (3.110)	12.38 (3.540)	13.02 (3.276)
	Change from Baseline to Week 4	n	39	39	39	39
		LS mean (SE)	1.06 (0.326)	1.25 (0.326)	0.24 (0.387)	1.48 (0.388)
		95% CI	0.41, 1.71	0.60, 1.90	-0.53, 1.01	0.71, 2.25
	Difference versus placebo at Week 4	LS mean (SE)	-	0.19 (0.462)	-	1.24 (0.525)
		95% CI	-	-0.73, 1.11	-	0.16, 2.31
		p-value	-	0.678	-	0.025
Physical domain	Baseline	n	40	40	39	40
		Mean (SD)	4.37 (1.004)	4.34 (0.928)	4.27 (1.117)	4.15 (1.018)
	Week 4	n	39	39	39	39
		Mean (SD)	4.58 (1.031)	4.64 (0.981)	4.33 (1.016)	4.51 (1.087)
	Change from Baseline to Week 4	n	39	39	39	39
		LS mean (SE)	0.18 (0.101)	0.25 (0.101)	0.07 (0.105)	0.34 (0.105)
		95% CI	-0.02, 0.39	0.05, 0.45	-0.14, 0.28	0.13, 0.55
	Difference versus placebo at Week 4	LS mean (SE)	-	0.07 (0.143)	-	0.27 (0.139)
		95% CI	-	-0.22, 0.35	-	-0.02, 0.56
		p-value	-	0.633	-	0.063
Psychological domain	Baseline	n	40	40	39	40
		Mean (SD)	3.97 (1.333)	4.16 (1.276)	3.98 (1.369)	3.67 (1.263)
	Week 4	n	39	39	39	39
		Mean (SD)	4.57 (1.455)	4.66 (1.191)	4.10 (1.471)	4.33 (1.248)
	Change from	n	39	39	39	39
		LS mean (SE)	0.55 (0.134)	0.48 (0.134)	0.15 (0.153)	0.60 (0.153)

Mean Change from Baseline to Week 4 in Leicester Cough Questionnaires (LCQ) Total and Domain Scores

			Orvepitant 10 mg Cohort (Nc=40)		Orvepitant 30 mg Cohort (Nc=40)	
			Placebo	Orvepitant	Placebo	Orvepitant
	Baseline to Week 4	95% CI	0.28, 0.81	0.21, 0.75	-0.16, 0.45	0.30, 0.90
	Difference versus placebo at Week 4	LS mean (SE)	-	-0.06 (0.185)	-	0.45 (0.214)
		95% CI	-	-0.44, 0.31	-	0.01, 0.89
		p-value	-	0.732	-	0.044
Social domain	Baseline	n	40	40	39	40
		Mean (SD)	4.05 (1.354)	3.92 (1.097)	3.98 (1.346)	3.56 (1.180)
	Week 4	n	39	39	39	39
		Mean (SD)	4.40 (1.460)	4.51 (1.243)	3.95 (1.491)	4.19 (1.335)
	Change from Baseline to Week 4	n	39	39	39	39
		LS mean (SE)	0.33 (0.142)	0.52 (0.142)	0.02 (0.174)	0.54 (0.174)
		95% CI	0.04, 0.61	0.24, 0.80	-0.33, 0.37	0.19, 0.89
	Difference versus placebo at Week 4	LS mean (SE)	-	0.19 (0.190)	-	0.52 (0.228)
		95% CI	-	-0.19, 0.58	-	0.05, 0.98
		p-value	-	0.318	-	0.030

ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; Nc = number of subjects in cohort; SD = standard deviation; SE = standard error.

Note: LS means, standard errors, CIs and p-values are from ANCOVA analysis for each cohort with fixed effects of treatment, Baseline score (period-specific), period and treatment by period interaction and random effect of subject.

Adverse Events

Summary of Serious Treatment Emergent Adverse Events (SAEs)

Nine SAEs were reported in seven subjects. None were considered related to study drug.
One SAE (Idiopathic pulmonary fibrosis) was fatal.

System Organ Class Preferred Term	**Orvepitant 10 mg Cohort (Nc=40)**		**Orvepitant 30 mg Cohort (Nc=39)**	
	Placebo (N=40) **m n (%)**	**Orvepitant (N=40)** **m n (%)**	**Placebo (N=38)** **m n (%)**	**Orvepitant (N=39)** **m n (%)**
Subject with at least One SAE	2 2 (5.0)	1 1 (2.5)	3 3 (7.9)	3 1 (2.6)
Cardiac disorders	**1 1 (2.5)**	**0**	**0**	**2 1 (2.6)**
Acute myocardial infarction	1 1 (2.5)	0	0	1 1 (2.6)
Angina pectoris	0	0	0	1 1 (2.6)
Infections and infestations	**1 1 (2.5)**	**0**	**1 1 (2.6)**	**0**
COVID-19	0	0	1 1 (2.6)	0
Pneumonia respiratory syncytial viral	1 1 (2.5)	0	0	0
Gastrointestinal disorders	**0**	**0**	**0**	**1 1 (2.6)**
Obstructive pancreatitis	0	0	0	1 1 (2.6)
Investigations	**0**	**0**	**1 1 (2.6)**	**0**
Oxygen saturation decreased	0	0	1 1 (2.6)	0
Musculoskeletal and connective tissue disorders	**0**	**0**	**1 1 (2.6)**	**0**
Arthralgia	0	0	1 1 (2.6)	0
Respiratory, thoracic and mediastinal disorders	**0**	**1 1 (2.5)**	**0**	**0**
Idiopathic pulmonary fibrosis*	**0**	1 1 (2.5)	0	0

SAE=Serious Adverse Event; m=number of events; n=number of subjects; N=number of subjects in cohort exposed to given treatment; Nc=number of subjects in cohort.
Note: The denominator for percent calculations is N, i.e., the number of subjects in given cohort who were exposed to given treatment.
Note: AEs that started during the wash-out period were assigned to the treatment received during Treatment Period A; AEs that started following first dose in Treatment Period B up to end of follow-up were assigned to the treatment received during Treatment Period B.
* Resulted in death

Most Common Treatment-emergent Adverse Events (Preferred Terms Reported in ≥5% of Subjects in Any Treatment Group, Either Cohort)

System Organ Class Preferred Term	Orvepitant 10 mg Cohort (Nc=40)				Orvepitant 30 mg Cohort (Nc=39)			
	Placebo (N=40)		Orvepitant (N=40)		Placebo (N=38)		Orvepitant (N=39)	
	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events
Any TEAE	19 (47.5)	46	30 (75.0)	59	17 (44.7)	36	22 (56.4)	48
Infections and infestations	**5 (12.5)**	**9**	**13 (32.5)**	**14**	**9 (23.7)**	**12**	**5 (12.8)**	**6**
Nasopharyngitis	1 (2.5)	1	3 (7.5)	3	4 (10.5)	4	0	0
Lower respiratory tract infection	0	0	3 (7.5)	3	2 (5.3)	3	2 (5.1)	2
COVID-19	1 (2.5)	1	1 (2.5)	1	1 (2.6)	1	2 (5.1)	2
Respiratory, thoracic and mediastinal disorders	**5 (12.5)**	**7**	**4 (10.0)**	**5**	**6 (15.8)**	**7**	**8 (20.5)**	**11**
Cough	1 (2.5)	1	2 (5.0)	2	1 (2.6)	1	3 (7.7)	3
Dyspnoea	2 (5.0)	2	0	0	2 (5.3)	2	3 (7.7)	3
Sputum increased	0	0	0	0	1 (2.6)	1	2 (5.1)	2
Haemoptysis	0	0	0	0	2 (5.3)	2	0	0
Gastrointestinal disorders	**4 (10.0)**	**5**	**8 (20.0)**	**8**	**3 (7.9)**	**3**	**8 (20.5)**	**10**
Diarrhoea	2 (5.0)	2	4 (10.0)	4	1 (2.6)	1	2 (5.1)	2
Abdominal pain upper	0	0	2 (5.0)	2	0	0	0	0
Nervous system disorders	**5 (12.5)**	**5**	**4 (10.0)**	**5**	**4 (10.5)**	**5**	**5 (12.8)**	**5**
Dizziness	1 (2.5)	1	2 (5.0)	2	2 (5.3)	2	2 (5.1)	2
Headache	3 (7.5)	3	1 (2.5)	1	1 (2.6)	1	1 (2.6)	1
Lethargy	0	0	2 (5.0)	2	0	0	0	0

Most Common Treatment-emergent Adverse Events (Preferred Terms Reported in ≥5% of Subjects in Any Treatment Group, Either Cohort)

System Organ Class Preferred Term	Orvepitant 10 mg Cohort (Nc=40)				Orvepitant 30 mg Cohort (Nc=39)			
	Placebo (N=40)		Orvepitant (N=40)		Placebo (N=38)		Orvepitant (N=39)	
	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events	No. of Subjects (%)	No. of Events
General disorders and administration site conditions	**3 (7.5)**	**3**	**4 (10.0)**	**5**	**1 (2.6)**	**1**	**4 (10.3)**	**4**
Fatigue	3 (7.5)	3	3 (7.5)	3	1 (2.6)	1	2 (5.1)	2
Musculoskeletal and connective tissue disorders	**3 (7.5)**	**3**	**5 (12.5)**	**6**	**2 (5.3)**	**2**	**2 (5.1)**	**2**
Back pain	1 (2.5)	1	2 (5.0)	2	0	0	1 (2.6)	1
Myalgia	1 (2.5)	1	3 (7.5)	3	0	0	0	0
Metabolism and nutrition disorders	**1 (2.5)**	**2**	**3 (7.5)**	**3**	**0**	**0**	**0**	**0**
Decreased appetite	0	0	3 (7.5)	3	0	0	0	0
Psychiatric disorders	**3 (7.5)**	**3**	**1 (2.5)**	**1**	**0**	**0**	**0**	**0**
Insomnia	2 (5.0)	2	0	0	0	0	0	0

N = number of subjects in cohort exposed to given treatment; Nc = number of subjects in cohort; No. = number; TEAE = treatment-emergent adverse event.
Note: TEAEs that started during the wash-out period were assigned to the treatment received during Treatment Period A; TEAEs that started following first dose in Treatment Period B up to end of follow-up were assigned to the treatment received during Treatment Period B.