Clinical trial results:
A Phase IIb, randomized, double blind, placebo controlled, dose ranging study to assess the effect of RPL554 in patients with moderate to severe COPD.

Summary

EudraCT number	2016-005205-40
Trial protocol	DE CZ BG GB RO
Global end of trial date	07 February 2018

Results information

Result version number	v1 (current)
This version publication date	13 March 2019
First version publication date	13 March 2019

Trial information

Trial identification

Sponsor protocol code	RPL554-CO-203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03443414
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Verona Pharma plc
Sponsor organisation address	3 More Riverside, London, United Kingdom, SE12RE
Public contact	Paula Siu, Verona Pharma plc, +44 203 283 4200, paula.siu@veronapharma.com
Scientific contact	Paula Siu, Verona Pharma plc, +44 203 283 4200, paula.siu@veronapharma.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 January 2018
Global end of trial reached?	Yes
Global end of trial date	07 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of RPL554 or placebo on change from baseline in peak forced expiratory volume in 1 second (FEV1) when administered to patients with moderate to severe Chronic Obstructive Pulmonary Disease (COPD)

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines and local law requirements

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 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	Poland: 93
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Bulgaria: 76
Country: Number of subjects enrolled	Czech Republic: 65
Country: Number of subjects enrolled	Germany: 111
Country: Number of subjects enrolled	Romania: 45
Worldwide total number of subjects	405
EEA total number of subjects	405

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)	221
From 65 to 84 years	184
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

405 adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) were randomized into this double-blind, multicenter study, and 403 received study medication. Patients were recruited to 47 study centers in Bulgaria, Czech Republic, Germany, Poland, Romania and the United Kingdom.

Pre-assignment

Screening details:

Patients with a clinical diagnosis of COPD as defined by the American Thoracic Society/European Respiratory Society guidelines with symptoms compatible with COPD for at least 1 year prior to screening, and with clinically stable symptoms in the 4 weeks prior to screening and randomization were screened for inclusion.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	0.75 mg RPL554

Arm description: -

Arm type	Experimental
Investigational medicinal product name	RPL554
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:

0.75 mg RPL554 administered using a jet nebuliser for 5-10 minutes until sputtering

Arm title	1.5 mg RPL554

Arm description: -

Arm type	Experimental
Investigational medicinal product name	RPL554
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:

1.5 mg RPL554 administered using a jet nebuliser for 5-10 minutes until sputtering

Arm title	3.0 mg RPL554

Arm description: -

Arm type	Experimental
Investigational medicinal product name	RPL554
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:
3.0 mg RPL554 administered using a jet nebuliser for 5-10 minutes until sputtering

Arm title	6.0 mg RPL554
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	RPL554
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:
6.0 mg RPL554 administered using a jet nebuliser for 5-10 minutes until sputtering

Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:
Placebo administered for 5-10 minutes until sputtering

Number of subjects in period 1	0.75 mg RPL554	1.5 mg RPL554	3.0 mg RPL554
Started	82	81	82
Completed	71	78	76
Not completed	11	3	6
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	3	2	2
Adverse event, non-fatal	6	-	4
Reason not specified	2	-	-

Number of subjects in period 1	6.0 mg RPL554	Placebo
Started	80	80
Completed	75	75
Not completed	5	5
Adverse event, serious fatal	1	-
Consent withdrawn by subject	2	1
Adverse event, non-fatal	2	3
Reason not specified	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Whole study

Reporting group description: -

Reporting group values	Whole study	Total	
Number of subjects	405	405	
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)	221	221	
From 65-84 years	184	184	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	62.3		
standard deviation	± 6.61	-	
Gender categorical Units: Subjects			
Female	160	160	
Male	245	245	
Race Units: Subjects			
White	405	405	
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
Unknown or Not Reported	0	0	
More than One Race	0	0	
Ethnicity Units: Subjects			
Not Hispanic or Latino	405	405	
Hispanic or Latino	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	0.75 mg RPL554
Reporting group description: -	
Reporting group title	1.5 mg RPL554
Reporting group description: -	
Reporting group title	3.0 mg RPL554
Reporting group description: -	
Reporting group title	6.0 mg RPL554
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Mean Change From Baseline in Peak FEV1 (Over 3 Hours) at Week 4

End point title	Mean Change From Baseline in Peak FEV1 (Over 3 Hours) at Week 4

End point description:

Spirometry assessments were used to assess pulmonary function including the forced expiratory volume in 1 second (FEV1). Peak FEV1 at Week 4 was defined as the maximum post-dose value among the 30 minutes, 1, 2 and 3 hour assessments collected at Visit 6. Baseline was defined as the FEV1 pre-dose assessment (-15 minutes) collected at Visit 2. A mixed model for repeated measures (MMRM) was used to model the change from baseline FEV1 using baseline FEV1 as a continuous fixed effect, randomized treatment, week and treatment-by-week as categorical fixed effect, and patient as random effect.
The least squares (LS) mean change from baseline FEV1 to peak FEV1 (as measured over 3 hours) at Week 4 is presented.

End point type	Primary

End point timeframe:

15 minutes pre-dose; 30 minutes and 1, 2 and 3 hours post-dose

End point values	0.75 mg RPL554	1.5 mg RPL554	3.0 mg RPL554	6.0 mg RPL554
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	81	82	80
Units: Litres				
least squares mean (confidence interval 95%)	0.203 (0.152 to 0.253)	0.209 (0.160 to 0.258)	0.257 (0.208 to 0.306)	0.196 (0.147 to 0.246)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Litres				
least squares mean (confidence interval 95%)	0.057 (0.007 to 0.106)			

Statistical analyses

Statistical analysis title	RPL554 6.0 mg versus Placebo
Statistical analysis description:	
Placebo corrected treatment effect: LS mean difference (RPL554 6.0 mg - Placebo)	
Comparison groups	6.0 mg RPL554 v Placebo
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.139
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.069
upper limit	0.21

Notes:

[1] - A fixed sequence testing approach was used, starting with the highest dose versus placebo. If a statistically significant difference was found at the 2-sided alpha level of 5%, the testing proceeded to the next highest dose.

Statistical analysis title	RPL554 3.0 mg versus Placebo
Statistical analysis description:	
Placebo corrected treatment effect: LS mean difference (RPL554 3.0 mg - Placebo)	
Comparison groups	3.0 mg RPL554 v Placebo
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	< 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.131
upper limit	0.27

Notes:

[2] - A fixed sequence testing approach was used, starting with the highest dose versus placebo. If a statistically significant difference was found at the 2-sided alpha level of 5%, the testing proceeded to the next highest dose.

Statistical analysis title	RPL554 1.5 mg versus Placebo
Statistical analysis description:	
Placebo corrected treatment effect: LS mean difference (RPL554 1.5 mg - Placebo)	

Comparison groups	1.5 mg RPL554 v Placebo
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.153
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.083
upper limit	0.222

Notes:

[3] - A fixed sequence testing approach was used, starting with the highest dose versus placebo. If a statistically significant difference was found at the 2-sided alpha level of 5%, the testing proceeded to the next highest dose.

Statistical analysis title	RPL554 0.75 mg versus Placebo

Statistical analysis description:

Placebo corrected treatment effect: LS mean difference (RPL554 0.75 mg - Placebo)

Comparison groups	0.75 mg RPL554 v Placebo
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	< 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.146
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.075
upper limit	0.216

Notes:

[4] - A fixed sequence testing approach was used, starting with the highest dose versus placebo. If a statistically significant difference was found at the 2-sided alpha level of 5%, the testing proceeded to the next highest dose.

Secondary: Mean Change from Baseline FEV1 to Morning Trough at Week 4

End point title	Mean Change from Baseline FEV1 to Morning Trough at Week 4

End point description:

Morning trough FEV1 was defined as the last pre-dose value at Visit 6. Baseline was defined as the FEV1 pre-dose assessment (-15 minutes) collected at Visit 2. MMRM was used to model the change from baseline FEV1 using baseline FEV1 as a continuous fixed effect, randomized treatment, week and treatment-by-week as categorical fixed effect, and patient as random effect.
The LS mean change from baseline FEV1 to morning trough FEV1 at Week 4 is presented.

End point type	Secondary

End point timeframe:

Pre-dose at baseline and pre-dose at Week 4

End point values	0.75 mg RPL554	1.5 mg RPL554	3.0 mg RPL554	6.0 mg RPL554
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	77	80	82	77
Units: Litres				
least squares mean (confidence interval 95%)	0.007 (-0.038 to 0.053)	-0.019 (-0.063 to 0.025)	0.040 (-0.003 to 0.084)	-0.026 (-0.071 to 0.018)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: Litres				
least squares mean (confidence interval 95%)	-0.028 (-0.072 to 0.016)			

Statistical analyses

Statistical analysis title	RPL554 6.0 mg versus Placebo
Statistical analysis description:	
Placebo corrected treatment effect: LS mean difference (RPL554 6.0 mg - Placebo)	
Comparison groups	6.0 mg RPL554 v Placebo
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.953
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.061
upper limit	0.065

Notes:

[5] - A fixed-sequence testing approach was used, starting with the highest dose versus placebo. If a statistically significant difference was found at the 2-sided alpha level of 5%, the testing proceeded to the next highest dose.

Statistical analysis title	RPL554 3.0 mg versus Placebo
Statistical analysis description:	
Placebo corrected treatment effect: LS mean difference (RPL554 3.0 mg - Placebo)	
Comparison groups	Placebo v 3.0 mg RPL554

Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.032
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.068
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.006
upper limit	0.13

Notes:

[6] - A fixed-sequence testing approach was used, starting with the highest dose versus placebo. If a statistically significant difference was found at the 2-sided alpha level of 5%, the testing proceeded to the next highest dose.

Statistical analysis title	RPL554 1.5 mg versus Placebo

Statistical analysis description:

Placebo corrected treatment effect: LS mean difference (RPL554 1.5 mg - Placebo)

Comparison groups	Placebo v 1.5 mg RPL554
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.773
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.053
upper limit	0.072

Notes:

[7] - A fixed-sequence testing approach was used, starting with the highest dose versus placebo. If a statistically significant difference was found at the 2-sided alpha level of 5%, the testing proceeded to the next highest dose.

Statistical analysis title	RPL554 0.75 mg versus Placebo

Statistical analysis description:

Placebo corrected treatment effect: LS mean difference (RPL554 0.75 mg - Placebo)

Comparison groups	Placebo v 0.75 mg RPL554
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.272
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.035

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.028
upper limit	0.099

Notes:

[8] - A fixed-sequence testing approach was used, starting with the highest dose versus placebo. If a statistically significant difference was found at the 2-sided alpha level of 5%, the testing proceeded to the next highest dose.

Secondary: Number of Patients with Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Patients with Treatment Emergent Adverse Events (TEAEs)

End point description:

The number of patients with TEAEs for each the following categories are presented: any TEAE, any drug-related TEAE, any severe TEAE, any serious TEAE, serious drug-related TEAE, any TEAE leading to drug interruption, any TEAE leading to drug discontinuation, and any TEAE leading to death.
All adverse events which started after the first dose of investigational product or started prior to first dose and worsened, based on the Investigator assessment of severity, on or after first dose were considered to be treatment-emergent

End point type	Secondary

End point timeframe:

Up to end of Study (Approximately 6 weeks)

End point values	0.75 mg RPL554	1.5 mg RPL554	3.0 mg RPL554	6.0 mg RPL554
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	81	82	80
Units: Number of Patients				
Any TEAE	27	36	29	29
Any drug-related TEAE	8	11	12	8
Any severe TEAE	4	1	2	1
Any serious TEAE	2	2	1	1
Any serious drug-related TEAE	1	1	0	0
Any TEAE leading to drug interruption	1	0	1	0
Any TEAE leading to drug discontinuation	6	1	4	2
Any TEAE leading to death	0	1	0	1

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Number of Patients				
Any TEAE	31			
Any drug-related TEAE	10			
Any severe TEAE	2			
Any serious TEAE	1			
Any serious drug-related TEAE	0			
Any TEAE leading to drug interruption	0			

Any TEAE leading to drug discontinuation	2			
Any TEAE leading to death	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in COPD Symptoms Using the Exacerbations of Chronic Pulmonary Disease Tool Patient- Reported Outcome (EXACT-PRO) Scoring at Week 4

End point title	Mean Change From Baseline in COPD Symptoms Using the Exacerbations of Chronic Pulmonary Disease Tool Patient-Reported Outcome (EXACT-PRO) Scoring at Week 4

End point description:

Patients completed an electronic diary (e-diary) once daily which used the 14-item EXACT-PRO instrument to assess COPD symptoms. The EXACT-PRO instrument contains 11 respiratory symptom questions that comprise the derivative Evaluating Respiratory Symptoms (E-RS) instrument that was used to measure the effect of treatment with RPL554 on the severity of COPD symptoms overall. The E-RS tool contains 3 subscales to assess breathlessness, cough/sputum and chest symptoms. In addition to the subscale scores, a total score for the E-RS part was obtained. The raw totals for the E-RS score and for each of the subscales were converted to a scale range of 0 to 100 (least symptomatic to most symptomatic). MMRM was used to model the change from baseline using baseline as a continuous fixed effect, randomised treatment, week and treatment-by-week as categorical fixed effect, and patient as random effect

End point type	Secondary

End point timeframe:

Baseline (pre-dose, Visit 2) and Week 4 (Visit 6)

End point values	0.75 mg RPL554	1.5 mg RPL554	3.0 mg RPL554	6.0 mg RPL554
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	74	76	74
Units: Units on a scale				
least squares mean (confidence interval 95%)				
E-RS Total Score	-1.07 (-2.00 to -0.14)	-1.26 (-2.16 to -0.35)	-0.80 (-1.69 to 0.10)	-0.92 (-1.81 to -0.02)
E-RS Breathlessness Score	-0.46 (-0.92 to -0.01)	-0.63 (-1.07 to -0.18)	-0.48 (-0.92 to -0.04)	-0.48 (-0.92 to -0.04)
E-RS Cough/Sputum Score	-0.22 (-0.50 to 0.07)	-0.30 (-0.58 to -0.03)	-0.14 (-0.41 to 0.13)	-0.21 (-0.48 to 0.06)
E-RS Chest Symptom Score	-0.39 (-0.70 to -0.08)	-0.32 (-0.62 to -0.02)	-0.19 (-0.48 to 0.11)	-0.22 (-0.52 to 0.07)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	76			
Units: Units on a scale				

least squares mean (confidence interval 95%)				
E-RS Total Score	1.19 (0.30 to 2.08)			
E-RS Breathlessness Score	0.47 (0.03 to 0.90)			
E-RS Cough/Sputum Score	0.36 (0.09 to 0.63)			
E-RS Chest Symptom Score	0.35 (0.05 to 0.64)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Breathlessness as Assessed Using the St George's Respiratory Questionnaire (SGRQ) at Week 4

End point title	Mean Change From Baseline in Breathlessness as Assessed Using the St George's Respiratory Questionnaire (SGRQ) at Week 4

End point description:

Patients completed the COPD specific SGRQ (SGRQ-C) which consisted of 14 questions in 2 parts. Part 1 produced the symptoms score, and Part 2 gave the activity and impacts scores. Each of the component scores was calculated separately by dividing the summed weights by the maximum possible weight for that component and expressing the score as a percentage (0 for least symptomatic and 100 for most symptomatic). A total score was also produced which was calculated by summing the weights to all positive responses in each component, where a positive item indicated the presence of symptoms. Baseline assessment was pre-dose at Visit 2. MMRM was used to model the change from baseline using baseline as a continuous fixed effect, randomized treatment, week and treatment-by-week as categorical fixed effect, patient as random effect.

End point type	Secondary

End point timeframe:

Baseline (pre-dose, Visit 2) and Week 4 (Visit 6)

End point values	0.75 mg RPL554	1.5 mg RPL554	3.0 mg RPL554	6.0 mg RPL554
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	74	75	71	77
Units: Units on a scale				
least squares mean (confidence interval 95%)				
SGRQ-C Total Score	-2.56 (-5.13 to 0.02)	-3.18 (-5.72 to -0.65)	-2.63 (-5.24 to -0.01)	-3.01 (-5.51 to -0.51)
SGRQ-C Symptoms Score	-4.73 (-7.99 to -1.46)	-1.89 (-5.11 to 1.33)	-2.17 (-5.50 to 1.17)	-4.33 (-7.51 to -1.16)
SGRQ-C Activity Score	-2.19 (-5.30 to 0.91)	-4.28 (-7.34 to -1.23)	-2.70 (-5.85 to 0.46)	-2.75 (-5.76 to 0.27)
SGRQ-C Impact Score	-1.73 (-4.91 to 1.46)	-2.93 (-6.06 to 0.20)	-2.96 (-6.20 to 0.28)	-2.80 (-5.89 to 0.29)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: Units on a scale				
least squares mean (confidence interval 95%)				
SGRQ-C Total Score	-0.33 (-2.90 to 2.23)			
SGRQ-C Symptoms Score	1.25 (-2.02 to 4.51)			
SGRQ-C Activity Score	-2.16 (-5.25 to 0.94)			
SGRQ-C Impact Score	0.11 (-3.07 to 3.28)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline FEV1 to Average FEV1 (Over 12 Hours) at Day 1 and Week 4

End point title	Mean Change From Baseline FEV1 to Average FEV1 (Over 12 Hours) at Day 1 and Week 4

End point description:

Average FEV1 over 12 hours was defined as the area under the curve from 0 to 12 hours post-dose (AUC[0-12]) of the FEV1 values collected during Day 1 or Week 4, divided by the length of the time interval of interest (in hours). The AUC was calculated using the trapezoidal rule. Baseline was defined as the FEV1 pre-dose assessment (-15 minutes) collected at Visit 2. MMRM was used to model the change from baseline FEV1 using baseline FEV1 as a continuous fixed effect, randomized treatment, week and treatment-by-week as categorical fixed effect, and patient as random effect.
The LS mean change from baseline FEV1 to average FEV1 over 12 hours at Day 1 and Week 4 are presented

End point type	Secondary

End point timeframe:

Baseline (pre-dose, Visit 2), up to 12 hours post-dose at Visit 2 (Day 1) and Visit 6 (Week 4)

End point values	0.75 mg RPL554	1.5 mg RPL554	3.0 mg RPL554	6.0 mg RPL554
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	81	82	79
Units: Litres				
least squares mean (confidence interval 95%)				
Day 1	0.088 (0.058 to 0.117)	0.077 (0.048 to 0.107)	0.103 (0.074 to 0.132)	0.095 (0.065 to 0.125)
Week 4	0.039 (-0.007 to 0.085)	0.052 (0.008 to 0.096)	0.085 (0.040 to 0.130)	0.031 (-0.014 to 0.076)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	78			
Units: Litres				
least squares mean (confidence interval 95%)				
Day 1	0.008 (-0.022 to 0.038)			
Week 4	-0.033 (-0.079 to 0.012)			

Statistical analyses

Statistical analysis title	RPL554 6.0 mg versus Placebo At Day 1
Statistical analysis description:	
Placebo corrected treatment effect: LS mean difference (RPL554 6.0 mg - Placebo) at Day 1	
Comparison groups	6.0 mg RPL554 v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	< 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.087
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.045
upper limit	0.129

Notes:

[9] - A fixed-sequence testing approach was used, starting with the highest dose versus placebo. If a statistically significant difference was found at the 2-sided alpha level of 5%, the testing proceeded to the next highest dose.

Statistical analysis title	RPL554 3.0 mg versus Placebo At Day 1
Statistical analysis description:	
Placebo corrected treatment effect: LS mean difference (RPL554 3.0 mg - Placebo) at Day 1	
Comparison groups	Placebo v 3.0 mg RPL554
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	< 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.095
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.053
upper limit	0.137

Notes:

[10] - A fixed-sequence testing approach was used, starting with the highest dose versus placebo. If a statistically significant difference was found at the 2-sided alpha level of 5%, the testing proceeded to the next highest dose.

Statistical analysis title	RPL554 1.5 mg versus Placebo At Day 1
Statistical analysis description:	
Placebo corrected treatment effect: LS mean difference (RPL554 1.5 mg - Placebo) at Day 1	
Comparison groups	Placebo v 1.5 mg RPL554
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.028
upper limit	0.112

Notes:

[11] - A fixed-sequence testing approach was used, starting with the highest dose versus placebo. If a statistically significant difference was found at the 2-sided alpha level of 5%, the testing proceeded to the next highest dose.

Statistical analysis title	RPL554 0.75 mg versus Placebo At Day 1
Statistical analysis description:	
Placebo corrected treatment effect: LS mean difference (RPL554 0.75 mg - Placebo) at Day 1	
Comparison groups	Placebo v 0.75 mg RPL554
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	< 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.038
upper limit	0.122

Notes:

[12] - A fixed-sequence testing approach was used, starting with the highest dose versus placebo. If a statistically significant difference was found at the 2-sided alpha level of 5%, the testing proceeded to the next highest dose.

Statistical analysis title	RPL554 6.0 mg versus Placebo At Week 4
Statistical analysis description:	
Placebo corrected treatment effect: LS mean difference (RPL554 6.0 mg - Placebo) at Week 4	
Comparison groups	6.0 mg RPL554 v Placebo

Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.048
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.065
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.129

Notes:

[13] - A fixed-sequence testing approach was used, starting with the highest dose versus placebo. If a statistically significant difference was found at the 2-sided alpha level of 5%, the testing proceeded to the next highest dose.

Statistical analysis title	RPL554 3.0 mg versus Placebo At Week 4

Statistical analysis description:

Placebo corrected treatment effect: LS mean difference (RPL554 3.0 mg - Placebo) at Week 4

Comparison groups	Placebo v 3.0 mg RPL554
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	< 0.001
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.119
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.055
upper limit	0.183

Notes:

[14] - A fixed-sequence testing approach was used, starting with the highest dose versus placebo. If a statistically significant difference was found at the 2-sided alpha level of 5%, the testing proceeded to the next highest dose.

Statistical analysis title	RPL554 1.5 mg versus Placebo At Week 4

Statistical analysis description:

Placebo corrected treatment effect: LS mean difference (RPL554 1.5 mg - Placebo) at Week 4

Comparison groups	Placebo v 1.5 mg RPL554
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.008
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.085

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.022
upper limit	0.149

Notes:

[15] - A fixed-sequence testing approach was used, starting with the highest dose versus placebo. If a statistically significant difference was found at the 2-sided alpha level of 5%, the testing proceeded to the next highest dose.

Statistical analysis title	RPL554 0.75 mg versus Placebo At Week 4

Statistical analysis description:

Placebo corrected treatment effect: LS mean difference (RPL554 0.75 mg - Placebo) at Week 4

Comparison groups	Placebo v 0.75 mg RPL554
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.028
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.072
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.008
upper limit	0.137

Notes:

[16] - A fixed-sequence testing approach was used, starting with the highest dose versus placebo. If a statistically significant difference was found at the 2-sided alpha level of 5%, the testing proceeded to the next highest dose.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAEs were collected from the first dose of investigational product up to 2 weeks after the end of the study (approximately 6 weeks).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	RPL554 0.75 mg
Reporting group description: -	
Reporting group title	RPL554 1.5 mg
Reporting group description: -	
Reporting group title	RPL554 3.0 mg
Reporting group description: -	
Reporting group title	RPL554 6.0 mg
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	RPL554 0.75 mg	RPL554 1.5 mg	RPL554 3.0 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 81 (2.47%)	2 / 81 (2.47%)	1 / 82 (1.22%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 81 (0.00%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	0 / 82 (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
Nervous system disorders			
Hepatic encephalopathy			

subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 81 (0.00%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Obstructive pancreatitis			
subjects affected / exposed	0 / 81 (0.00%)	0 / 81 (0.00%)	1 / 82 (1.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	0 / 82 (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			
Completed suicide			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	0 / 82 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0

Serious adverse events	RPL554 6.0 mg	Placebo	

Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 80 (1.25%)	1 / 79 (1.27%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 80 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 80 (0.00%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	0 / 80 (0.00%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 80 (1.25%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Obstructive pancreatitis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 80 (0.00%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic cirrhosis			

subjects affected / exposed	0 / 80 (0.00%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 80 (0.00%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 80 (0.00%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	RPL554 0.75 mg	RPL554 1.5 mg	RPL554 3.0 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 81 (33.33%)	36 / 81 (44.44%)	29 / 82 (35.37%)
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 81 (0.00%)	0 / 81 (0.00%)	0 / 82 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 81 (2.47%)	1 / 81 (1.23%)	4 / 82 (4.88%)
occurrences (all)	3	1	4
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 81 (2.47%)	1 / 81 (1.23%)	1 / 82 (1.22%)
occurrences (all)	2	1	1
Supraventricular extrasystoles			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	0 / 82 (0.00%)
occurrences (all)	0	1	0
Ventricular extrasystoles			

subjects affected / exposed	2 / 81 (2.47%)	1 / 81 (1.23%)	1 / 82 (1.22%)
occurrences (all)	2	1	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 81 (0.00%)	2 / 81 (2.47%)	0 / 82 (0.00%)
occurrences (all)	0	2	0
Headache			
subjects affected / exposed	4 / 81 (4.94%)	4 / 81 (4.94%)	7 / 82 (8.54%)
occurrences (all)	4	4	8
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 81 (0.00%)	0 / 81 (0.00%)	2 / 82 (2.44%)
occurrences (all)	0	0	2
Dry mouth			
subjects affected / exposed	0 / 81 (0.00%)	0 / 81 (0.00%)	2 / 82 (2.44%)
occurrences (all)	0	0	2
Nausea			
subjects affected / exposed	3 / 81 (3.70%)	2 / 81 (2.47%)	2 / 82 (2.44%)
occurrences (all)	3	2	3
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	4 / 81 (4.94%)	5 / 81 (6.17%)	3 / 82 (3.66%)
occurrences (all)	4	5	3
Cough			
subjects affected / exposed	4 / 81 (4.94%)	4 / 81 (4.94%)	6 / 82 (7.32%)
occurrences (all)	4	4	6
Dyspnoea			
subjects affected / exposed	3 / 81 (3.70%)	1 / 81 (1.23%)	1 / 82 (1.22%)
occurrences (all)	3	1	1
Productive cough			
subjects affected / exposed	0 / 81 (0.00%)	3 / 81 (3.70%)	1 / 82 (1.22%)
occurrences (all)	0	5	1
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	0 / 81 (0.00%)	0 / 81 (0.00%)	2 / 82 (2.44%)
occurrences (all)	0	0	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 81 (2.47%)	4 / 81 (4.94%)	4 / 82 (4.88%)
occurrences (all)	2	5	4
Rhinitis			
subjects affected / exposed	1 / 81 (1.23%)	1 / 81 (1.23%)	0 / 82 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	RPL554 6.0 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 80 (36.25%)	31 / 79 (39.24%)	
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 80 (1.25%)	2 / 79 (2.53%)	
occurrences (all)	1	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 80 (3.75%)	1 / 79 (1.27%)	
occurrences (all)	4	1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 80 (0.00%)	0 / 79 (0.00%)	
occurrences (all)	0	0	
Supraventricular extrasystoles			
subjects affected / exposed	1 / 80 (1.25%)	2 / 79 (2.53%)	
occurrences (all)	1	2	
Ventricular extrasystoles			
subjects affected / exposed	0 / 80 (0.00%)	0 / 79 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 80 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	2	
Headache			

subjects affected / exposed	4 / 80 (5.00%)	3 / 79 (3.80%)	
occurrences (all)	5	4	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 80 (0.00%)	1 / 79 (1.27%)	
occurrences (all)	0	1	
Dry mouth			
subjects affected / exposed	1 / 80 (1.25%)	0 / 79 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 80 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 80 (3.75%)	6 / 79 (7.59%)	
occurrences (all)	3	6	
Cough			
subjects affected / exposed	1 / 80 (1.25%)	1 / 79 (1.27%)	
occurrences (all)	1	1	
Dyspnoea			
subjects affected / exposed	1 / 80 (1.25%)	5 / 79 (6.33%)	
occurrences (all)	1	7	
Productive cough			
subjects affected / exposed	0 / 80 (0.00%)	0 / 79 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 80 (1.25%)	1 / 79 (1.27%)	
occurrences (all)	1	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 80 (6.25%)	7 / 79 (8.86%)	
occurrences (all)	5	7	
Rhinitis			

subjects affected / exposed occurrences (all)	0 / 80 (0.00%) 0	2 / 79 (2.53%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2017	• Inclusion criterion 3 updated to the reduce duration of contraception requirements after the last dose of study medication from 1 month to 2 weeks • Inclusion criterion 12 updated to add 'current and former smokers' to the smoking pack history criteria • If necessary, the Investigator could unblind the investigational product without prior contact with the Sponsor. In addition, study personnel were instructed not to discuss the medication appearance with patients, and patients were instructed to seal the medication kit before returning it at their next visit • Schedule for post-dose assessments of vital signs updated to include a 30 minute (post dose) time point • Schedule of pre-dose assessments updated to include 12-lead ECGs and vital signs • Statistical analysis amended to include details of consolidation of data from sites to the country level. A closed testing procedure to test active dose vs. placebo for the primary endpoint was added. • Statistical analysis amended to include details of how PD parameters were to be calculated for each visit with missing visit values imputed • Sample size determination amended to state the detectable limit was considered sufficient to conclusively identify a minimal effective dose of RPL554. • A definition of 'woman of childbearing potential' added
15 September 2017	• Number of study centres increased from 45 to 50 • Text clarified to state that the number of patients was 'approximately 400' • Historical MRI or CT scans were permitted, in addition to historical chest X-rays, in the 12 months prior to Screening (with equivalent results) • Exclusion criterion 14 amended to state: Patients with a history of current chronic uncontrolled disease including, but not limited to, endocrine, active hyperthyroidism thyroid disease, neurological, hepatic, gastrointestinal, renal, hematological, urological, immunological, or ophthalmic diseases that the Investigator believes are clinically significant • Exclusion criterion 16 clarified to be specific for oral beta blockers • Albuterol/salbutamol could be used on an as needed basis • Ocular beta blockers added to oral mucolytics as specified allowed therapies • Rescue medications should only be used during treatment visits when absolutely necessary • Requirement to discuss the re screening of patients with the Sponsor removed • Holter monitor removal was to occur at least 23 hours after placement and the number of PVCs seen in the screening Holter monitor assessment was to be standardized to 24 hours for the exclusion criterion of >1000 PVCs per 24 hours • Serum and urine pregnancy tests were to be performed on all females not just those of childbearing potential • Short acting bronchodilators were not to be used within 8 hours prior to the reversibility test

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported