Clinical trial results:
A Phase IIa, randomised, double blind, placebo controlled, three way crossover study to assess the pharmacokinetics of RPL554 administered to adult patients with Cystic Fibrosis.

Summary

EudraCT number	2015-004263-36
Trial protocol	GB DE
Global end of trial date	03 November 2017

Results information

Result version number	v1 (current)
This version publication date	17 November 2018
First version publication date	17 November 2018

Trial information

Trial identification

Sponsor protocol code	RPL554-010-2015

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Verona Pharma Plc
Sponsor organisation address	3 More London Riverside, London, United Kingdom, SE1 2RE
Public contact	Brian Maurer, Verona Pharma plc, +44 2032834200, brian.maurer@veronapharma.com
Scientific contact	Brian Maurer, Verona Pharma plc, +44 2032834200, brian.maurer@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	03 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 November 2017
Global end of trial reached?	Yes
Global end of trial date	03 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate pharmacokinetics of single nebulised doses of RPL554 in patients with Cystic Fibrosis.

Protection of trial subjects:

Standard procedures for emergency care were followed for any individual adverse events if clinically needed. Short acting bronchodilators could be used as rescue medication.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 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: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	10
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 16 patients were screened for the study and 10 were treated. Patients received study treatment between 20 March 2017 and 30 October 2017. A total of nine patients completed the study and one was withdrawn

Pre-assignment

Screening details:

16 patients were screened. The reasons for screen failure were: (1) ECG/heart rate not meeting protocol ranges, (2) withdrew consent, (3) patient unwell, (4) prednisolone use, (5) spirometry <40% predicted normal and (6) chest infection

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	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	1.5 mg RPL554

Arm description:

1.5 mg RPL554 administered with a nebuliser

Arm type	Experimental
Investigational medicinal product name	1.5 mg 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 nebuliser

Arm title	6 mg RPL554

Arm description:

6 mg RPL554

Arm type	Experimental
Investigational medicinal product name	6 mg RPL554
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:

6 mg RPL554 administered using a nebuliser

Arm title	Placebo

Arm description:

Placebo

Arm type	Experimental

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 using a nebuliser

Number of subjects in period 1	1.5 mg RPL554	6 mg RPL554	Placebo
Started	10	9	10
Completed	10	9	10

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	10	10	
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)	10	10	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	32.6		
standard deviation	± 10.2	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	6	6	

End points

End points reporting groups

Reporting group title	1.5 mg RPL554
Reporting group description:	
1.5 mg RPL554 administered with a nebuliser	
Reporting group title	6 mg RPL554
Reporting group description:	
6 mg RPL554	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Primary: Plasma concentration area under the curve to time t

End point title	Plasma concentration area under the curve to time t[1][2]
End point description:	
AUC from time 0 to time t was estimated	
End point type	Primary
End point timeframe:	
For 24 hours after each dose	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics by treatment group were applied

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics were not applicable to the placebo arm

End point values	1.5 mg RPL554	6 mg RPL554		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	9		
Units: pg.h/mL				
arithmetic mean (standard deviation)	2342 (± 1029.9)	7699 (± 2965.7)		

Statistical analyses

No statistical analyses for this end point

Primary: Maximum plasma concentration

End point title	Maximum plasma concentration[3][4]
End point description:	
End point type	Primary
End point timeframe:	
Over 24 hours after each dose	

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics by treatment group were applied

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics were not applicable to the placebo arm

End point values	1.5 mg RPL554	6 mg RPL554		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	9		
Units: pg/mL				
arithmetic mean (standard deviation)	270.1 (± 91.9)	828.3 (± 256.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Time to maximum plasma concentration

End point title	Time to maximum plasma concentration[5][6]

End point description:

End point type	Primary

End point timeframe:

Over 24 hours after each dose

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics by treatment group were applied

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetics were not applicable to the placebo arm

End point values	1.5 mg RPL554	6 mg RPL554		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	9		
Units: hours				
median (full range (min-max))	1.2 (0.4 to 2.2)	1.3 (0.4 to 2.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Peak forced expired volume in 1 second (FEV1)

End point title	Peak forced expired volume in 1 second (FEV1)

End point description:

End point type	Secondary

End point timeframe:

Over 4 hours after each dose

End point values	1.5 mg RPL554	6 mg RPL554	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	9	10	
Units: Litres				
arithmetic mean (standard deviation)	2.247 (± 0.72)	2.384 (± 0.73)	2.256 (± 0.71)	

Statistical analyses

Statistical analysis title	1.5 mg RPL554 versus placebo
Comparison groups	1.5 mg RPL554 v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0196
Method	ANCOVA
Parameter estimate	Contrast ratio
Point estimate	1.038
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.007
upper limit	1.07

Statistical analysis title	6 mg RPL554 versus placebo
Comparison groups	6 mg RPL554 v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0802
Method	ANCOVA
Parameter estimate	Contrast ratio
Point estimate	1.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.997
upper limit	1.052

Statistical analysis title	6 mg RPL554 versus 1.5 mg RPL554
Comparison groups	1.5 mg RPL554 v 6 mg RPL554
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3487
Method	ANCOVA
Parameter estimate	Contrast ratio
Point estimate	0.986
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.957
upper limit	1.017

Secondary: Area under the curve for FEV1 over 4 hours	
End point title	Area under the curve for FEV1 over 4 hours
End point description:	
End point type	Secondary
End point timeframe:	
Over 4 hours after each dose	

End point values	1.5 mg RPL554	6 mg RPL554	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	9	10	
Units: Litres				
arithmetic mean (standard deviation)	2.194 (± 0.72)	2.313 (± 0.73)	2.133 (± 0.73)	

Statistical analyses

Statistical analysis title	1.5 mg RPL554 versus placebo
Comparison groups	1.5 mg RPL554 v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0043
Method	ANCOVA
Parameter estimate	Contrast ratio
Point estimate	1.072

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.026
upper limit	1.12

Statistical analysis title	6 mg RPL554 versus placebo
Comparison groups	6 mg RPL554 v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0109
Method	ANCOVA
Parameter estimate	Contrast ratio
Point estimate	1.055
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.014
upper limit	1.096

Statistical analysis title	6 mg RPL554 versus 1.5 mg RPL554
Comparison groups	1.5 mg RPL554 v 6 mg RPL554
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4306
Method	ANCOVA
Parameter estimate	Contrast ratio
Point estimate	0.984
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.942
upper limit	1.027

Secondary: Area under the curve for FEV1 over 6 hours	
End point title	Area under the curve for FEV1 over 6 hours
End point description:	

End point type	Secondary
End point timeframe:	
Over 6 hours after each dose	

End point values	1.5 mg RPL554	6 mg RPL554	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	9	10	
Units: Litres				
arithmetic mean (standard deviation)	2.188 (± 0.73)	2.304 (± 0.74)	2.133 (± 0.73)	

Statistical analyses

Statistical analysis title	1.5 mg RPL554 versus placebo
Comparison groups	1.5 mg RPL554 v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0064
Method	ANCOVA
Parameter estimate	Contrast ratio
Point estimate	1.065
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.021
upper limit	1.11

Statistical analysis title	6 mg RPL554 versus placebo
Comparison groups	6 mg RPL554 v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0149
Method	ANCOVA
Parameter estimate	Contrast ratio
Point estimate	1.049
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.011
upper limit	1.089

Statistical analysis title	6 mg RPL554 versus 1.5 mg RPL554
Comparison groups	1.5 mg RPL554 v 6 mg RPL554

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.466
Method	ANCOVA
Parameter estimate	Contrast ratio
Point estimate	0.986
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.945
upper limit	1.027

Secondary: Area under the curve for FEV1 over 8 hours

End point title	Area under the curve for FEV1 over 8 hours
End point description:	

End point type	Secondary
End point timeframe:	
Over 8 hours after each dose	

End point values	1.5 mg RPL554	6 mg RPL554	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	9	10	
Units: Litres				
arithmetic mean (standard deviation)	2.185 (± 0.74)	2.287 (± 0.75)	2.130 (± 0.74)	

Statistical analyses

Statistical analysis title	1.5 mg RPL554 versus placebo
Comparison groups	1.5 mg RPL554 v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0093
Method	ANCOVA
Parameter estimate	Contrast ratio
Point estimate	1.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.017
upper limit	1.107

Statistical analysis title	6 mg RPL554 versus placebo
Comparison groups	6 mg RPL554 v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0333
Method	ANCOVA
Parameter estimate	Contrast ratio
Point estimate	1.042
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.004
upper limit	1.082

Statistical analysis title	6 mg RPL554 versus 1.5 mg RPL554
Comparison groups	1.5 mg RPL554 v 6 mg RPL554
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3693
Method	ANCOVA
Parameter estimate	Contrast ratio
Point estimate	0.982
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.941
upper limit	1.024

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From informed consent to the end of study visit	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1
Reporting groups	
Reporting group title	1.5 mg RPL554
Reporting group description: 1.5 mg RPL554 administered with a nebuliser	
Reporting group title	6 mg RPL554
Reporting group description: 6 mg RPL554	
Reporting group title	Placebo
Reporting group description: Placebo	

Serious adverse events	1.5 mg RPL554	6 mg RPL554	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (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

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	1.5 mg RPL554	6 mg RPL554	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 10 (60.00%)	6 / 9 (66.67%)	3 / 10 (30.00%)
Investigations			
Forced expiratory volume decreased			

subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pulmonary function test decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 10 (20.00%)	2 / 9 (22.22%)	1 / 10 (10.00%)
occurrences (all)	2	2	1
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Dry mouth			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	1 / 10 (10.00%)	2 / 9 (22.22%)	0 / 10 (0.00%)
occurrences (all)	2	2	0
Nasal congestion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Bak pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Oral candidiasis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 10 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2017	The range for ECG heart rate in inclusion criterion 3 was amended from 45 to 90 bpm to 45 to 100 bpm. In addition, the reference for predicted spirometry values was updated from Quanjer, 1993 to GLI Quanjer, 2012 and there was a change to the timeframe in which pharmacokinetic blood samples must be centrifuged after collection to within 30 minutes instead of 15 minutes. The address for the biomarker laboratory was also updated

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported