Clinical trial results:
A phase II, randomised, double blind, placebo controlled, three way crossover study to assess the bronchodilator effect of RPL554 administered in addition to open label tiotropium in patients with COPD.

Summary

EudraCT number	2016-004450-15
Trial protocol	GB
Global end of trial date	24 July 2017

Results information

Result version number	v1 (current)
This version publication date	09 August 2018
First version publication date	09 August 2018

Trial information

Trial identification

Sponsor protocol code	RPL554-CO-202

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, +44 203 283 4200, brian.maurer@veronapharma.com
Scientific contact	Brian Maurer, Verona Pharma plc, +44 203 283 4200, 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	25 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 July 2017
Global end of trial reached?	Yes
Global end of trial date	24 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the bronchodilator effect on peak FEV1 measured in first 4 hours after dosing and average FEV1 over 12 hours of nebulised RPL554, dosed twice daily for 3 days (five total doses), as compared to placebo when administered in addition to once daily tiotropium.

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	27 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: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	15
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was consented on 27 January 2017. Overall, 74 patients were screened for the study and 30 were treated. Patients received study treatment between 14 February 2017 and 07 July 2017. A total of 26 patients completed the study and 4 were withdrawn.

Pre-assignment

Screening details:

74 were screened. The main reasons for screen failure were reversibility test criteria not met (21 patients), withdrew consent (5 patients) and unsuitable COPD history (4 patients). Patients had to discontinue long acting bronchodilators on the day prior to screening and short acting bronchodilators for 8 hours before all spirometry assessments

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	Tiotropium+1.5 mg RPL554

Arm description:

18 mcg tiotropium once daily and 1.5 mg RPL554 twice daily

Arm type	Experimental
Investigational medicinal product name	Tiotropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

18 mcg tiotropium administered by dry powder inhaler

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	Tiotropium+6 mg RPL554

Arm description:

18 mcg tiotropium once daily and 6 mg RPL554 twice daily

Arm type	Experimental
Investigational medicinal product name	Tiotropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

18 mcg tiotropium administered by dry powder inhaler

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	Tiotropium+placebo

Arm description:

18 mcg tiotropium once daily and placebo twice daily

Arm type	Experimental
Investigational medicinal product name	Tiotropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

18 mcg tiotropium administered by dry powder inhaler

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	Tiotropium+1.5 mg RPL554	Tiotropium+6 mg RPL554	Tiotropium+placebo
Started	29	27	28
Completed	29	27	28

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	30	30	
Age categorical			
Age at time of informed consent			
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)	15	15	
From 65-84 years	15	15	
85 years and over	0	0	
Age continuous			
Units: years			
median	64.5		
full range (min-max)	47 to 73	-	
Gender categorical			
Units: Subjects			
Female	13	13	
Male	17	17	

End points

End points reporting groups	
Reporting group title	Tiotropium+1.5 mg RPL554
Reporting group description: 18 mcg tiotropium once daily and 1.5 mg RPL554 twice daily	
Reporting group title	Tiotropium+6 mg RPL554
Reporting group description: 18 mcg tiotropium once daily and 6 mg RPL554 twice daily	
Reporting group title	Tiotropium+placebo
Reporting group description: 18 mcg tiotropium once daily and placebo twice daily	

Primary: Peak FEV1 on Day 3	
End point title	Peak FEV1 on Day 3
End point description: Change from baseline in peak FEV1	
End point type	Primary
End point timeframe: Over 4 hours after morning dosing on Day 3	

End point values	Tiotropium+1.5 mg RPL554	Tiotropium+6 mg RPL554	Tiotropium+placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	27	27	
Units: Litres				
arithmetic mean (standard deviation)	0.477 (± 0.1673)	0.500 (± 0.2157)	0.373 (± 0.1970)	

Statistical analyses

Statistical analysis title	Tiotropium+1.5 mg RPL554 versus tiotropium+placebo
Comparison groups	Tiotropium+1.5 mg RPL554 v Tiotropium+placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0022
Method	ANCOVA
Parameter estimate	LS Mean Ratio
Point estimate	1.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	1.09

Statistical analysis title	Tiotropium+6 mg RPL554 versus tiotropium+placebo
Comparison groups	Tiotropium+placebo v Tiotropium+6 mg RPL554
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Means Ratio
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	1.12

Primary: Area under the curve over 12 hours for FEV1 on Day 3	
End point title	Area under the curve over 12 hours for FEV1 on Day 3
End point description:	
Change from baseline in area under the curve for FEV1 over 12 hours	
End point type	Primary
End point timeframe:	
Over 12 hours after morning dosing on Day 3	

End point values	Tiotropium+1.5 mg RPL554	Tiotropium+6 mg RPL554	Tiotropium+placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	27	27	
Units: Litres*hour				
arithmetic mean (standard deviation)	3.804 (± 1.8512)	3.967 (± 2.2134)	3.197 (± 2.2826)	

Statistical analyses

Statistical analysis title	Tiotropium+1.5 mg RPL554 versus tiotropium+placebo
Comparison groups	Tiotropium+1.5 mg RPL554 v Tiotropium+placebo

Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0988
Method	ANCOVA
Parameter estimate	LS Means Ratio
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.06

Statistical analysis title	Tiotropium+6 mg RPL554 versus tiotropium+placebo
Comparison groups	Tiotropium+6 mg RPL554 v Tiotropium+placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0009
Method	ANCOVA
Parameter estimate	LS Mean Ratio
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	1.09

Secondary: Peak FEV1 on Day 1	
End point title	Peak FEV1 on Day 1
End point description: Change from baseline in peak FEV1	
End point type	Secondary
End point timeframe: Over 4 hours after morning dosing on Day 1	

End point values	Tiotropium+1.5 mg RPL554	Tiotropium+6 mg RPL554	Tiotropium+placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	27	27	
Units: Litres				
arithmetic mean (standard deviation)	0.383 (± 0.1448)	0.432 (± 0.1720)	0.337 (± 0.1854)	

Statistical analyses

Statistical analysis title	Tiotropium+1.5 mg RPL554 versus tiotropium+placebo
Comparison groups	Tiotropium+placebo v Tiotropium+1.5 mg RPL554
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2496
Method	ANCOVA
Parameter estimate	LS Mean Ratio
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.06

Statistical analysis title	Tiotropium+6 mg RPL554 versus tiotropium+placebo
Comparison groups	Tiotropium+6 mg RPL554 v Tiotropium+placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0039
Method	ANCOVA
Parameter estimate	LS Mean Ratio
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	1.1

Secondary: Area under the curve over 12 hours for FEV1 on Day 1

End point title	Area under the curve over 12 hours for FEV1 on Day 1

End point description:

Change from baseline in area under the curve for FEV1 over 12 hours

End point type	Secondary

End point timeframe:

Over 12 hours after morning dosing on Day 1

End point values	Tiotropium+1.5 mg RPL554	Tiotropium+6 mg RPL554	Tiotropium+placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	27	27	
Units: Litres*hour				
arithmetic mean (standard deviation)	3.058 (± 1.4851)	3.094 (± 1.9624)	2.510 (± 1.9381)	

Statistical analyses

Statistical analysis title	Tiotropium+1.5 mg RPL554 versus tiotropium+placebo
Comparison groups	Tiotropium+1.5 mg RPL554 v Tiotropium+placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1404
Method	ANCOVA
Parameter estimate	LS Mean Ratio
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.06

Statistical analysis title	Tiotropium+6 mg RPL554 versus tiotropium+placebo
Comparison groups	Tiotropium+6 mg RPL554 v Tiotropium+placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0228
Method	ANCOVA
Parameter estimate	LS Mean Ratio
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	1.08

Secondary: Area under the curve over 4 hours on Day 1

End point title	Area under the curve over 4 hours on Day 1
End point description: Change from baseline in area under the curve for FEV1 over 4 hours	
End point type	Secondary
End point timeframe: Over 4 hours after morning dosing on Day 1	

End point values	Tiotropium+1.5 mg RPL554	Tiotropium+6 mg RPL554	Tiotropium+placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	27	27	
Units: Litres*hour				
arithmetic mean (standard deviation)	1.208 (± 0.5740)	1.376 (± 0.6630)	0.894 (± 0.6161)	

Statistical analyses

Statistical analysis title	Tiotropium+1.5 mg RPL554 versus tiotropium+placebo
Comparison groups	Tiotropium+1.5 mg RPL554 v Tiotropium+placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0073
Method	ANCOVA
Parameter estimate	LS Mean Ratio
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	1.08

Statistical analysis title	Tiotropium+6 mg RPL554 versus tiotropium+placebo
Comparison groups	Tiotropium+6 mg RPL554 v Tiotropium+placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Ratio
Point estimate	1.08

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	1.12

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From informed consent until the end of the study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Tiotropium+1.5 mg RPL554
Reporting group description: -	
Reporting group title	Tiotropium+6 mg RPL554
Reporting group description: -	
Reporting group title	Tiotropium+placebo
Reporting group description: -	

Serious adverse events	Tiotropium+1.5 mg RPL554	Tiotropium+6 mg RPL554	Tiotropium+placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 29 (3.45%)	0 / 27 (0.00%)	0 / 28 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 27 (0.00%)	0 / 28 (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

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Tiotropium+1.5 mg RPL554	Tiotropium+6 mg RPL554	Tiotropium+placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 29 (41.38%)	12 / 27 (44.44%)	12 / 28 (42.86%)
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 29 (6.90%)	5 / 27 (18.52%)	3 / 28 (10.71%)
occurrences (all)	2	8	3
General disorders and administration site conditions			

Medical device site reaction			
subjects affected / exposed	4 / 29 (13.79%)	1 / 27 (3.70%)	4 / 28 (14.29%)
occurrences (all)	4	1	4
Chest discomfort			
subjects affected / exposed	1 / 29 (3.45%)	1 / 27 (3.70%)	2 / 28 (7.14%)
occurrences (all)	1	1	3
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 29 (3.45%)	1 / 27 (3.70%)	2 / 28 (7.14%)
occurrences (all)	1	1	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 April 2017	The exclusion criteria were amended to remove the prohibition against prior exposure to RPL554.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported