Clinical trial results:
A phase II, randomised, double blind, placebo controlled, six way crossover study to assess the bronchodilator effect of RPL554 administered on top of salbutamol and ipratropium in patients with COPD

Summary

EudraCT number	2015-002536-41
Trial protocol	GB
Global end of trial date	17 December 2015

Results information

Result version number	v1 (current)
This version publication date	04 November 2017
First version publication date	04 November 2017

Trial information

Trial identification

Sponsor protocol code	RPL554-009-2015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02542254
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	Kenneth Newman, Verona Pharma plc, +44 203 283 4200, ken.newman@veronapharma.com
Scientific contact	Kenneth Newman, Verona Pharma plc, +44 203 283 4200, ken.newman@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	17 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 December 2015
Global end of trial reached?	Yes
Global end of trial date	17 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the bronchodilator effect on lung function over 8 hours of single nebulised doses of RPL554, as compared to placebo, when administered in addition to standard care bronchodilators (salbutamol, ipratropium) or placebo.

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:

Short acting bronchodilators could be used as rescue medication.

Evidence for comparator: -

Actual start date of recruitment	17 August 2015
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: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	23
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was consented on 28 September 2015. Overall, 71 patients were screened for the study and 36 were treated . Patients received study treatment between 7 October 2015 and 14 December 2015. A total of 30 patients completed the study and six were withdrawn

Pre-assignment

Screening details:

71 patients were screened. The main reasons for screen failure were reversibility test criteria not met (7 patients), ECG or blood pressure abnormal (7 patients) and unsuitable medical history (6 patients). Patients had to discontinue LABAs and LAMAs on the day of screening and SABAs and SAMAs for 8 hours before all spirometry.

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	Salbutamol and RPL554

Arm description:

200 ug salbutamol pMDI and 6 mg nebulised RPL554

Arm type	Experimental
Investigational medicinal product name	Salbutamol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

200 ug by pressurised metered dose inhaler

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 mg RPL554 administered using a nebuliser

Arm title	Salbutamol

Arm description:

200 ug salbutamol pMDI. Nebulised placebo was also given to effect a double dummy design

Arm type	Active comparator
Investigational medicinal product name	Salbutamol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

200 mcg by pressurised metered dose inhaler

Arm title	Ipratropium and RPL554
Arm description:	
40 ug ipratropium pMDI and 6 mg nebulised RPL554	
Arm type	Experimental
Investigational medicinal product name	Ipratropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use
Dosage and administration details:	
40 ug by pressurised metered dose inhaler	
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 mg RPL554 administered using a nebuliser	
Arm title	Ipratropium
Arm description:	
40 ug ipratropium pMDI. Nebulised placebo was also given to effect a double dummy design	
Arm type	Active comparator
Investigational medicinal product name	Ipratropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use
Dosage and administration details:	
40 ug ipratropium administered using a pMDI	
Arm title	RPL554
Arm description:	
6 mg nebulised RPL554. A placebo pMDI was also given to effect a double dummy design	
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 mg RPL554 administered using a nebuliser	
Arm title	Placebo
Arm description:	
Nebulised placebo and placebo pMDI	
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 given by nebuliser

Number of subjects in period 1	Salbutamol and RPL554	Salbutamol	Ipratropium and RPL554
Started	31	32	34
Completed	31	32	33
Not completed	0	0	1
Adverse event, non-fatal	-	-	1

Number of subjects in period 1	Ipratropium	RPL554	Placebo
Started	33	31	31
Completed	32	31	31
Not completed	1	0	0
Adverse event, non-fatal	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	36	36	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	62		
full range (min-max)	52 to 70	-	
Gender categorical Units: Subjects			
Female	17	17	
Male	19	19	

End points

End points reporting groups

Reporting group title	Salbutamol and RPL554
Reporting group description: 200 ug salbutamol pMDI and 6 mg nebulised RPL554	
Reporting group title	Salbutamol
Reporting group description: 200 ug salbutamol pMDI. Nebulised placebo was also given to effect a double dummy design	
Reporting group title	Ipratropium and RPL554
Reporting group description: 40 ug ipratropium pMDI and 6 mg nebulised RPL554	
Reporting group title	Ipratropium
Reporting group description: 40 ug ipratropium pMDI. Nebulised placebo was also given to effect a double dummy design	
Reporting group title	RPL554
Reporting group description: 6 mg nebulised RPL554. A placebo pMDI was also given to effect a double dummy design	
Reporting group title	Placebo
Reporting group description: Nebulised placebo and placebo pMDI	

Primary: Peak FEV1

End point title	Peak FEV1
End point description:	
End point type	Primary
End point timeframe: Over 8 hours post-dose	

End point values	Salbutamol and RPL554	Salbutamol	Ipratropium and RPL554	Ipratropium
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	32	32	31
Units: Litres				
arithmetic mean (standard deviation)	1.713 (± 0.4339)	1.624 (± 0.4378)	1.7 (± 0.4364)	1.596 (± 0.426)

End point values	RPL554	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	31		
Units: Litres				
arithmetic mean (standard deviation)	1.635 (±	1.418 (±		

0.423)	0.3863)

Statistical analyses

Statistical analysis title	Peak FEV1 Salbutamol/RPL554 vs salbutamol
Comparison groups	Salbutamol and RPL554 v Salbutamol
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	Peak FEV1 Ipratropium/RPL554 vs ipratropium
Comparison groups	Ipratropium and RPL554 v Ipratropium
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	Peak FEV1 Salbutamol/RPL554 vs Ipratropium/RPL554
Comparison groups	Ipratropium and RPL554 v Salbutamol and RPL554
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.998
Method	ANCOVA

Statistical analysis title	Peak FEV1 Salbutamol/RPL554 vs RPL554
Comparison groups	Salbutamol and RPL554 v RPL554
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.004
Method	ANCOVA

Statistical analysis title	Peak FEV1 Ipratropium/RPL554 vs RPL554

Comparison groups	RPL554 v Ipratropium and RPL554
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.005
Method	ANCOVA

Statistical analysis title	Peak FEV1 Salbutamol vs Ipratropium
Comparison groups	Salbutamol v Ipratropium
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.737
Method	ANCOVA

Statistical analysis title	Peak FEV1 Salbutamol vs Placebo
Comparison groups	Salbutamol v Placebo
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	Peak FEV1 Ipratropium vs Placebo
Comparison groups	Placebo v Ipratropium
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	Peak FEV1 RPL554 vs Placebo
Comparison groups	Placebo v RPL554
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA

Primary: AUC FEV1

End point title	AUC FEV1

End point description:

End point type	Primary

End point timeframe:

Over 8 hours post-dose

End point values	Salbutamol and RPL554	Salbutamol	Ipratropium and RPL554	Ipratropium
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	32	32	31
Units: Litres				
arithmetic mean (standard deviation)	1.548 (± 0.4347)	1.453 (± 0.4262)	1.531 (± 0.4224)	1.462 (± 0.4227)

End point values	RPL554	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	31		
Units: Litres				
arithmetic mean (standard deviation)	1.477 (± 0.4287)	1.317 (± 0.4031)		

Statistical analyses

Statistical analysis title	AUC FEV1 Salbutamol/RPL554 vs Salbutamol
Comparison groups	Salbutamol and RPL554 v Salbutamol
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	AUC FEV1 Ipratropium/RPL554 vs Ipratropium
Comparison groups	Ipratropium and RPL554 v Ipratropium
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	AUC FEV1 Salbutamol/RPL554 vs Ipratropium/RPL554
Comparison groups	Ipratropium and RPL554 v Salbutamol and RPL554
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.97
Method	ANCOVA

Statistical analysis title	AUC FEV1 Salbutamol/RPL554 vs RPL554
Comparison groups	Salbutamol and RPL554 v RPL554
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	AUC FEV1 Ipratropium/RPL554 vs R...
Comparison groups	RPL554 v Ipratropium and RPL554
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	AUC FEV1 Salbutamol vs ipratropium
Comparison groups	Salbutamol v Ipratropium
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.029
Method	ANCOVA

Statistical analysis title	AUC FEV1 Salbutamol vs placebo
Comparison groups	Salbutamol v Placebo

Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	AUC FEV1 Ipratropium vs placebo
Comparison groups	Placebo v Ipratropium
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA

Statistical analysis title	AUC FEV1 RPL554 vs placebo
Comparison groups	Placebo v RPL554
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA

Adverse events

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

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Salbutamol and RPL554
Reporting group description: -	
Reporting group title	Salbutamol
Reporting group description: -	
Reporting group title	Ipratropium and RPL554
Reporting group description: -	
Reporting group title	Ipratropium
Reporting group description: -	
Reporting group title	RPL554
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Salbutamol and RPL554	Salbutamol	Ipratropium and RPL554
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	0 / 33 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Ipratropium	RPL554	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	0 / 31 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Salbutamol and RPL554	Salbutamol	Ipratropium and RPL554
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 31 (45.16%)	16 / 32 (50.00%)	13 / 33 (39.39%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	2 / 33 (6.06%)
occurrences (all)	0	0	2
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 31 (0.00%)	2 / 32 (6.25%)	1 / 33 (3.03%)
occurrences (all)	0	2	1
Headache			
subjects affected / exposed	0 / 31 (0.00%)	2 / 32 (6.25%)	0 / 33 (0.00%)
occurrences (all)	0	2	0
Migraine			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Catheter site bruise			
subjects affected / exposed	1 / 31 (3.23%)	1 / 32 (3.13%)	0 / 33 (0.00%)
occurrences (all)	1	1	0
Chest discomfort			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 33 (3.03%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 31 (0.00%)	1 / 32 (3.13%)	0 / 33 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 31 (0.00%)	0 / 32 (0.00%)	1 / 33 (3.03%)
occurrences (all)	0	0	1

Cough			
subjects affected / exposed	5 / 31 (16.13%)	7 / 32 (21.88%)	8 / 33 (24.24%)
occurrences (all)	5	7	8
Dyspnoea			
subjects affected / exposed	0 / 31 (0.00%)	2 / 32 (6.25%)	1 / 33 (3.03%)
occurrences (all)	0	2	1
Oropharyngeal pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 32 (0.00%)	0 / 33 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 31 (0.00%)	2 / 32 (6.25%)	2 / 33 (6.06%)
occurrences (all)	0	2	2
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 31 (0.00%)	2 / 32 (6.25%)	0 / 33 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 31 (6.45%)	0 / 32 (0.00%)	0 / 33 (0.00%)
occurrences (all)	2	0	0

Non-serious adverse events	Ipratropium	RPL554	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 32 (28.13%)	7 / 31 (22.58%)	11 / 31 (35.48%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 32 (3.13%)	1 / 31 (3.23%)	0 / 31 (0.00%)
occurrences (all)	2	1	0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1

Headache			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Migraine			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Catheter site bruise			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
Chest discomfort			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 32 (3.13%)	1 / 31 (3.23%)	0 / 31 (0.00%)
occurrences (all)	1	1	0
Cough			
subjects affected / exposed	2 / 32 (6.25%)	4 / 31 (12.90%)	4 / 31 (12.90%)
occurrences (all)	2	4	4
Dyspnoea			
subjects affected / exposed	1 / 32 (3.13%)	2 / 31 (6.45%)	0 / 31 (0.00%)
occurrences (all)	1	2	0
Oropharyngeal pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 31 (0.00%)	3 / 31 (9.68%)
occurrences (all)	0	0	3
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			

Back pain subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 31 (0.00%) 0	0 / 31 (0.00%) 0
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	0 / 31 (0.00%) 0	0 / 31 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 August 2015	Amend window between Visits 7 and 8 from 2-10 days to 3-10 days Addition of exclusion criteria: 21. Patients with known hypersensitivity to atropine or its derivatives, or to ipratropium bromide or its excipients. 22. Patients with known hypersensitivity to salbutamol or its excipients. 23. Patients with known hypersensitivity to RPL554 or its excipients/components.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported