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/OLODATEROL IN PATIENTS WITH COPD

Summary

EudraCT number	2018-001037-41
Trial protocol	GB
Global end of trial date	13 November 2018

Results information

Result version number	v1 (current)
This version publication date	18 August 2019
First version publication date	18 August 2019

Trial information

Trial identification

Sponsor protocol code	RPL554-CO-204

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03673670
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Verona Pharma plc
Sponsor organisation address	3 More London Riverside, London, United Kingdom, SE12RE
Public contact	Paula Siu, Verona Pharma plc, 44 2032834200, paula.siu@veronapharma.com
Scientific contact	Paula Siu, Verona Pharma plc, 44 2032834200, 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	13 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 November 2018
Global end of trial reached?	Yes
Global end of trial date	13 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the bronchodilator effect on peak forced expired volume in 1 second (FEV1) (measured in the first 4 hours after dosing) of nebulised RPL554 dosed twice daily for 3 days, as compared to placebo, when administered in addition to once daily tiotropium/olodaterol. The peak FEV1 is measured after the morning dose on Day 3.)

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	09 July 2018
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: 4
Country: Number of subjects enrolled	United States: 75
Worldwide total number of subjects	79
EEA total number of subjects	4

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)	41
From 65 to 84 years	38
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited in the United States of America and the United Kingdom. The first patient was consented on 16 July 2018.

Pre-assignment

Screening details:

A total of 142 patients were screened, of which 63 screen failed and 79 were treated

Period 1

Period 1 title	Treatment Period 1
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	1.5 mg RPL554: 6 mg RPL554: Placebo

Arm description:

Patients received 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

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 administered using a jet nebuliser

Investigational medicinal product name	Tiotropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

5/5 mcg from a Respimat device

Arm title	1.5 mg RPL554: Placebo: 6 mg RPL554

Arm description:

Patients received 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

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

Dosage and administration details: 5/5 mcg from a Respimat device	
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 administered using a jet nebuliser	
Arm title	6 mg RPL554: 1.5 mg RPL554: Placebo
Arm description: Patients received 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods	
Arm type	Experimental
Investigational medicinal product name	Tiotropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details: 5/5 mcg from a Respimat device	
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 Jet nebuliser	
Arm title	6 mg RPL554: Placebo: 1.5 mg RPL554
Arm description: Patients received 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods	
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 Jet nebuliser	
Investigational medicinal product name	Tiotropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details: 5/5 mcg from a Respimat device	
Arm title	Placebo: 1.5 mg RPL554: 6 mg RPL554

Arm description:

Patients received placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

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

Dosage and administration details:

5/5 mcg from a Respimat device

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:

Placebo administered using a Jet nebulider

Arm title	Placebo: 6 mg RPL554: 1.5 mg RPL554

Arm description:

Patients received placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

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

Dosage and administration details:

Placebo administered using a Jet nebulider

Investigational medicinal product name	Tiotropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

5/5 mcg from a Respimat device

Number of subjects in period 1	1.5 mg RPL554: 6 mg RPL554: Placebo	1.5 mg RPL554: Placebo: 6 mg RPL554	6 mg RPL554: 1.5 mg RPL554: Placebo
Started	14	14	13
Completed	13	14	12
Not completed	1	0	1
Consent withdrawn by subject	1	-	-

Physician decision	-	-	1
Alpha 1 antitrypsin deficiency	-	-	-
Adverse event, non-fatal	-	-	-

Number of subjects in period 1	6 mg RPL554: Placebo: 1.5 mg RPL554	Placebo: 1.5 mg RPL554: 6 mg RPL554	Placebo: 6 mg RPL554: 1.5 mg RPL554
Started	12	13	13
Completed	12	13	11
Not completed	0	0	2
Consent withdrawn by subject	-	-	-
Physician decision	-	-	-
Alpha 1 antitrypsin deficiency	-	-	1
Adverse event, non-fatal	-	-	1

Period 2	
Period 2 title	Treatment Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms	
Are arms mutually exclusive?	Yes
Arm title	1.5 mg RPL554: 6 mg RPL554: Placebo

Arm description:

Patients received 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

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

Dosage and administration details:

5/5 mcg from a Respimat device

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 Jet nebuliser

Arm title	1.5 mg RPL554: Placebo: 6 mg RPL554

Arm description:

Patients received 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

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

Dosage and administration details:

5/5 mcg from a Respimat device

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:

Placebo administered using a Jet nebulider

Arm title	6 mg RPL554: 1.5 mg RPL554: Placebo

Arm description:

Patients received 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

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

Dosage and administration details:

5/5 mcg from a Respimat device

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 administered using a jet nebuliser

Arm title	6 mg RPL554: Placebo: 1.5 mg RPL554

Arm description:

Patients received 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

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

Dosage and administration details: 5/5 mcg from a Respimat device	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser suspension
Routes of administration	Inhalation use
Dosage and administration details: Placebo administered using a Jet nebulider	
Arm title	Placebo: 1.5 mg RPL554: 6 mg RPL554
Arm description: Patients received placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods	
Arm type	Experimental
Investigational medicinal product name	Tiotropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details: 5/5 mcg from a Respimat device	
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 administered using a jet nebuliser	
Arm title	Placebo: 6 mg RPL554: 1.5 mg RPL554
Arm description: Patients received placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods	
Arm type	Experimental
Investigational medicinal product name	Tiotropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details: 5/5 mcg from a Respimat device	
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 Jet nebuliser	

Number of subjects in period 2	1.5 mg RPL554: 6 mg RPL554: Placebo	1.5 mg RPL554: Placebo: 6 mg RPL554	6 mg RPL554: 1.5 mg RPL554: Placebo
Started	13	14	12
Completed	13	14	11
Not completed	0	0	1
Adverse event, non-fatal	-	-	1

Number of subjects in period 2	6 mg RPL554: Placebo: 1.5 mg RPL554	Placebo: 1.5 mg RPL554: 6 mg RPL554	Placebo: 6 mg RPL554: 1.5 mg RPL554
Started	12	13	11
Completed	12	12	11
Not completed	0	1	0
Adverse event, non-fatal	-	1	-

Period 3	
Period 3 title	Treatment Period 3
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms	
Are arms mutually exclusive?	Yes
Arm title	1.5 mg RPL554: 6 mg RPL554: Placebo

Arm description:

Patients received 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

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

Dosage and administration details:

5/5 mcg from a Respimat device

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:

Placebo administered using a Jet nebulider

Arm title	1.5 mg RPL554: Placebo: 6 mg RPL554

Arm description:

Patients received 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

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

Dosage and administration details:

5/5 mcg from a Respimat device

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 Jet nebuliser

Arm title	6 mg RPL554: 1.5 mg RPL554: Placebo

Arm description:

Patients received 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

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

Dosage and administration details:

5/5 mcg from a Respimat device

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:

Placebo administered using a Jet nebulider

Arm title	6 mg RPL554: Placebo: 1.5 mg RPL554

Arm description:

Patients received 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

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

Dosage and administration details:

5/5 mcg from a Respimat device

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 administered using a jet nebuliser

Arm title	Placebo: 1.5 mg RPL554: 6 mg RPL554

Arm description:

Patients received placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

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

Dosage and administration details:

5/5 mcg from a Respimat device

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 Jet nebuliser

Arm title	Placebo: 6 mg RPL554: 1.5 mg RPL554

Arm description:

Patients received placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

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

Dosage and administration details:

5/5 mcg from a Respimat device

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 administered using a jet nebuliser

Number of subjects in period 3	1.5 mg RPL554: 6 mg RPL554: Placebo	1.5 mg RPL554: Placebo: 6 mg RPL554	6 mg RPL554: 1.5 mg RPL554: Placebo
Started	13	14	11
Completed	13	14	11
Not completed	0	0	0
Adverse event, non-fatal	-	-	-
Pre-dose FEV1 not 20% of baseline	-	-	-

Number of subjects in period 3	6 mg RPL554: Placebo: 1.5 mg RPL554	Placebo: 1.5 mg RPL554: 6 mg RPL554	Placebo: 6 mg RPL554: 1.5 mg RPL554
Started	12	12	11
Completed	12	10	11
Not completed	0	2	0
Adverse event, non-fatal	-	1	-
Pre-dose FEV1 not 20% of baseline	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Treatment Period 1

Reporting group description: -

Reporting group values	Treatment Period 1	Total	
Number of subjects	79	79	
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			
Age at the time of informed consent			
Units: years			
median	64.0		
full range (min-max)	43 to 77	-	
Gender categorical Units: Subjects			
Female	49	49	
Male	30	30	

End points

End points reporting groups

Reporting group title	1.5 mg RPL554: 6 mg RPL554: Placebo

Reporting group description:

Patients received 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

Reporting group title	1.5 mg RPL554: Placebo: 6 mg RPL554

Reporting group description:

Patients received 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

Reporting group title	6 mg RPL554: 1.5 mg RPL554: Placebo

Reporting group description:

Patients received 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

Reporting group title	6 mg RPL554: Placebo: 1.5 mg RPL554

Reporting group description:

Patients received 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

Reporting group title	Placebo: 1.5 mg RPL554: 6 mg RPL554

Reporting group description:

Patients received placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

Reporting group title	Placebo: 6 mg RPL554: 1.5 mg RPL554

Reporting group description:

Patients received placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

Reporting group title	1.5 mg RPL554: 6 mg RPL554: Placebo

Reporting group description:

Patients received 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

Reporting group title	1.5 mg RPL554: Placebo: 6 mg RPL554

Reporting group description:

Patients received 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

Reporting group title	6 mg RPL554: 1.5 mg RPL554: Placebo

Reporting group description:

Patients received 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

Reporting group title	6 mg RPL554: Placebo: 1.5 mg RPL554

Reporting group description:

Patients received 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

Reporting group title	Placebo: 1.5 mg RPL554: 6 mg RPL554

Reporting group description:

Patients received placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

Reporting group title	Placebo: 6 mg RPL554: 1.5 mg RPL554

Reporting group description:

Patients received placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

Reporting group title	1.5 mg RPL554: 6 mg RPL554: Placebo

Reporting group description:

Patients received 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

Reporting group title	1.5 mg RPL554: Placebo: 6 mg RPL554

Reporting group description:

Patients received 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

Reporting group title	6 mg RPL554: 1.5 mg RPL554: Placebo

Reporting group description:

Patients received 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

Reporting group title	6 mg RPL554: Placebo: 1.5 mg RPL554

Reporting group description:

Patients received 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

Reporting group title	Placebo: 1.5 mg RPL554: 6 mg RPL554

Reporting group description:

Patients received placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

Reporting group title	Placebo: 6 mg RPL554: 1.5 mg RPL554

Reporting group description:

Patients received placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 1, 6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 2 then 1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days in Treatment Period 3 with a 7-14 day washout between treatment periods

Subject analysis set title	1.5 mg RPL554
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients who received 1.5 mg RPL554 and had data to compute the pharmacodynamic parameters

Subject analysis set title	6 mg RPL554
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients who received 6 mg RPL554 and had data to compute the pharmacodynamic parameters	
Subject analysis set title	Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients who received placebo and had data to compute the pharmacodynamic parameters	

Primary: Change From Baseline in Peak FEV1 on Day 3

End point title	Change From Baseline in Peak FEV1 on Day 3
End point description:	
Change from baseline FEV1 to peak FEV1 in the 4 hours post-dose after the morning dose on Day 3	
End point type	Primary
End point timeframe:	
Pre-dose; 5, 15 and 30 minutes and 1, 1.5, 2, 4 on Day 3 (after the morning dose)	

End point values	1.5 mg RPL554	6 mg RPL554	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	74	73	73	
Units: Litres				
arithmetic mean (standard deviation)	0.565 (± 0.2783)	0.506 (± 0.2506)	0.519 (± 0.2809)	

Statistical analyses

Statistical analysis title	1.5 mg RPL554 placebo-corrected treatment effect
Comparison groups	Placebo v 1.5 mg RPL554
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.168
Method	ANCOVA
Parameter estimate	Geomean ratio
Point estimate	1.021
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.991
upper limit	1.052

Notes:

[1] - A hierarchical fixed-sequence testing strategy was employed to test the significance of the treatment effect for each of the two RPL554 doses against placebo, starting with the highest dose (6 mg). If a statistically significant difference was found at the 2-sided α level of 5%, the testing proceeded with the next highest dose. Otherwise, testing was stopped, and the remaining null hypotheses were accepted without testing.

Statistical analysis title	6 mg RPL554 placebo-corrected treatment effect

Comparison groups	6 mg RPL554 v Placebo
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.731
Method	ANCOVA
Parameter estimate	GeoMean ratio
Point estimate	0.995
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.966
upper limit	1.025

Notes:

[2] - A hierarchical fixed-sequence testing strategy was employed to test the significance of the treatment effect for each of the two RPL554 doses against placebo, starting with the highest dose (6 mg). If a statistically significant difference was found at the 2-sided α level of 5%, the testing proceeded with the next highest dose. Otherwise, testing was stopped, and the remaining null hypotheses were accepted without testing.

Statistical analysis title	6 mg RPL554 lower-dose corrected treatment effect
Comparison groups	1.5 mg RPL554 v 6 mg RPL554
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.088
Method	ANCOVA
Parameter estimate	GeoMean ratio
Point estimate	0.974
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.946
upper limit	1.004

Notes:

[3] - A hierarchical fixed-sequence testing strategy was employed to test the significance of the treatment effect for each of the two RPL554 doses against placebo, starting with the highest dose (6 mg). If a statistically significant difference was found at the 2-sided α level of 5%, the testing proceeded with the next highest dose. Otherwise, testing was stopped, and the remaining null hypotheses were accepted without testing.

Secondary: Change From Baseline to Trough FEV1 on Day 4

End point title	Change From Baseline to Trough FEV1 on Day 4

End point description:

Change from baseline to morning trough FEV1 on Day 4

End point type	Secondary

End point timeframe:

Pre-dose on Day 4

End point values	1.5 mg RPL554	6 mg RPL554	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	74	73	73	
Units: Litres				
arithmetic mean (standard deviation)	0.186 (± 0.2496)	0.178 (± 0.2123)	0.150 (± 0.2218)	

Statistical analyses

Statistical analysis title	1.5 mg RPL554 placebo-corrected treatment effect
Comparison groups	1.5 mg RPL554 v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.115
Method	ANCOVA
Parameter estimate	GeoMean ratio
Point estimate	1.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.994
upper limit	1.055

Notes:

[4] - A hierarchical fixed-sequence testing strategy was employed to test the significance of the treatment effect for each of the two RPL554 doses against placebo, starting with the highest dose (6 mg). If a statistically significant difference was found at the 2-sided α level of 5%, the testing proceeded with the next highest dose. Otherwise, testing was stopped, and the remaining null hypotheses were accepted without testing.

Statistical analysis title	6 mg RPL554 placebo-corrected treatme...
Comparison groups	Placebo v 6 mg RPL554
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.111
Method	ANCOVA
Parameter estimate	GeoMean ratio
Point estimate	1.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.994
upper limit	1.055

Notes:

[5] - A hierarchical fixed-sequence testing strategy was employed to test the significance of the treatment effect for each of the two RPL554 doses against placebo, starting with the highest dose (6 mg). If a statistically significant difference was found at the 2-sided α level of 5%, the testing proceeded with the next highest dose. Otherwise, testing was stopped, and the remaining null hypotheses were accepted without testing.

Statistical analysis title	6 mg RPL554 lower dose-corrected treatme...

Comparison groups	6 mg RPL554 v 1.5 mg RPL554
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.978
Method	ANCOVA
Parameter estimate	GeoMean ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.971
upper limit	1.03

Notes:

[6] - A hierarchical fixed-sequence testing strategy was employed to test the significance of the treatment effect for each of the two RPL554 doses against placebo, starting with the highest dose (6 mg). If a statistically significant difference was found at the 2-sided α level of 5%, the testing proceeded with the next highest dose. Otherwise, testing was stopped, and the remaining null hypotheses were accepted without testing.

Secondary: Change From Baseline in AUC0-4h FEV1 on Day 3

End point title	Change From Baseline in AUC0-4h FEV1 on Day 3
End point description:	
Change from baseline FEV1 to AUC FEV1 over 4 hours post-dose after the morning dose on Day 3	
End point type	Secondary
End point timeframe:	
Pre-dose; 5, 15 and 30 minutes and 1, 1.5, 2, 4 hours on Day 3 (after the morning dose)	

End point values	1.5 mg RPL554	6 mg RPL554	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	74	73	73	
Units: Litres				
arithmetic mean (standard deviation)	0.429 (± 0.2518)	0.390 (± 0.2246)	0.377 (± 0.2485)	

Statistical analyses

Statistical analysis title	1.5 mg RPL554 placebo-corrected treatment effect
Comparison groups	1.5 mg RPL554 v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.039
Method	ANCOVA
Parameter estimate	GeoMean ratio
Point estimate	1.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.002
upper limit	1.058

Notes:

[7] - A hierarchical fixed-sequence testing strategy was employed to test the significance of the treatment effect for each of the two RPL554 doses against placebo, starting with the highest dose (6 mg). If a statistically significant difference was found at the 2-sided α level of 5%, the testing proceeded with the next highest dose. Otherwise, testing was stopped, and the remaining null hypotheses were accepted without testing.

Statistical analysis title	6 mg RPL554 placebo-corrected treatme...
Comparison groups	Placebo v 6 mg RPL554
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.303
Method	ANCOVA
Parameter estimate	GeoMean ratio
Point estimate	1.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.987
upper limit	1.043

Notes:

[8] - A hierarchical fixed-sequence testing strategy was employed to test the significance of the treatment effect for each of the two RPL554 doses against placebo, starting with the highest dose (6 mg). If a statistically significant difference was found at the 2-sided α level of 5%, the testing proceeded with the next highest dose. Otherwise, testing was stopped, and the remaining null hypotheses were accepted without testing.

Statistical analysis title	6 mg RPL554 lower dose-corrected treatme...
Comparison groups	6 mg RPL554 v 1.5 mg RPL554
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.294
Method	ANCOVA
Parameter estimate	GeoMean ratio
Point estimate	0.985
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.958
upper limit	1.013

Notes:

[9] - A hierarchical fixed-sequence testing strategy was employed to test the significance of the treatment effect for each of the two RPL554 doses against placebo, starting with the highest dose (6 mg). If a statistically significant difference was found at the 2-sided α level of 5%, the testing proceeded with the next highest dose. Otherwise, testing was stopped, and the remaining null hypotheses were accepted without testing.

Secondary: Change From Baseline in Peak FEV1 on Day 1

End point title	Change From Baseline in Peak FEV1 on Day 1

End point description:

Change from baseline FEV1 to peak FEV1 in the 4 hours post-dose after the morning dose on Day 1

End point type	Secondary

End point timeframe:

Pre-dose; 5, 15 and 30 minutes and 1, 1.5, 2, 4 hours on Day 1 (after the morning dose)

End point values	1.5 mg RPL554	6 mg RPL554	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	74	73	73	
Units: Litres				
arithmetic mean (standard deviation)	0.490 (± 0.2219)	0.467 (± 0.2393)	0.445 (± 0.2306)	

Statistical analyses

Statistical analysis title	1.5 mg RPL554 placebo-corrected treatment effect
Comparison groups	1.5 mg RPL554 v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.02
Method	ANCOVA
Parameter estimate	GeoMean ratio
Point estimate	1.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.005
upper limit	1.061

Notes:

[10] - A hierarchical fixed-sequence testing strategy was employed to test the significance of the treatment effect for each of the two RPL554 doses against placebo, starting with the highest dose (6 mg). If a statistically significant difference was found at the 2-sided α level of 5%, the testing proceeded with the next highest dose. Otherwise, testing was stopped, and the remaining null hypotheses were accepted without testing.

Statistical analysis title	6 mg RPL554 placebo-corrected treatme...
Comparison groups	Placebo v 6 mg RPL554
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.404
Method	ANCOVA
Parameter estimate	GeoMean ratio
Point estimate	1.012

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.984
upper limit	1.039

Notes:

[11] - A hierarchical fixed-sequence testing strategy was employed to test the significance of the treatment effect for each of the two RPL554 doses against placebo, starting with the highest dose (6 mg). If a statistically significant difference was found at the 2-sided α level of 5%, the testing proceeded with the next highest dose. Otherwise, testing was stopped, and the remaining null hypotheses were accepted without testing.

Statistical analysis title	6 mg RPL554 lower dose-corrected treatme...
Comparison groups	6 mg RPL554 v 1.5 mg RPL554
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.134
Method	ANCOVA
Parameter estimate	GeoMean ratio
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.953
upper limit	1.006

Notes:

[12] - A hierarchical fixed-sequence testing strategy was employed to test the significance of the treatment effect for each of the two RPL554 doses against placebo, starting with the highest dose (6 mg). If a statistically significant difference was found at the 2-sided α level of 5%, the testing proceeded with the next highest dose. Otherwise, testing was stopped, and the remaining null hypotheses were accepted without testing.

Secondary: Change From Baseline in AUC0-12h FEV1 on Day 3

End point title	Change From Baseline in AUC0-12h FEV1 on Day 3

End point description:

Change from baseline in AUC over 12 hours post-dose after the morning dose on Day 3

End point type	Secondary

End point timeframe:

Pre-dose; 5, 15 and 30 minutes and 1, 1.5, 2, 4, 6, 8, 12 hours on Day 3 (after the morning dose)

End point values	1.5 mg RPL554	6 mg RPL554	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	74	73	73	
Units: Litres				
arithmetic mean (standard deviation)	0.390 (± 0.2426)	0.347 (± 0.2219)	0.337 (± 0.2447)	

Statistical analyses

Statistical analysis title	1.5 mg RPL554 placebo-corrected treatment effect
Comparison groups	1.5 mg RPL554 v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.067
Method	ANCOVA
Parameter estimate	GeoMean Ratio
Point estimate	1.027
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.998
upper limit	1.057

Notes:

[13] - A hierarchical fixed-sequence testing strategy was employed to test the significance of the treatment effect for each of the two RPL554 doses against placebo, starting with the highest dose (6 mg). If a statistically significant difference was found at the 2-sided α level of 5%, the testing proceeded with the next highest dose. Otherwise, testing was stopped, and the remaining null hypotheses were accepted without testing.

Statistical analysis title	6 mg RPL554 placebo-corrected treatme...
Comparison groups	Placebo v 6 mg RPL554
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.395
Method	ANCOVA
Parameter estimate	GeoMean Ratio
Point estimate	1.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.984
upper limit	1.042

Notes:

[14] - A hierarchical fixed-sequence testing strategy was employed to test the significance of the treatment effect for each of the two RPL554 doses against placebo, starting with the highest dose (6 mg). If a statistically significant difference was found at the 2-sided α level of 5%, the testing proceeded with the next highest dose. Otherwise, testing was stopped, and the remaining null hypotheses were accepted without testing.

Statistical analysis title	6 mg RPL554 lower dose-corrected treatme...
Comparison groups	6 mg RPL554 v 1.5 mg RPL554
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.324
Method	ANCOVA
Parameter estimate	GeoMean Ratio
Point estimate	0.986

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.958
upper limit	1.015

Notes:

[15] - A hierarchical fixed-sequence testing strategy was employed to test the significance of the treatment effect for each of the two RPL554 doses against placebo, starting with the highest dose (6 mg). If a statistically significant difference was found at the 2-sided α level of 5%, the testing proceeded with the next highest dose. Otherwise, testing was stopped, and the remaining null hypotheses were accepted without testing.

Secondary: Change From Baseline in Peak FEV1 After Evening Dose on Day 3

End point title	Change From Baseline in Peak FEV1 After Evening Dose on Day 3

End point description:

Change from baseline FEV1 to peak FEV1 in the 4 hours post-dose after the evening dose on Day 3

End point type	Secondary

End point timeframe:

Pre-dose; 5, 15 and 30 minutes and 1, 1.5, 2, 4 hours on Day 3 (after the evening dose)

End point values	1.5 mg RPL554	6 mg RPL554	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	74	73	73	
Units: Litres				
arithmetic mean (standard deviation)	0.453 (± 0.2625)	0.405 (± 0.2581)	0.324 (± 0.2211)	

Statistical analyses

Statistical analysis title	1.5 mg RPL554 placebo-corrected treatment effect
Comparison groups	1.5 mg RPL554 v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	GeoMean ratio
Point estimate	1.082
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.043
upper limit	1.123

Notes:

[16] - A hierarchical fixed-sequence testing strategy was employed to test the significance of the treatment effect for each of the two RPL554 doses against placebo, starting with the highest dose (6 mg). If a statistically significant difference was found at the 2-sided α level of 5%, the testing proceeded with the next highest dose. Otherwise, testing was stopped, and the remaining null hypotheses were

accepted without testing.

Statistical analysis title	6 mg RPL554 placebo-corrected treatme...
Comparison groups	Placebo v 6 mg RPL554
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.002
Method	ANCOVA
Parameter estimate	GeoMean ratio
Point estimate	1.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.023
upper limit	1.101

Notes:

[17] - A hierarchical fixed-sequence testing strategy was employed to test the significance of the treatment effect for each of the two RPL554 doses against placebo, starting with the highest dose (6 mg). If a statistically significant difference was found at the 2-sided α level of 5%, the testing proceeded with the next highest dose. Otherwise, testing was stopped, and the remaining null hypotheses were accepted without testing.

Statistical analysis title	6 mg RPL554 lower dose-corrected treatme...
Comparison groups	6 mg RPL554 v 1.5 mg RPL554
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.288
Method	ANCOVA
Parameter estimate	GeoMean ratio
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.945
upper limit	1.017

Notes:

[18] - A hierarchical fixed-sequence testing strategy was employed to test the significance of the treatment effect for each of the two RPL554 doses against placebo, starting with the highest dose (6 mg). If a statistically significant difference was found at the 2-sided α level of 5%, the testing proceeded with the next highest dose. Otherwise, testing was stopped, and the remaining null hypotheses were accepted without testing.

Secondary: Change From Baseline in AUC0-12h FEV1 on Day 1	
End point title	Change From Baseline in AUC0-12h FEV1 on Day 1
End point description:	
Change from baseline FEV1 to AUC FEV1 over 12 hours post-dose after the morning dose on Day 1	
End point type	Secondary
End point timeframe:	
Pre-dose; 5, 15 and 30 minutes and 1, 1.5, 2, 4, 6, 8, 12 hours on Day 1 (after the morning dose)	

End point values	1.5 mg RPL554	6 mg RPL554	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	74	73	73	
Units: Litres				
arithmetic mean (standard deviation)	0.333 (± 0.1815)	0.308 (± 0.1854)	0.303 (± 0.1920)	

Statistical analyses

Statistical analysis title	1.5 mg RPL554 placebo-corrected treatment effect
Comparison groups	1.5 mg RPL554 v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.096
Method	ANCOVA
Parameter estimate	GeoMean ratio
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.997
upper limit	1.043

Notes:

[19] - A hierarchical fixed-sequence testing strategy was employed to test the significance of the treatment effect for each of the two RPL554 doses against placebo, starting with the highest dose (6 mg). If a statistically significant difference was found at the 2-sided α level of 5%, the testing proceeded with the next highest dose. Otherwise, testing was stopped, and the remaining null hypotheses were accepted without testing.

Statistical analysis title	6 mg RPL554 placebo-corrected treatme...
Comparison groups	Placebo v 6 mg RPL554
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	= 0.862
Method	ANCOVA
Parameter estimate	GeoMean ratio
Point estimate	1.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.979
upper limit	1.025

Notes:

[20] - A hierarchical fixed-sequence testing strategy was employed to test the significance of the treatment effect for each of the two RPL554 doses against placebo, starting with the highest dose (6 mg). If a statistically significant difference was found at the 2-sided α level of 5%, the testing proceeded

with the next highest dose. Otherwise, testing was stopped, and the remaining null hypotheses were accepted without testing.

Statistical analysis title	6 mg RPL554 lower dose-corrected treatme...
Comparison groups	6 mg RPL554 v 1.5 mg RPL554
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	= 0.135
Method	ANCOVA
Parameter estimate	GeoMean ratio
Point estimate	0.983
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.006

Notes:

[21] - A hierarchical fixed-sequence testing strategy was employed to test the significance of the treatment effect for each of the two RPL554 doses against placebo, starting with the highest dose (6 mg). If a statistically significant difference was found at the 2-sided α level of 5%, the testing proceeded with the next highest dose. Otherwise, testing was stopped, and the remaining null hypotheses were accepted without testing.

Secondary: Determination of Onset of Action on Day 1

End point title	Determination of Onset of Action on Day 1
End point description:	
Time to >10% increase in FEV1 from pre-first dose, censored at 2 hours	
End point type	Secondary
End point timeframe:	
Pre-dose; 5, 15 and 30 minutes and 1, 1.5, 2 hours on Day 1 (after the morning dose)	

End point values	1.5 mg RPL554	6 mg RPL554	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	74	73	73	
Units: Hours				
median (full range (min-max))	10 (5 to 15)	6 (5 to 12)	11 (6 to 14)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From informed consent until the end of the study	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0
Reporting groups	
Reporting group title	1.5 mg RPL554
Reporting group description:	
1.5 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days	
Reporting group title	6 mg Dose RPL554
Reporting group description:	
6 mg RPL554 twice daily plus tiotropium 5/5 mcg once daily for 3 days	
Reporting group title	Placebo
Reporting group description:	
Placebo twice daily plus tiotropium 5/5 mcg once daily for 3 days	

Serious adverse events	1.5 mg RPL554	6 mg Dose RPL554	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	0 / 76 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	0 / 76 (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

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

Non-serious adverse events	1.5 mg RPL554	6 mg Dose RPL554	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 75 (20.00%)	15 / 74 (20.27%)	8 / 76 (10.53%)
Investigations			
Blood glucose increased			

subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	0 / 76 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	0 / 76 (0.00%)
occurrences (all)	1	1	0
Injury, poisoning and procedural complications			
Upper limb fracture			
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	0 / 76 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	1 / 76 (1.32%)
occurrences (all)	0	2	1
Cardiac disorders			
Ventricular extrasystoles			
subjects affected / exposed	2 / 75 (2.67%)	3 / 74 (4.05%)	0 / 76 (0.00%)
occurrences (all)	3	3	0
Accelerated idioventricular rhythm			
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	0 / 76 (0.00%)
occurrences (all)	1	0	0
Atrioventricular block second degree			
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	1 / 76 (1.32%)
occurrences (all)	1	0	1
Tachycardia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	0 / 76 (0.00%)
occurrences (all)	1	0	0
Ventricular tachycardia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	0 / 76 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 75 (6.67%)	5 / 74 (6.76%)	1 / 76 (1.32%)
occurrences (all)	5	6	1
Syncope			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1

General disorders and administration site conditions			
Medical device site rash			
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	0 / 76 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	0 / 76 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	0 / 76 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	1 / 76 (1.32%)
occurrences (all)	0	1	1
Chronic onstructive pulmonary disease			
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	1 / 76 (1.32%)
occurrences (all)	1	1	1
Dyspnoea			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	1 / 76 (1.32%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	1 / 76 (1.32%)
occurrences (all)	1	1	1
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	1 / 76 (1.32%)
occurrences (all)	1	0	1
Bronchitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	0 / 76 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2018	• Inclusion Criterion 3 clarified to specify that the time frames indicated for contraception use applied to both males and females. • Exclusion Criterion 4 updated to add atropine to list of drugs with known hypersensitivity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported