Verona Pharma

CLINICAL STUDY PROTOCOL

A PHASE II, RANDOMISED STUDY TO ASSESS THE PHARMACOKINETICS, SAFETY AND PHARMACODYNAMICS OF SINGLE AND REPEAT DOSES OF RPL554 ADMINISTERED BY PRESSURISED METERED DOSE INHALER IN PATIENTS WITH COPD

STUDY NO. RPL554-MD-201

Version:	**3.0**
Date:	**24 December 2019**
Phase:	**II**
Investigational Medicinal Product:	**RPL554**
EudrACT number:	**2018-004896-11**

THIS STUDY WILL BE CONDUCTED IN ACCORDANCE WITH THE INTERNATIONAL COUNCIL ON HARMONISATION GUIDELINES FOR GOOD CLINICAL PRACTICE (DIRECTIVE CPMP/ICH/135/95), THE DECLARATION OF HELSINKI (1964) AS AMENDED AND APPLICABLE REGULATORY REQUIREMENTS

SPONSOR SIGNATURE PAGE

THIS DOCUMENT HAS BEEN APPROVED BY VERONA PHARMA PLC:

[redacted]

24 Dec 2019

INVESTIGATOR SIGNATURE PAGE

I, the undersigned, am responsible for the conduct of the study at my study centre and agree to the following:

I understand that this protocol is a confidential document for the use of the Investigator's team and other persons involved in the study only, and for the information of the Independent Ethics Committee (IEC). The information contained herein must not be communicated to a third party without prior written approval from the Sponsor.

I understand and will conduct the study according to the protocol, any approved protocol amendments, ICH GCP and all applicable regulatory authority requirements and national laws. To ensure compliance with the guidelines, the study will be monitored by a representative of the Sponsor and may be audited by an independent body. I agree, by written consent to the protocol, to fully co-operate with compliance checks by allowing access to all documentation by authorised individuals.

I have read and understand fully the Investigator Brochure and I am familiar with the study medication and its use according to this protocol.

Name and Title	Signature	Date

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A full list of all vendors will be provided to all participating study centres and maintained in the study file.

DETAIL OF AMENDMENTS SINCE THE PREVIOUS VERSION

Synopsis

The Planned Study Period has been extended to June 2020.

Section 4.1, Inclusion Criteria

In Inclusion Criterion 4, the range for heart rate obtained from ECG has been changed from 50-90 to 45-109 beats per minute.

Section 4.2, Exclusion Criteria

Wording for Exclusion Criterion 14 has been changed as follows:

From: Documented cardiovascular disease, including any history (<1 year) of arrhythmias, angina, recent or suspected myocardial infarction, congestive heart failure, unstable or uncontrolled hypertension, or diagnosis of hypertension within 3 months prior to Screening.

To: Historical or current evidence of clinically significant cardiovascular disease. Significant is defined as any disease that in the opinion of the investigator could put the safety of the patient at risk, or could affect the efficacy or safety analyses if the condition were to exacerbate during the study. In particular, the following are excluded:

- Myocardial infarction within 1 year prior to Screening
- Unstable angina within 6 months prior to Screening
- Unstable or life-threatening arrythmia requiring intervention within 3 months prior to Screening
- Diagnosis of NYHA class III or IV heart disease

Section 6.4.1.2, Study Medication Administration

During Day 1 of each treatment period in Part B, the time window for administering the second (evening) dose has been increased from ±10 minutes to ±30 minutes.

SYNOPSIS

Title of Study:	A Phase II, Randomised Study to Assess the Pharmacokinetics, Safety and Pharmacodynamics of Single and Repeat Doses of RPL554 Administered by Pressurised Metered Dose Inhaler in Patients with COPD
Protocol Number:	RPL554-MD-201
EudrACT Number:	2018-004896-11
Phase:	II
Sponsor:	Verona Pharma plc
Study Centre(s):	Two or three study centres in the UK
Planned Study Period:	April 2019 to June 2020
Objectives:	**Part A:** **Primary Objective** To investigate the pharmacokinetic (PK) profile of single doses of RPL554, administered by pressurised metered dose inhaler (pMDI), in patients with moderate to severe chronic obstructive pulmonary disease (COPD). **Secondary Objectives** • To investigate the safety and tolerability of single doses of RPL554 administered by pMDI, including effects on peak pulse and heart rate • To investigate the bronchodilator effect of single doses of RPL554 administered by pMDI, in terms of peak forced expiratory volume in 1 second (FEV_1), average FEV_1 area under the curve $(AUC)_{0-4h}$ and average FEV_1 AUC_{0-12h} **Part B:** **Primary Objective** To investigate the bronchodilator effect of repeat doses of RPL554 administered by pMDI, assessed in terms of peak FEV_1. **Secondary Objectives** • To investigate the safety and tolerability of repeat doses of RPL554, administered by pMDI • To investigate the bronchodilator effect of RPL554 administered by pMDI, in terms of average FEV_1 AUC_{0-12h}, average FEV_1 AUC_{0-4h}, and trough FEV_1 • To determine the onset of action of RPL554 administered by pMDI • To evaluate the PK profile of RPL554 administered by pMDI • To evaluate the amount of rescue medication use during treatment periods **Exploratory Objectives** • To assess the dose response of RPL554 on peak and average FEV_1 AUC_{0-12h} after morning dose on Day 7, and morning trough FEV_1 prior to the last dose on Day 7 • To examine the effect of RPL554 administered by pMDI on a Likert dyspnoea scale
Study Design and Methodology:	This study will consist of two parts: Part A is a parallel group, placebo controlled single dose study to ascertain the PK profile, safety and bronchodilator effect of RPL554 administered via a pMDI. There will be six treatment arms; five will be double blind and one will be single-blind (due to the different number of puffs administered). Part B is a placebo controlled, complete block crossover, repeat dose study to assess the bronchodilator effect of repeat doses of RPL554 dosed twice daily via a pMDI over 7 days. The treatments will be double blind.

	Patients will be screened for eligibility, including a reversibility test (spirometry both pre- and post-four puffs of salbutamol) between 7 and 14 days before the first dose of study medication. Part A: After passing Screening and meeting all inclusion and no exclusion criteria, approximately 36 patients will participate in a parallel group, single dose treatment. They will be randomised equally to one of six treatment arms with approximately six patients per arm. A single dose of RPL554 or placebo will be administered followed by 12 hours of study assessments, including PK, safety and serial spirometry. Patients will return the following day for assessments at 24 hours post-dose. The data from Part A will be locked, unblinded and analysed prior to commencing Part B. Safety, PK and efficacy/pharmacodynamic data will be assessed for each treatment arm to determine which dose levels from Treatment Arms 1 through 4 will be evaluated in Part B. Part B: Patients from Part A will then be randomly assigned to one of up to five treatment sequences in a crossover design, consisting of up to five 1-week treatment periods separated by a 7 to 10 day washout period. Each treatment sequence will include up to four dose levels of RPL554 administered by pMDI (selected from Part A) and a double blind placebo pMDI treatment. Each treatment period consists of 6 days of twice daily dosing, followed by a morning dose administered only on Day 7. Patients will undergo study assessments over 12 hours on Days 1 and 7 in each treatment period. Patients will return for an End of Study Visit approximately 7 days after the completion of the final Treatment Period (or sooner in the case of early termination). The pre-dose FEV_1 on Day 1 of Treatment Periods 2 and forward must be within ±20% of the pre-dose FEV_1 on Day 1 of Treatment Period 1, in order to ensure consistent baseline FEV_1 for each study treatment. Patients will be dispensed rescue medication to be used as needed during the Screening, treatment and washout periods.
Study Procedures:	The following will be performed at each treatment visit: • Measurements of lung function (FEV_1 and forced vital capacity [FVC]) by spirometry – Screening – Part A: Pre-dose and up to 12 hours post-dose – Part B: Pre-dose up to 12 hours post-dose on Days 1 and 7 – End of Study Visit • 12-lead electrocardiogram (ECG) – Screening – Part A: Pre-dose and up to 8 hours post dose – Part B: Pre-dose on Days 1 and 7 • Vital signs – Screening – Part A: Pre-dose and up to 24 hours post-dose – Part B: Pre-dose and up to 12 hours post-dose on Days 1 and 7 – End of Study Visit • PK – Part A: Pre-dose and up to 24 hours post-dose – Part B: Pre-dose and up to 12 hours post-dose on Days 1 and 7 • Laboratory safety tests – Screening, pre-dose on Days 1 and 7 of each treatment period in Part B, and End of Study Visit Adverse events will be recorded throughout the study.

Number of Patients Planned:	Approximately 36 randomised patients
Main Criteria for Eligibility:	***Inclusion Criteria*** Male and female patients with moderate to severe COPD, with a post-bronchodilator FEV_1 of 40 to 80% of predicted and FEV_1/FVC ratio of ≤0.70. They must have a baseline increase in FEV_1 of ≥150 mL following four puffs of salbutamol. They must have at least a 10 pack-year smoking history, and may be either a current or former smoker. ***Exclusion Criteria*** Patients must be clinically stable without recent COPD exacerbations or hospitalisations. They must not have uncontrolled disease or chronic heart failure.
Study Treatments:	In Part A (parallel group), study medication will be administered as a single dose as follows: Treatment Arm 1: RPL554 100 μg double blind Treatment Arm 2: RPL554 300 μg double blind Treatment Arm 3: RPL554 1000 μg double blind Treatment Arm 4: RPL554 3000 μg double blind Treatment Arm 5: RPL554 6000 μg single-blind Treatment Arm 6: Placebo double blind In Part B (double blind crossover), study medication will be administered as repeat doses (twice daily) over either four or five treatment periods within a putative range of 100 μg up to 3000 μg, plus placebo, depending on the results from Part A.
Duration of Treatment:	Part A: 7 to 14 day Screening period, followed by single dose treatment and then an analysis period (exact timing to be determined). Part B: Four or five treatment periods, each consisting of 7 days treatment, separated by 7 to 10 day washout periods.
Statistical Methods:	Treatments will be compared using appropriate analysis of covariance models for Parts A and B, respectively. Multiplicative models will be used for FEV_1 and additive models for blood pressure, pulse rate and ECG heart rate. RPL554 by pMDI treatments will be compared to placebo using a closed test procedure starting with the highest dose of RPL554.
Sample Size Determination:	The sample size is determined for Part B. Assuming a residual coefficient of variation of 6% for peak FEV_1, 30 patients will give an 80% power to detect a pairwise difference in peak FEV_1 of 4.6%. Assuming a mean baseline FEV_1 of 1.5 L, this will correspond to a difference of about 70 mL. To account for withdrawals, approximately 36 patients will be randomised to Part A.

TABLE OF CONTENTS AND LIST OF TABLES AND FIGURES

Table of Contents

List of Tables and Figures

LIST OF ABBREVIATIONS

ATS	American Thoracic Society
AUC	Area under the curve
BMI	Body mass index
C_{max}	Maximum concentration
COPD	Chronic obstructive pulmonary disease
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
DPI	Dry powder inhaler
EDTA	Ethylenediaminetetraacetic acid
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HFA	Hydrofluoroalkane
HRT	Hormone replacement therapy
ICH	International Council on Harmonisation
ICS	Inhaled corticosteroid
ID	Identification
IEC	Independent Ethics Committee
IUPAC	International Union of Pure and Applied Chemistry
LABA	Long acting β_2-agonists
LAMA	Long acting muscarinic antagonists
MedDRA	Medical Dictionary for Regulatory Activities
NHANES	National Health and Nutrition Examination Survey
PDE	Phosphodiesterase
PK	Pharmacokinetics
pMDI	Pressurised metered dose inhaler
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SAS	Statistical analysis software
SOC	System organ class
SUSAR	Suspected, unexpected serious adverse reaction
t_{max}	Time to maximum concentration

1 INTRODUCTION

1.1 Disease and Study Medication Review

Chronic obstructive pulmonary disease (COPD) is characterised by progressive airflow obstruction that is not fully reversible. Chronic inflammation of the respiratory tract, acute exacerbations primarily caused by viral and/or bacterial infections, airway remodelling, and excessive mucus production are believed to contribute to the airflow obstruction and lung parenchymal destruction. COPD is predicted to be the third leading cause of death and fourth most common cause of disability worldwide by 2030, and chronic tobacco smoke exposure is believed to be a key etiological factor (Stuckler, 2008).

Current standard of care treatments include inhaled short- and long-acting bronchodilators, inhaled corticosteroids and, more recently, the phosphodiesterase (PDE) 4 inhibitor roflumilast. These therapies have little or no effect on disease progression or mortality, although there is evidence to suggest that they can reduce exacerbation rates and improve quality of life (Rabe et al, 2005; Calverley et al, 2007; Rennard et al, 2006, Singh et al, 2015). Approximately 30% to 40% of moderate to severe COPD patients on triple inhaled therapy (inhaled corticosteroid [ICS]/long acting muscarinic antagonists [LAMA]/long acting β_2-agonists [LABA]) remain uncontrolled and continue to experience airway obstruction, COPD symptoms and exacerbations (Vestbo et al, 2017). Thus, there is an urgent unmet medical need for drugs with novel mechanisms of action that can be used by these patients in addition to current therapies.

RPL554, a small molecule isoquinolone derivative, is a dual inhibitor of two isoforms (type 3 and 4) of the PDE family of enzymes. PDE3 and PDE4 are known to have a role in modulating the inflammatory airway response in respiratory diseases, including COPD, allergic asthma and allergic rhinitis. In general, PDE3 inhibitors act as bronchodilators (through interaction with smooth muscle cells), whilst PDE4 inhibitors have anti-inflammatory properties. There is also evidence to suggest that combined inhibition of PDE3 and PDE4 can have additive or synergistic anti-inflammatory and bronchodilator effects (Abbott-Banner & Page, 2014). Pharmacological evidence from pre-clinical experiments with dual PDE3/4 inhibitors suggests that RPL554 may have potential therapeutic activity in COPD, cystic fibrosis and possibly asthma.

PDE4 inhibitors, administered orally, have exhibited anti-inflammatory actions; however, they have been associated with unfavourable gastrointestinal side effects such as nausea, emesis, diarrhoea, abdominal pain, loss of appetite and weight loss (Harbinson et al, 1997; van Schalkwyk et al, 2005; Compton et al, 2001; Rabe et al, 2005; Rennard et al, 2006; Calverley et al, 2007; Gamble et al, 2003; Grootendorst et al, 2007). Dual PDE3/PDE4 inhibitor, administered by inhalation, have exhibited both bronchodilator and anti-inflammatory actions, with a more favourable side effect profile (Ukena et al, 1995). It is plausible that increased efficacy with reduced side effects may be achievable with administration of a dual PDE3/4 inhibitor by the inhaled route compared to orally administered PDE3 or PDE4 inhibitors. It has also been demonstrated in tracheal ring preparations that RPL554 causes a synergistic bronchodilator effect when added to anti-muscarinic agents, as well as additive properties with β_2-agonists (Calzetta et al, 2013; Calzetta et al, 2015). Therefore, RPL554 has the potential to benefit patients not satisfactorily treated with existing medicines.

The safety, bronchodilator, bronchoprotective and anti-inflammatory activities of RPL554 have been evaluated in 12 completed clinical studies involving over 730 subjects. Initially, five studies were done in healthy subjects, patients with mild to moderate persistent asthma and

[redacted]

to have exceptional bronchodilator activity in healthy volunteers and patients with asthma and COPD, and to significantly improve symptoms and health status in patients with COPD.

RPL554 was well tolerated in all seven studies, with adverse event rates that were similar to the subjects treated with placebo. All clinical studies are described in the Investigator's Brochure.

A new formulation has been developed to allow for delivery of RPL554 using a convenient, hand-held pressurised metered dose inhaler (pMDI). Although the current study will be the first clinical assessment of the pMDI formulation of RPL554 in humans, the RPL554 active pharmaceutical ingredient used in the pMDI formulation is the identical physical form and morphology as that used in the nebuliser suspension product in previous studies. Furthermore, a non-clinical assessment of local and systemic toxic potential of a dry powder inhaler (DPI)

[redacted]

The purpose of this study is to assess the efficacy, safety and pharmacokinetics (PK) of RPL554 administered via pMDI, in order to support further development of RPL554 in a pMDI format.

1.2 Summary of Risks and Benefits

[redacted]

RPL554 has been demonstrated to have favourable non-clinical toxicology and PK profiles when delivered via the inhaled route as both a nebulised suspension and as a DPI.

While there have been few adverse events related to the cardiovascular or gastrointestinal systems, small and transient increases in heart rate at doses of 6 and 12 mg have been reported. Holter assessments have indicated no arrhythmogenic potential in the completed studies.

In single dose studies, there appears to be an increase in the rate of headache that is most pronounced at doses over 6 mg. Results from multiple dose data in patients with COPD suggests a transient increase in dizziness, the majority of which occurred during spirometry manoeuvres or dosing; otherwise, the rate of adverse events was similar between RPL554 and placebo treated patients.

2 OBJECTIVES

2.1 Part A

2.1.1 Primary Objective

To investigate the PK profile of single doses of RPL554, administered by pMDI, in patients with moderate to severe COPD.

2.1.2 Secondary Objectives

- To investigate the safety and tolerability of single doses of RPL554 administered by pMDI, including effects on peak pulse and heart rate
- To investigate the bronchodilator effect of single doses of RPL554 administered by pMDI, in terms of peak forced expiratory volume in 1 second (FEV1), average FEV1 area under the curve (AUC)0-4h and average FEV1 AUC0-12h

2.2 Part B

2.2.1 Primary Objective

To investigate the bronchodilator effect of repeat doses of RPL554 administered by pMDI, assessed in terms of peak FEV_1.

2.2.2 Secondary Objectives

- To investigate the safety and tolerability of repeat doses of RPL554, administered by pMDI
- To investigate the bronchodilator effect of RPL554 administered by pMDI, in terms of average FEV_1 $AUC_{0\text{-}4h}$, average FEV_1 $AUC_{0\text{-}12h}$ and trough FEV_1
- To determine the onset of action of RPL554 administered by pMDI
- To evaluate the PK profile of RPL554 administered by pMDI
- To evaluate the amount of rescue medication use during treatment periods

2.2.3 Exploratory Objectives

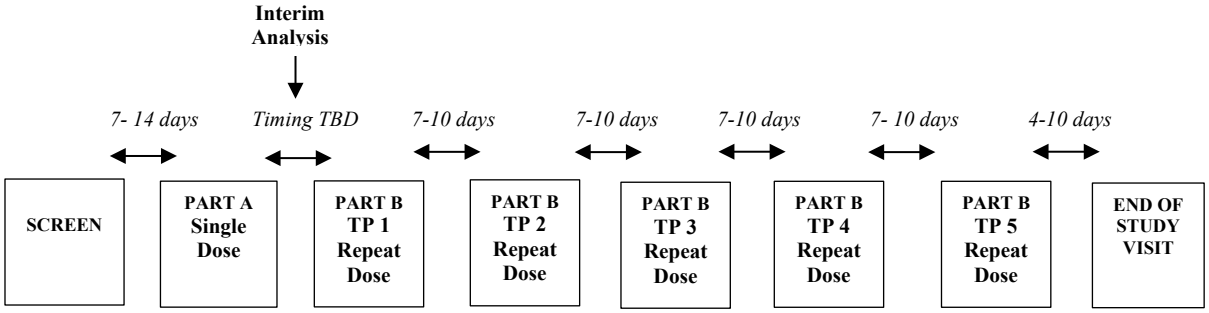
- To assess the dose response of RPL554 on peak FEV_1 and average FEV_1 $AUC_{0\text{-}12h}$ after morning dose on Day 7, and morning trough FEV_1 prior to the last dose on Day 7
- To examine the effect of RPL554 administered by pMDI on a Likert dyspnoea scale

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan Description

This is a Phase II, randomised, placebo controlled, two part study. Part A is a parallel group, single dose assessment of RPL554 administered by pMDI, with all but one of the treatment arms double blind (see Section 3.2). Part B is a double blind, complete block crossover, repeat dose assessment of RPL554 administered by pMDI. The study design is shown in Figure 1.

Figure 1 Study Flow Chart



Abbreviations: TBD=to be determined; TP=Treatment Period

In Part A, patients will be screened for eligibility, including a reversibility test with salbutamol. Between 7 and 14 days later, a total of approximately 36 patients will be given a single dose of RPL554 or placebo and will be assessed over 12 hours in the clinic. Patients will receive three inhalers and will be administered either six or 12 puffs via pMDI (depending on treatment arm assignment; see Section 5). Patients will return to the clinic the following day for a 24-hour post-dose assessment of PK and lung function. At the conclusion of Part A, the database will be locked and the data unblinded and analysed prior to commencing Part B (see Section 9.4.9 for details on the unblinding of Part A). Specific treatments are shown in Table 1.

In Part B, the patients from Part A will be randomly assigned in crossover fashion to one of 10 treatment sequences, each consisting of up to five 1-week treatment periods separated by a 7 to 10 day washout period. Each treatment period consists of 6 days of twice daily doses of RPL554, and a single morning dose on Day 7. In each treatment period, patients will undergo assessments over 12 hours on Days 1 and 7. Specific treatments are shown in Table 2.

Patients will return for an End of Study Visit approximately 7 days after the completion of the final Treatment Period (or sooner in the case of early termination).

3.2 Discussion of Study Design, Including the Choice of Control Groups

Part A is designed as a single dose, parallel group study to evaluate the safety and terminal PK profile of a range of doses of RPL554 in a new pMDI formulation compared to placebo. The safety and bronchodilatory response following a single dose will also be assessed.

In Part A, five dose levels ranging from 100 µg up to 6000 µg have been selected to evaluate the safety, PK and efficacy/pharmacodynamic characteristics of this formulation over a dose range covering a 60-fold increase in doses. Approximately 36 COPD patients aged 40 to 80 years (inclusive) will be randomised. Patients in Part A will be randomly assigned to receive either RPL554 or placebo via pMDI. Following an analysis of the safety, PK and efficacy/pharmacodynamics, up to four doses will be selected for Part B. Study medication administered via pMDI will be double blind, except for the 6000 µg treatment arm in Part A which will be single blind due to the number of puffs required, in order to minimise any potential bias in the overall assessment of treatment effect and safety.

Part B is designed as a crossover study to assess the steady state efficacy/pharmacodynamic effect of up to four dose levels of RPL554 administered by pMDI after a week of twice daily dosing, and to compare that effect with placebo pMDI. Steady state PK and safety will also be assessed. One week of treatment was selected to evaluate efficacy/pharmacodynamics, PK and safety at steady state, as clinical data to date has shown that steady state PK is achieved after approximately 3 days of twice-daily dosing with the nebulised formulation.

In Part B, all patients from Part A will undergo up to five treatment periods in a randomised, crossover design; therefore, each patient will act as his or her own control. This design makes it possible to obtain unbiased inferences about differences between treatments, based on intra-patient differences.

The washout period between the treatment periods has been selected based upon the available PK of RPL554 in healthy subjects, and patients with asthma or COPD. Five half-lives is considered as the time for elimination of RPL554 from the body. In this study, a washout period of 7 to 10 days from the last dose of study medication has been deemed adequate to ensure there is no overlap between the PK profiles of treatments with RPL554 in consecutive treatment periods.

The pre-dose FEV_1 on Day 1 of Treatment Periods 2 and forward each must be within ±20% of the pre-dose FEV_1 on Day 1 of Treatment Period 1 in order to ensure consistent baseline FEV_1 for each study treatment. If the FEV_1 varies by more than 20%, the start of the treatment period will be rescheduled.

3.3 Planned Duration of the Study

The approximate planned duration for each patient (not counting the interim analysis period) will be between 75 and 100 days: 7 to 14 days Screening, 24 hours for Part A, up to five treatment periods of 7 days each in Part B separated by 7 to 10 days, and an End of Study Visit 4 to 10 days after Day 7 of the last treatment period. Repeat, rescheduled and unscheduled visits are permitted at the discretion of the Investigator.

3.4 Definition of the End of the Study

The end of the study is defined as the date of the End of Study Visit of the last patient to complete the study.

4 SELECTION OF STUDY POPULATION

The population to be recruited into this study are stable patients with moderate to severe COPD without significant heart disease. Specific criteria are as follows:

4.1 Inclusion Criteria

1. Sign an informed consent document indicating they understand the purpose of and procedures required for the study and are willing to participate in the study.
2. Male or female aged between 40 and 80 years inclusive, at the time of informed consent.
3. Must agree to meet the following from the first dose up to 1 month after the last dose of study medication:

   If male:

   - Not donate sperm
   - *Either:* be sexually abstinent in accordance with a patient's usual and preferred lifestyle (but agree to abide by the contraception requirements below should their circumstances change)

     Or: use a condom with all sexual partners. If the partner is of childbearing potential the condom must be used with spermicide and a second reliable form of contraception must also be used (e.g. diaphragm/cap with spermicide, established hormonal contraception, intra-uterine device)

   If female: be of non-childbearing potential or use a highly effective form of contraception as defined in Section 14.1.
4. Have a 12-lead electrocardiogram (ECG) recording at Screening and pre-dose in Part A showing the following:
   - Heart rate at least 45 beats per minute and less than 110 beats per minute (Sinus bradycardia <45 bpm and tachycardia ≥110 bpm should be confirmed by 2 additional readings at least 5 minutes apart)
   - QT interval corrected for heart rate using Fridericia's formula (QTcF) ≤450 msec for males, and ≤470 msec for females
   - QRS interval ≤120 msec
   - No clinically significant abnormality including morphology (e.g. left bundle branch block, atrioventricular nodal dysfunction, ST segment abnormalities consistent with ischemia)
5. Capable of complying with all study restrictions and procedures including ability to use the pMDI correctly.
6. Body mass index (BMI) between 18 and 35 kg/m^2 (inclusive) with a minimum weight of 45 kg.
7. COPD diagnosis: Patients with a diagnosis of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (Celli and MacNee, 2004) with symptoms compatible with COPD for at least 1 year prior to Screening.
8. Ability to perform acceptable and reproducible spirometry.
9. Post-bronchodilator (four puffs of salbutamol) spirometry at Screening demonstrating the following:
   - FEV_1/forced vital capacity (FVC) ratio of ≤0.70
   - FEV_1 ≥40 % and ≤80% of predicted normal

- ≥150 mL increase from pre-bronchodilator FEV_1

10. Clinically stable COPD in the 4 weeks prior to Screening and during the period between Screening and Part A. In particular, the average pre-dose FEV_1 in Part A must be within ±20% of the value obtained at the Screening Visit.
11. A chest X-ray (posterior-anterior) at Screening, or in the 12 months prior to Screening showing no clinically significant abnormalities unrelated to COPD.
12. Meet the concomitant medication restrictions (within the time intervals defined in Section 5.8.1) and be expected to do so for the rest of the study.
13. Current and former smokers with smoking history of ≥10 pack-years.
14. Capable of withdrawing from long acting bronchodilators for the duration of the study, and short acting bronchodilators for 6 hours prior to spirometry testing.

4.2 Exclusion Criteria

1. A history of life-threatening COPD including Intensive Care Unit admission and/or requiring intubation.
2. COPD exacerbation requiring oral or parenteral steroids, or lower respiratory tract infection requiring antibiotics, within 3 months of Screening or prior to Part A.
3. A history of one or more hospitalisations for COPD or pneumonia within 6 months of Screening or prior to Part A.
4. Intolerance or hypersensitivity to salbutamol or RPL554 or any of its excipients/components.
5. Other respiratory disorders: Patients with a current diagnosis of asthma, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, interstitial lung diseases, sleep apnoea, known alpha-1 antitrypsin deficiency, core pulmonale, clinically significant pulmonary hypertension or other active pulmonary diseases.
6. Previous lung resection or lung reduction surgery.
7. Use of immunosuppressive therapy, including oral corticosteroids.
8. Pulmonary rehabilitation, unless such treatment has been stable from 4 weeks prior to Screening and remains stable during the study.
9. History of, or reason to believe a patient has, drug or alcohol abuse within the past 5 years.
10. Women who are pregnant or breastfeeding
11. Received an experimental drug within 30 days or five half-lives, whichever is longer.
12. Patients with uncontrolled disease including, but not limited to, endocrine, active hyperthyroidism, neurological, hepatic, gastrointestinal, renal, haematological, urological, immunological, psychiatric, or ophthalmic diseases that the Investigator believes are clinically significant.
13. Historical or current evidence of clinically significant cardiovascular disease. Significant is defined as any disease that in the opinion of the investigator could put the safety of the patient at risk, or could affect the efficacy or safety analyses if the condition were to exacerbate during the study. In particular, the following are excluded:
    - Myocardial infarction within 1 year prior to Screening
    - Unstable angina within 6 months prior to Screening
    - Unstable or life-threatening arrythmia requiring intervention within 3 months prior to Screening

- Diagnosis of NYHA class III or IV heart disease

14. Use of non-selective oral β-blockers.
15. Major surgery (requiring general anaesthesia) within 6 weeks prior to Screening, lack of full recovery from surgery at Screening, or planned surgery through the end of the study.
16. A disclosed history or one known to the Investigator, of significant non-compliance in previous investigational studies or with prescribed medications.
17. Required use of oxygen therapy, even on an occasional basis.
18. History of malignancy of any organ system within 5 years, with the exception of localised skin cancers (basal or squamous cell).
19. Clinically significant abnormal values for viral serology or laboratory safety tests (haematology, biochemistry or urinalysis) at Screening, as determined by the Investigator (see Section 7.1.4 and Section 7.4.3). In particular, alanine aminotransferase or aspartate aminotransferase cannot be more than twice the upper limit of normal.
20. Any other reason that the Investigator considers makes the patient unsuitable to participate.

4.3 Removal of Patients from Therapy or Assessment

4.3.1 Study Treatment Discontinuation

Study treatment must be discontinued for the following reasons:

- Unacceptable toxicity related to study treatment
- Intolerable or persistent adverse events of any severity
- General or specific changes in the patient's condition rendering the patient unacceptable for further treatment in the judgment of the Investigator
- Clinically significant progression of disease
- Pregnancy in a female patient

4.3.2 Patient Withdrawal

Investigators have the authority to withdraw a patient at any time for medical or non-compliance reasons. Should the Investigator decide it is necessary to withdraw any patient for specific reasons, this should be recorded in writing and transmitted to the patient in question. Such reasons for withdrawal are expected to be medical or related to lack of co-operation by the patient.

The patient has the right to withdraw at any time and for any reason, without explanation and without jeopardising any subsequent treatment by the clinician, if applicable. However, anyone withdrawing should be encouraged to offer an explanation for their withdrawal, particularly if it relates or is perceived to relate in any way to the study medication, or to the conduct of the study. Patients can also be withdrawn in case of protocol violations and non-compliance.

If a patient withdraws following randomisation, every attempt should be made to contact the patient to determine the reason for withdrawal and to complete the recording of any available efficacy/pharmacodynamic data and all adverse event data. The reasons for withdrawal and results of all relevant tests will be recorded in the electronic case report form (eCRF). These patients should have an End of Study Visit unless it is considered by the Investigator that they require greater medical supervision and/or investigations and in which case an unscheduled visit prior to and in addition to the scheduled follow up visit may be performed.

If a patient had signed a consent form but withdrew from the study without receiving any study treatment, no further follow-up is necessary.

4.3.3 Study Discontinuation

Conditions that may warrant termination of the study include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- The decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of RPL554
- Serious failure of the Investigator to comply with the International Council on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP) or local regulations
- Submission of knowingly false information from the research facility to the Sponsor, the Independent Ethics Committee (IEC) or any national regulatory officials
- Major, repeated, non-adherence to the protocol

The Sponsor must be informed immediately in the event of any major protocol deviation or serious breach of ICH GCP.

Study termination and follow-up will be performed in compliance with the conditions set forth in ICH GCP. The decision to discontinue the study is at the discretion of the Sponsor, the Investigator, the regulatory authority or IEC and should if possible be taken by mutual agreement. A record of such a discussion will be prepared and stored in the study file. The Sponsor will ensure the regulatory authorities and IECs are notified.

4.3.4 Replacement Policy

It is planned to have 30 patients complete the study; it is expected that approximately 36 patients will be randomised to meet this target. Withdrawn patients may need to be replaced, depending on the actual discontinuation rate.

5 STUDY TREATMENTS

5.1 Study Treatments Administered

5.1.1 Treatments Administered in Part A

Patients will be randomly assigned to receive a single dose of one of six possible treatments, as shown in Table 1. For Treatment Arms 1 through 4 and 6, each patient will be instructed to take two puffs (inhalations) from each of Inhalers 1 through 3, for a total of six inhalations. For Treatment Arm 5, each patient will be instructed to take four puffs from each of Inhalers 1 through 3, for a total of 12 inhalations.

Table 1 Treatment Arms, Inhaler and Puff Combinations in Part A

Arm	No. of Patients	No. of Puffs per Inhaler	Total Dose	[redacted]
1	6	2	100 µg	
2	6	2	300 µg	
3	6	2	1000 µg	
4	6	2	3000 µg	
5*	6	4	6000 ug	
6	6	2	Placebo	

* Single-blind (see Section 5.7)

5.1.2 Treatments Administered in Part B

During Part B, patients will undergo four or five repeat dose treatment periods in a crossover fashion, with the sequence to be randomly assigned. Each treatment period will consist of 7 days of dosing, which will occur in the morning and evening of Days 1 through 6 and morning only on Day 7.

The doses to be used in Part B will be determined from the analyses performed on data from Part A; however, the highest dose will not exceed 3000 µg. The dosage strengths, in addition to placebo, will be as follows: 100 µg, and/or 300 µg, and/or 1000 µg, and/or 3000 µg (either 3 or 4 of these values), dosed twice daily.

Each patient will be instructed to inhale two puffs from each inhaler dispensed to them (depending on the doses chosen for Part B) twice daily, for a total of six inhalations for each morning or evening dose.

5.2 Identity, Preparation and Labelling of Study Treatments

The International Union of Pure and Applied Chemistry (IUPAC) name for RPL554 drug substance is 9,10-dimethoxy-2-(2,4,6-trimethylphenylimino)-3-(*N*-carbamoyl-2-aminoethyl)-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-a]isoquinolin-4-one. The RPL554 pMDI is manufactured in accordance with Good Manufacturing Practice (GMP) guidelines.

The compositions of the pMDI formulations are shown in Table 2.

[REDACTED]

5.3 Selection of Doses and Dosing Schedule

5.3.1 Selection of Doses in the Study

The doses of RPL554 have been selected to cover a 60-fold dose range of the pMDI formulation. The top dose level in Part B will not exceed 3000 μg, dosed twice daily, due to the logistical infeasibility of repeated administration of 12 puffs required to deliver a 6000 μg dose, and the enhanced possibility for poor treatment compliance. In prior studies, up to 24 mg of RPL554 has been evaluated as a twice daily nebulised suspension, and was well tolerated clinically.

Efficacy and safety data from Part A will be evaluated to determine if a dose can be dropped from the dose range in Part B.

5.3.2 Timing of Dose for Each Patient

In Part A and the first dose of each treatment period in Part B study medication is to be administered between 7 and 11 am. All subsequent doses in Part B are to be taken at 12-hour intervals (±30 minutes) relative to the Day 1 first dose.

5.4 Storage

RPL554 and placebo drug products should not be stored above 25°C. Temperature logs should be maintained in areas where study medication is stored. If temperature conditions have been compromised or any study medication has not been stored appropriately, this should be documented, and the study medication quarantined until the Sponsor has been notified and confirmed whether it may be used.

Study medication will be stored under the control of the Investigator or designee in a secure facility appropriate for the advised storage conditions. Study medications that are to be returned by the Investigator/staff or have expired must be stored separately from the unused study medications.

5.5 Accountability

The Investigator will be responsible for the dispensing, inventory and accountability of study medication, exercising accepted medical and pharmaceutical practices and ensuring that an accurate, timely record of the disposition is maintained. The study medication supplies and

inventory must be available for inspection by the designated representatives of the Sponsor upon request.

Upon receipt of the study medication, the Investigator or designee will inspect the contents and return the completed acknowledgement of receipt. Copies of all study medication inventory records must be retained for accountability of study products and supplies. Accountability must be documented from the time of initial receipt at the study centre to their final removal from the centre.

Written records must also be maintained to confirm the purpose and reason for any study medication disposal, e.g. the amount contaminated, broken, or lost, and the name/signature of the personnel responsible for reporting the event.

At the end of the study, the unused study medication can be destroyed locally after accountability has been verified and written authorisation has been provided by the Sponsor.

5.6 Method of Assigning Patients to Treatment Groups

All patients consented will be assigned a patient identification number upon signing of the informed consent using the following convention: XXX-YYY where XXX is the centre number and YYY is the patient number (001, 002, etc.).

In Part A of the study, patients will be randomly assigned to receive a single dose of one of six possible treatments (see Section 5.1.1). In Part B, patients will again be randomised and assigned to a set of selected treatment sequences balanced with respect to both period and first-order carry-over effects (see Section 5.1.2). Available randomisation numbers must be used sequentially for the next enrolled patient, to determine the treatment dose to be dispensed and administered.

5.7 Blinding

[redacted]

puffs required. The placebo is the same as the active medication (RPL554) except for the omission of the active ingredient.

In Part B, the treatments will be double blind.

The blind should be broken only if specific emergency treatment would be dictated by knowing the treatment status of the patient. If the blind needs to be broken, the Investigator should contact the Sponsor as soon as feasible. The Investigator may unblind the study medication immediately if he/she feels it is necessary prior to contacting the Sponsor. However, the Investigator should promptly document and explain to the Sponsor any premature unblinding. Otherwise, all blinding will be maintained until all queries are resolved and the database is locked. Blind break envelopes will be provided to the study centre and must be kept in a secure access area.

5.8 Prior and Concomitant Therapies and Medications

5.8.1 Prior and Concomitant COPD Medications

All prior therapies for COPD taken in the 3 months prior to the first study medication administration and all concomitant COPD therapies will be recorded in the eCRF, with the medication, dose, route and start and stop date(s) and time(s) clearly recorded to document all required washout periods and compliance with the Inclusion and Exclusion Criteria.

Upon providing informed consent, patients will discontinue COPD medications for the time periods described in Table 3 Restrictions for COPD Medications Prior to Screening prior to both the Screening visit for Part A and Day 1 of Part B. Patients will remain off these medications until the completion of Part A, at which point maintenance LAMA or LABA therapy may be temporarily resumed. However, patients must discontinue these prohibited medications according to the time periods described in Table 3 prior to Day 1, Treatment Period 1 of Part B, and remain off these medications (except for rescue use) until the end of Day 7 of the final treatment period.

Table 3 Restrictions for COPD Medications Prior to Screening and Part B

Medication	Time Interval Prior to Screening and Start of Part B
Oral COPD therapies – e.g. oral steroids, theophylline, roflumilast	3 months
Antibiotics	3 months
Terbutaline	1 day
Long acting bronchodilators (LABAs or LAMAs) • Once-daily bronchodilators • Twice daily bronchodilators	 • 48 hours • 24 hours
Inhaled corticosteroids	Allowed if dose is stable ≥4 weeks prior to Screening and expected to remain stable throughout the study

Abbreviations: COPD=chronic obstructive pulmonary disorder; LABA=long acting β_2-agonist; LAMA=long acting muscarinic antagonist

The following therapies are subject to restriction as indicated:

- Patients taking LAMAs and LABAs should be placed on short acting bronchodilators (e.g. salbutamol, ipratropium or Combivent®) as per the discretion of the Investigator. These can be dosed on a regularly scheduled basis or as needed (subject to additional restrictions in the 3rd bullet below)
- Patients taking LABA/ICS combination products should be prescribed the ICS at the same or equivalent dose contained in the combination product to allow continuation of steroid use regularly throughout the study while stopping the LABA component.ICS medication should be procured via prescription for patients requiring its use
- No scheduled regular use of salbutamol or ipratropium is allowed during the 7-day treatment periods; but may be used as a rescue medication (see Section 5.9). Short-acting bronchodilators must be withheld for at least 6 hours prior to spirometry (per below), and this is to be confirmed in the eCRF at the start of each treatment period. If this withhold is not met, the patient should be rescheduled for a repeat visit within permitted windows. Short acting bronchodilators should be withheld as follows:
  - Screening: 6 hours prior to pre-reversibility spirometry
  - Part A:
    - Day 1: 6 hours prior to pre-dose spirometry until completion of the 12-hour post-dose spirometry
    - Day 2: 6 hours prior to 24-hour post-dose spirometry
  - Part B, Days 1 and 7 of each treatment period:
    - 6 hours prior to pre-dose spirometry until completion of the 12-hour post-dose spirometry

If following the above requirements provides inadequate symptom control, patients should contact the Investigator.

- Pulmonary rehabilitation programs should not be started or completed during participation in the study, although an ongoing maintenance program is acceptable in accordance with Exclusion Criterion #8
- Oxygen therapy and non-selective oral β-blockers are Exclusion Criteria and are not to be used at any time during the study
- Oral mucolytics and ocular β-blockers are allowed

5.8.2 Other (non-COPD) Prior and Concomitant Medications

All concomitant medications must be documented in the eCRF, as well as any medications taken within 3 months prior to the Screening visit.

Patients may continue other prescribed non-respiratory therapies during the study that the Investigator considers to neither compromise patient safety nor affect study data. Such other prior prescription or non-prescription medications (medication, dose, route, treatment duration and indication) taken within 3 months before the first study medication administration must be recorded in order to confirm compliance with the Inclusion and Exclusion Criteria.

5.9 Rescue Medications

Short acting bronchodilators may be used as rescue medication. Salbutamol is to be used for primary rescue use. Rescue medication will be sourced by the study centre and dispensed as follows: 1) at the time informed consent is provided, and 2) on Day 2 at the end of Part A (in sufficient quantity to cover the discontinuation of COPD medications prior to Part B, as well as full duration of Part B). See Section 5.8.1 for withholding requirements prior to spirometry and rescheduled visit allowances.

Rescue medication use during each study visit must be separately documented in the eCRF (medication, dose, route, and date and time of each administration). During Part B, rescue use between Days 1 and 7 of each treatment period will be determined primarily by information provided by patients on paper diaries, which will be transcribed into the eCRF. The day(s) on which rescue was used and the number of puffs taken on each day of use will be recorded. In the event of missing or incomplete diaries (which will be noted as a protocol deviation), rescue use will be determined analytically, based on changes in the weight of the canister which will be recorded in the eCRF.

5.10 Treatment Compliance

In Part A, the single dose of study medication will be administered at the study centre by study personnel.

In Part B, patients will also be dosed at the study centre on the morning and evening of Day 1 and on the morning of Day 7. Patients will self-administer study medication for the other dosing times (i.e. on Days 2 through 6). The pMDIs dispensed and returned will be recorded, and will be weighed at the beginning and end of each visit.

The precise date and time of dose administrations performed in clinic at study visits, and in the evening prior to study visits, shall be documented in the eCRF. Additionally, on Day 7 patients will be queried on how many doses (if any) since Day 1 were missed; this information shall also be documented in the eCRF.

6 STUDY PROCEDURES AT EACH VISIT

The study will consist of the following:

- Screening will take place in the period between 7 and 14 days prior to the first study medication administration in Part A. Screening procedures may be performed as a single visit or more than one visit
- Part A will consist of a single dose of study medication, with assessments over the ensuing 12 hours and again at 24 hours on the following day
- Part B will commence at a time to be determined, following database lock and analysis of Part A and will consist of up to five 7-day treatment periods of repeat doses of study medication, each separated by a washout period of 7 to 10 days
- An End of Study Visit will occur between 4 and 10 days after the completion of the final treatment period

Patients who screen fail may be considered for re-screening upon consultation with the Medical Monitor.

Repeat, rescheduled, and unscheduled visits and procedures are permitted at the discretion of the Investigator.

The schedules of assessments are shown in Table 4 for Part A and Table 5 for Part B. Assessments are listed by visit in Section 6.2 to Section 6.5 and are described in Section 7.

Post-dose assessments generally should be performed in the following order (as applicable): 1) 12-lead ECG, 2) vital signs, 3) PK blood sample, 4) spirometry (prioritised on the timepoint).

Table 4 Schedule of Assessments for Screening and Part A

	Screen (Day -14 to -7)	Day 1												Day 2
		Time Relative to End of Dosing												
		Pre-dose	**0**	**5m**	**15m**	**30m**	**1h**	**1.5h**	**2h**	**4h**	**8h**	**11h**	**12h**	**24h**
Informed consent	X[1]													
Rescue medication dispensing	X[1]													X
Demographics including height & weight	X													
Viral serology test	X													
FSH test (if required)	X[2]													
Medical/surgical and disease history	X													
Eligibility criteria	X	X												
Physical examination Full	X													
Physical examination Brief		X												
Vital signs	X	X					X		X	X	X		X	X
Prior/concomitant medications/therapies	X	X												
Pregnancy testing (as applicable)[3]	X	X												
Laboratory safety tests[4]	X													
Urinalysis	X													
12-lead ECG	X	X					X		X	X	X			
Chest X-ray (as required)	X													
Reversibility testing	X													
Spirometry	X	X[5]		X	X	X	X	X	X	X	X	X	X	
Rescue canister weight		X												X
Inhalation training		X												
Randomisation		X												
Study medication administered			X											
Pharmacokinetic sample		X			X	X	X	X	X	X	X		X	X
Adverse events	X	X												X

Abbreviations: ECG=electrocardiogram; FEV_1=forced expiratory volume in 1 second; FSH=follicle stimulating hormone; h=hours; m=minutes

1. May need to be performed prior to screening, to accommodate washout of prohibited medications
2. To confirm post-menopausal status
3. For women of childbearing potential only. Serum and urine pregnancy test at Screening, urine pregnancy test only Pre-dose.
4. Haematology and blood chemistry
5. Pre-dose spirometry shall be conducted at -1 hour (±5 minutes) and immediately (within 5 minutes) pre-dose. The average FEV_1 value must be within ±20% of the pre-salbutamol value obtained at Screening

Table 5 Schedule of Assessments for Part B, Days 1 and 7 of each Treatment Period and End of Study Visit

	Day 1											Day 7[1]										4-10 days after TP 4
	Pre-dose	0	5 m	15m	30m	1h	1.5h	2h	4h	8h	12h	Pre-dose	0	30m	1h	1.5h	2h	4h	8h	11h	12h	
Physical examination Full																						X
Physical examination Brief	X											X										
Vital signs	X					X		X	X	X	X	X			X		X	X	X		X	X
pMDI weight	X										X	X									X	
Rescue canister weight											X	X										
Recording of prior evening dose time												X										
Urine pregnancy test[2]	X																					X
Urinalysis	X																					X
Laboratory safety tests[3]	X											X										X
12-lead ECG	X											X										
Spirometry	X[4]		X	X	X	X	X	X	X	X	X	X[4]		X	X	X	X	X	X	X	X	X
Dyspnoea scale	X				X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	
Inhalation training	X																					
Randomisation	X[5]																					
Study medication administered in-clinic		X									X		X									
Pharmacokinetic sample	X			X	X	X	X	X	X	X	X	X		X	X	X	X	X	X		X	
Study medication, rescue medication and paper diary dispensed[6]											X											
Study medication and paper diary collected												X										
Study medication compliance												X										
Adverse events	X											X										X
Prior/concomitant medications	X											X										X

Abbreviations: ECG=electrocardiogram; FEV_1=forced expiratory volume in 1 second; h=hours; m=minutes; pMDI=pressurised metered dose inhaler; TP=Treatment Period

1. Patients will be contacted by phone the night before their Day 7 visits to remind them of the requirements stipulated in Section 6.4.1.3
2. For women of childbearing potential only
3. Haematology and blood chemistry
4. Pre-dose spirometry shall be conducted at -1 hour (±5 minutes) and immediately (within 5 minutes) pre-dose. The pre-dose FEV_1 on Day 1 of Treatment Periods 2 and forward must be within ±20% of the pre-dose FEV_1 on Day 1 of Treatment Period 1, in order to ensure consistent baseline FEV_1 for each study treatment
5. Treatment Period 1 only
6. Patients will be instructed to take study medication in the morning and evening on Days 2 through 6. Study medication should be withheld on the morning of Day 7 prior to the visit, to allow for administration in the clinic. Additional rescue medication may also be dispensed if needed

6.1 Pre-visit Restrictions

The following restrictions should be adhered to (for all study visits except where noted):

- Patients should refrain, when possible, from xanthine (chocolate, caffeine containing drinks and food), for at least 24 hours before and during visits. Decaffeinated beverages are permitted
- Patients should refrain from alcohol for 24 hours before and during visits (including visits for safety laboratory tests) and until all procedures for that study visit are completed
- Patients must fast (water permitted) from 2 hours pre-dose until 1 hour post-dose (does **not** apply to Screening)
- Patients should refrain from smoking at least 1 hour pre-dose, and at least 1 hour before any measurement of lung function
- Patients should refrain from strenuous exercise for 72 hours prior to visits and should undertake no unaccustomed strenuous exercise from Screening until the End of Study Visit

6.2 Screening

Written informed consent will be obtained by the Investigator as specified in Section 10.3 prior to any study related procedures being performed. This typically will need to be performed prior to the Screening visit to allow for discontinuation of any prohibited medications (see Section 5.8.1). Screening procedures may be performed over more than 1 day.

Patients will be screened to determine eligibility against the Inclusion and Exclusion Criteria between 7 and 14 days before the first dose of study medication. Patients must observe the medication restrictions described in Section 5.8.1, and other restrictions described in Section 6.1. To account for diurnal variability in pulmonary function, the Screening visit is to take place in the morning.

The following assessments will be performed, generally in the order indicated (to the extent feasible):

- Obtain informed consent (if not done prior to Screening)
- Recording of demographic information, including height and weight
- Recording of medical/surgical and disease history
- Recording of prior medications and therapies; confirming that medications were withheld as required
- Vital signs
- Full physical examination (see Section 7.4.5)
- 12-lead ECG
- Reversibility test:
  - Pre-reversibility spirometry
  - Four puffs of salbutamol
  - Post-reversibility spirometry (20 to 30 minutes after salbutamol)
- Blood samples for laboratory screening and safety tests:
  - Viral serology

  - Follicle stimulating hormone (FSH; if required to confirm post-menopausal status)
  - Serum pregnancy (for women of childbearing potential only)
  - Haematology and blood chemistry
- Urinalysis
- Urine pregnancy (for women of childbearing potential only) – results should be obtained prior to the chest X-ray
- Chest X-ray (unless historical X-ray performed in last 12 months is available)
- Questioning for adverse events

If the patient meets all of the Inclusion and none of the Exclusion Criteria:

- Dispense rescue medication
- Instruct patient to return in 7 to 14 days for Part A treatment

6.3 Part A: Single Dose Treatment

Patients must withhold all medications described in Section 5.8.1 prior to the treatment in accordance with the washout times provided. If not, the visit must be rescheduled so as to occur within the permitted windows. All restrictions defined in Section 6.1 should also be adhered to.

6.3.1 Pre-dose Assessments

The following assessments will be performed prior to dosing:

- Assess concomitant medications; confirm that medications were withheld as required, and that all eligibility criteria continue to be met
- Question for adverse events
- Weigh rescue medication canister
- Urine pregnancy test (women of childbearing potential only)
- 12-lead ECG
- Vital signs
- Brief physical examination (see Section 7.4.5)
- Spirometry; 1 hour (±5 minutes) and immediately (within 5 minutes) pre-dose. **Note:** The average of the two pre-dose FEV_1 values must be within ±20% of the pre-salbutamol value at Screening; otherwise, the patient will be screen failed in accordance with Inclusion Criterion #10
- PK sampling
- Inhalation training
- Assign randomisation number from next in sequence available at the study centre

6.3.2 Study Medication Administration

Patients will be dosed once with either blinded RPL554 or placebo according to the randomisation scheme. Those assigned to receive the 6000 µg treatment will be instructed to take 4 puffs per inhaler; all others will be instructed to take 2 puffs per inhaler. **Note:**

Instructions will be given in such a way as to preserve the single blind; i.e., patients should not be informed that the number of puffs differs among treatment groups.

6.3.3 Post-dose Assessments

The following assessments will be performed, at the times indicated relative to the end of dosing:

- 12-lead ECGs at 1, 2, 4 and 8 hours (all ±10 minutes)
- Vital signs at 1, 2, 4, 8, 12 and 24 hours (all ±10 minutes)
- PK sampling at 15 (±5) and 30 (±10) minutes and 1, 1.5, 2, 4, 8, 12 and 24 hours (the latter assessments all ±15 minutes)
- Spirometry at 5 (±2), 15 (±5) and 30 (±10) minutes and 1, 1.5, 2, 4, 8, 11 and 12 hours (the latter assessments all ±15 minutes)
- Weigh rescue medication canister, if used during visit
- Dispense new rescue medication after the 24 hour assessment
- Question for adverse events

Patients will be discharged from the study centre after the 12-hour assessments and instructed to return the next morning; alternatively, they may remain resident at the study centre overnight at Investigator discretion. Patients will be informed that they will be contacted at some point after discharge to schedule the first visit for Part B and to assess for any adverse events and concomitant medication use.

Early terminated patients should have an End of Study Visit, whether or not they participate in Part B.

6.4 Part B: Repeat Dose Treatment

Prior to each visit in Part B, patients must withhold all medications described in Section 5.8.1 in accordance with the washout times provided. If not, the visit must be rescheduled so as to occur within the permitted windows. All restrictions defined in Section 6.1 should also be adhered to. Study centre staff will call the patient the day prior to the start of Part B to remind patients of the following: to adhere to the medication restrictions above and, prior to the Day 7 visit only, 1) to take study medication that evening at the scheduled time and 2) **not** to take study medication the following morning prior to arriving at the clinic.

6.4.1 Day 1 of Each Treatment Period

6.4.1.1 Pre-dose Assessments

The following assessments will be performed prior to dosing:

- Assess concomitant medications and confirm that medications were withheld as required
- Counsel/remind patient of daily dosing schedule as needed
- Question for adverse events
- Dyspnoea scale
- PK sampling
- Blood samples for laboratory safety tests (haematology and blood chemistry)
- Urine pregnancy test (women of childbearing potential only)

- Urinalysis
- 12-lead ECG
- Vital signs
- Brief physical examination (see Section 7.4.5)
- Spirometry; 1 hour (±5 minutes) and immediately (within 5 minutes) pre-dose. **Note:** The pre-dose FEV_1 on Day 1 of Treatment Periods 2 and forward must be within ±20% of the pre-dose FEV_1 on Day 1 of Treatment Period 1, in order to ensure consistent baseline FEV_1 for each study treatment. If this requirement is not met, the visit is to be rescheduled within protocol-defined windows
- Inhalation training
- Dispense inhaler and study medication
- Dispense additional rescue medication (if required)
- Weigh pMDI (pMDI is to be weighed after priming; see Pharmacy Manual)
- At Treatment Period 1 only, assign randomisation number from next in sequence available at the study centre

6.4.1.2 Study Medication Administration

Patients will be dosed once with either RPL554 or placebo according to the randomisation scheme. The first two doses of study medication on Day 1 will be administered in the clinic. The second dose will be administered 12 hours (±30 minutes) after the first dose.

6.4.1.3 Post-dose Assessments

The following assessments will be performed, at the times indicated relative to dosing:

- Vital signs at 1, 2, 4, 8 and 12 hours (all ±10 minutes)
- Dyspnoea scale at 30 (±10) minutes and 1, 1.5, 2, 4, 8 and 12 hours (the latter assessments all ±15 minutes)
- PK sampling at 15 (±10) and 30 (±10) minutes and 1, 1.5, 2, 4, 8 and 12 hours (the latter assessments all ±15 minutes)
- Spirometry at 5 (±2), 15 (±5) and 30 (±10) minutes and 1, 1.5, 2, 4, 8 and 12 hours (the latter assessments all ±15 minutes)
- Question for adverse events
- After evening dose is administered, weigh pMDI and rescue medication canister
- Give study medication, rescue medication and paper diary to patient to take home

Patients will be discharged from the study centre after the 12-hour assessments and instructed to return 6 days later for Day 7. Patients will be contacted by phone the night before the Day 7 visit to remind them to: 1) take their study medication in the evening of Day 6 and record the time, 2) withhold study medication prior to the visit the next day, 3) return their medication during the visit and 4) follow other medication and activity restrictions as described in Sections 5.8.1 and Section 6.1.

6.4.2 Day 7 of Each Treatment Period

6.4.2.1 Pre-dose Assessments

The following assessments will be performed prior to dosing:

- Collect study medication and paper diary
- Weigh pMDI and rescue medication canister
- Assess study medication compliance (see Section 5.10); record time of prior evening dose of study medication and query patient on whether any doses were missed since Day 1
- Assess concomitant medications; confirm that medications were withheld as required
- Question for adverse events
- Dyspnoea scale
- PK sampling
- Blood samples for laboratory safety tests (haematology and blood chemistry)
- 12-lead ECG
- Vital signs
- Brief physical examination (see Section 7.4.5)
- Spirometry; 1 hour (±5 minutes) and immediately (within 5 minutes) pre-dose

6.4.2.2 Study Medication Administration

Patients will be dosed once with either RPL554 or placebo according to the randomisation scheme.

6.4.2.3 Post-dose Assessments

The following assessments will be performed, at the times indicated relative to dosing:

- Vital signs at 1, 2, 4, 8 and 12 hours (all ±10 minutes)
- Dyspnoea scale at 30 (±10) minutes and 1, 1.5, 2, 4, 8, 11 and 12 hours (the latter assessments all ±15 minutes)
- PK sampling at 30 (±10) minutes and 1, 1.5, 2, 4, 8 and 12 hours (the latter assessments all ±15 minutes)
- Spirometry at 30 minutes (±10) and 1, 1.5, 2, 4, 8, 11.5 and 12 hours (the latter assessments all ±15 minutes)
- Question for adverse events
- Weigh pMDI

Patients will be discharged from the study centre after the 12-hour assessments and instructed to return as follows: 1) for all but the final treatment period, 7 to 10 days later for Day 1 of the next treatment period, 2) for the final treatment period, 4 to 10 days later for the End of Study visit.

6.5 End of Study Visit

All completed and early terminated patients should complete the End of Study visit. The following will be performed:

- Assess concomitant medications
- Full physical examination
- Vital signs
- Blood samples for laboratory safety tests (haematology and blood chemistry)
- Urinalysis
- Urine pregnancy test (women of childbearing potential only)
- Spirometry
- Question for adverse events

7 STUDY METHODOLOGY

7.1 Demographics, Baseline Characteristics and Eligibility Assessments

Safety assessments (laboratory safety tests, vital signs, 12-lead ECG and physical examination) will be performed at Screening as part of the eligibility assessment as described in Section 7.4.3 to Section 7.4.6.

7.1.1 Demographic Variables

Demographic variables, including date of birth, sex, height, weight, BMI (weight [kg]/height $[m]^2$), race and smoking status will be collected at Screening.

7.1.2 Medical and Disease History

All active medical conditions and all surgeries will be recorded at Screening. Disease history, including date of diagnosis will also be recorded.

7.1.3 Reversibility Test

Reversibility in response to salbutamol will be assessed at Screening as an eligibility measure. Spirometry (FEV_1 and FVC) assessment before and after four puffs (400 µg) of salbutamol, administered using a pMDI, will be performed.

Three technically acceptable measurements should be made and recorded in the eCRF. Spirometry assessments may be performed up to eight times to obtain three acceptable readings according to ATS guidelines (Miller et al, 2005). The highest reading from each assessment will be used for calculation of predicted values and increase from baseline.

The following must be confirmed for inclusion:

- Post-bronchodilator FEV_1/FVC ratio of ≤0.70
- Post-bronchodilator FEV_1 ≥40 % and ≤80% of predicted normal*
- Demonstrates ≥150 mL increase from pre-bronchodilator FEV_1

*National Health and Nutrition Examination Survey (NHANES) III (Hankinson et al, 1999) will be used as a reference for normal predicted values.

7.1.4 Screening Laboratory Assessments, Chest X-ray

At Screening, blood samples will be taken and analysed for viral serology (human immunodeficiency virus, hepatitis B and hepatitis C). A serum pregnancy test will be performed on women of childbearing potential. An FSH test will be performed, if required to confirm post-menopausal status. Regarding viral serology, patients who received a hepatitis B vaccination and are positive for hepatitis B surface antibody, but are negative for both hepatitis B surface antigen and hepatitis B core antibody, do not need to be excluded from the study. Samples will be taken and handled according to the laboratory manual and analysed locally.

A chest X-ray (posterior-anterior) must be performed at Screening or in the 12 months prior to Screening.

7.1.5 Prior and Concomitant Medications and Therapies

Prior COPD therapies and medications will be recorded at Screening and concomitant use during the study recorded as described in Section 5.8.1.

Other prior medications will be separately recorded at Screening and concomitant use during the study recorded as described in Section 5.8.2.

7.1.6 Eligibility Check

Patients will be confirmed as eligible according to the Inclusion and Exclusion Criteria from assessments made at Screening with a final check of all results pre-dose in Part A.

7.2 Efficacy/Pharmacodynamic Assessments

7.2.1 Pulmonary Function Tests

Post-dose measurements will be taken in relation to the morning dose of RPL554 or placebo.

Spirometry assessments (FEV_1 and FVC) will be made in accordance with ATS/ERS guidelines (Miller et al, 2005). At all timepoints, three technically acceptable measurements will be made and recorded. Spirometry assessments may be performed up to eight times to obtain three acceptable readings. The highest FEV_1 and FVC readings from each assessment will be used for analysis even if the FEV_1 and FVC values come from two different forced exhalations.

Spirometry will be performed using site-owned equipment and reviewed centrally, and sites will be instructed in proper use of the equipment prior to study initiation.

7.2.2 Dyspnoea Scale

Patients will be interviewed by a blinded member of study staff to assess their dyspnoea. An 11-point Likert scale will be utilised, which will be anchored from 0 to 10 (Davis et al, 2006). The interview will be worded as follows: “On a scale from zero to 10, please rate your current shortness of breath, with zero indicating no shortness of breath and 10 indicating the worst shortness of breath you can imagine.” This scale will be an instantaneous measurement of their dyspnoea at that moment, and not reflective.

7.2.3 Rescue Medication

The use of rescue medication will be assessed as follows: 1) during study visits, by recording the amount of and time that rescue was taken, and 2) between Days 1 and 7 of each treatment period, by recording the weight of the canister.

7.3 Pharmacokinetic Assessments

Samples of 4 mL per time point will be collected by venepuncture or via indwelling cannula in the forearm into lithium heparin tubes and will be immediately chilled (ice bath). The blood will be centrifuged within 15 minutes of collection. The plasma will be separated in a refrigerated centrifuge (about 4°C) at 1100g for 15 minutes and transferred into polypropylene tubes. After each blood collection, the plasma will be dispensed into two aliquots. After appropriate labelling, the plasma samples will be stored at, or below -20°C. The plasma samples will then be transported in dry ice to an external laboratory where they will be stored

at or below -20°C until they are submitted for analysis with a validated method. Analysis will be performed by a central laboratory.

7.4 Safety Assessments

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

An adverse event is defined as any undesirable experience occurring to a patient, or worsening in a patient, during a clinical study, whether or not considered related to the study medication. An adverse event may be any of the following:

- A new illness
- An exacerbation of a sign or symptom of the underlying condition under treatment or of a concomitant illness
- Unrelated to participation in the clinical study or an effect of the study medication
- A combination of one or more of the above factors

No causal relationship with the study medication is implied by the use of the term "adverse event." An exacerbation of a pre-existing condition or illness is defined as a more frequent occurrence or as an increase in the severity of the pre-existing condition or illness during the study. Planned or elective surgical or invasive procedures for pre-existing conditions that have not worsened are not adverse events. However, any complication that occurs during a planned or elective surgery is an adverse event (if the event fits the serious criteria, such as an extended hospitalisation, it will be considered to be serious). Conditions leading to unplanned surgical procedures may be adverse events.

An adverse reaction is defined as all untoward and unintended responses to study medication related to any dose administered.

A serious adverse event (SAE) is any adverse experience that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity, OR
- Is a congenital anomaly/birth defect
- Other medical events*

*Important medical events that may not be immediately life-threatening or result in death or hospitalisation may be considered a SAE when, based on appropriate medical judgement, they may jeopardise the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

An unexpected adverse reaction is an adverse reaction in which the nature or severity of which is not consistent with the Investigator Brochure.

A suspected unexpected serious adverse reactions (SUSAR) is any suspected adverse reaction related to the study medication that is both unexpected and serious.

Standard procedures for emergency care should be followed for any individual adverse event, whenever clinically needed (decision to be taken by the Investigator).

7.4.1.2 Recording and Assessing Adverse Events

Any adverse events occurring during the following times are to be recorded in the eCRF:

- Part A: From signing of the Informed Consent form until 28 days after administration of the single dose.
- Part B: From 2 days prior to the start of Treatment Period 1 until the End of Study Visit, which for patients who complete the study will occur 4 to 10 days after the completion of the final treatment period

In view of the above, the period starting 29 days after Part A up to and including 3 days prior to the start of Part B (assuming they are separated by at least 29 days) will be considered to be outside the reporting period for adverse events, given the length of time between treatments with study medication.

All adverse events, whether reported spontaneously by the patient, in response to open questioning on treatment days or observed by the Investigator or his/her staff, will be recorded from informed consent until the End of Study Visit. The start and stop time will be recorded and adverse events will be assessed by the Investigator for the following:

7.4.1.2.1 Severity

Mild:	Resolved without treatment
Moderate:	Resolved or was tolerated with specific treatment without affecting study activities
Severe:	Did not resolve or was not tolerated with treatment

7.4.1.2.2 Chronicity

Single occasion:	Single event with limited duration
Intermittent:	Several episodes of an event, each of limited duration
Persistent:	Event which remained indefinitely

7.4.1.2.3 Causality

The Investigator will assess causal relationship between the study medication and each adverse event, and answer "yes" or "no" to the question, "Do you consider that there is a reasonable possibility that the event may have been caused by the study medication?"

For SAEs, causal relationship will also be assessed for study procedures, additional study medication, and other medication. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as "yes".

A guide to the interpretation of the causality question is found in Section 14.2.

7.4.1.2.4 Action and Outcome

- Action taken with study medication (none, study medication stopped, study medication temporarily interrupted)
- Other actions (none, concomitant medication, study discontinuation, hospitalisation, other)

- The outcome and date of outcome according to the following definitions:
  - Recovered or resolved (adverse event disappeared)
  - Recovering or resolving (patient is recovering)
  - Not recovered or not resolved (adverse event remains without signs of improvement)
  - Recovered or resolved with sequelae (adverse event has resulted in permanent disability or incapacity)
  - Fatal
  - Unknown (only applicable if patient has been lost to follow-up)
- Seriousness (yes or no)

7.4.1.3 Reporting Procedure for SAEs

The Investigator must report all SAEs to the Sponsor as soon as practical, but in call cases within 24 hours of awareness. Any fatal SAEs notified in the 28-day period after the last dose of study medication must also be reported.

SUSARs will be determined by the Sponsor's Medical Monitor.

SAEs will be reported to the IEC and regulatory authority(ies) according to local requirements.

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the patient's general physician or a medical specialist.

It is the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.4.2 Pregnancy

In addition to the Screening serum pregnancy test (see Section 7.1.4), urine pregnancy tests will also be performed by the study centre on women of childbearing potential at Screening (confirmed to be negative prior to the chest X-ray) and during the study.

Should a female patient become pregnant, or if a male patient fathers a child during the study or in the 30 days after the end of the study, the Investigator must be informed immediately. The Investigator will report this information to the Sponsor within 7 days of awareness. The Investigator will make all reasonable efforts to ascertain the progress and outcome of the pregnancy. If the outcome meets the criteria for immediate classification of a SAE (e.g. spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital anomaly, birth defect), the Investigator must follow the procedure for reporting SAEs.

7.4.3 Laboratory Assessments

In addition to the laboratory tests detailed below, unscheduled and/or repeat testing may be performed at the discretion of the Investigator. Any additional laboratory results will also be merged into the final database. Laboratory results will be provided to the Investigator for each patient and each visit. The Investigator should assign whether each abnormal result is not clinically significant or a clinically significant.

Samples will be taken and handled according to the laboratory manual and analysed locally.

7.4.3.1 Haematology

The following will be measured: haemoglobin, haematocrit, total white cell count, leucocyte differential count and platelet count.

For each assessment, a sample of venous blood will be collected in a collection tube containing ethylenediaminetetraacetic acid (EDTA).

7.4.3.2 Blood Chemistry

The following will be measured: creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine transaminase, gamma-glutamyl transferase, lactate dehydrogenase, creatine kinase, thyroid stimulating hormone, triiodothyronine and thyroxine, glucose, potassium, sodium and calcium.

For each assessment, a sample of venous blood will be collected in a vacutainer collection tube.

7.4.3.3 Urinalysis

A midstream urine sample will be collected in a sterile container. The following will be tested: leucocytes, blood, ketones, bilirubin, urobilinogen, protein and glucose. If urinalysis on dipstick is positive for leucocytes and/or blood/haemoglobin, a microscopic examination including erythrocytes, leucocytes, bacteria, casts, epithelial cells and crystals will be performed.

7.4.4 Vital Signs

The vital signs to be collected are blood pressure and pulse rate.

Post-dose measurements will be taken in relation to the morning dose. Therefore, 12-hour measurements will be taken prior to the evening dose.

For each assessment, supine vital signs will be assessed while the patient has been at rest for at least 5 minutes.

7.4.5 Physical Examination

A full physical examination, covering major body systems (assessments of the nose, throat, skin, thyroid gland, neurological system, respiratory system, cardiovascular system, abdomen [liver and spleen], lymph nodes and extremities) will be performed at Screening. Results will be recorded in the eCRF as normal, abnormal not clinically significant or abnormal clinically significant and abnormal results described. The full physical examination will be repeated at the End of Study Visit, and any changes only recorded.

A brief physical examination, including assessments of the skin, respiratory system, cardiovascular system, and abdomen (liver and spleen) will be performed pre-dose for Part A, and pre-dose on Days 1 and 7 for Part B.

7.4.6 12-Lead ECG

Each 12-lead ECG should be taken after at least 5 minutes in the supine position. An overall assessment (normal, abnormal not clinically significant or abnormal clinically significant) will be recorded in the eCRF by the Investigator. ECG recordings will be assessed locally.

Post-dose measurements in Part A will be taken in relation to the single, morning dose of RPL554 or placebo.

8 QUALITY ASSURANCE AND QUALITY CONTROL

The study will be conducted in accordance with the current approved protocol, standard operating procedures and all applicable guidelines and requirements (see Section 10).

8.1 Audit and Inspection

The Sponsor, or its designee may conduct a quality assurance audit. An inspection of this study may also be carried out by regulatory authorities at their discretion. Such audits or inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the Investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his time and the time of his staff to the auditor or inspector to discuss findings and any relevant issues.

8.2 Monitoring and Source Document Verification

The study will be monitored by a monitor approved by the Sponsor. During these visits, all procedures will be monitored for compliance with the protocol. Source documents will be reviewed and compared with the data entries in the eCRFs to ensure consistency. The Sponsor will ensure that the study is monitored in accordance with the principles of ICH GCP. The frequency of monitoring visits will be determined, in part, by the rate of patient recruitment.

The following are examples of items that will be reviewed at these visits:

- Compliance with the protocol
- Consent procedure
- Source documents
- Adverse event procedures
- Storage and accountability of materials

The monitoring visits also provide the Sponsor with the opportunity to ensure that timely patient accrual and the other Investigator's obligations and all applicable requirements are being fulfilled.

The Investigator must permit the study monitor, the IEC, the Sponsor's auditors and representatives from regulatory authorities' direct access to all source documents for confirmation of the accuracy and reliability of data contained within the eCRFs (source document verification). Patient confidentiality will be protected at all times.

Source documents are defined as the results of original observations and activities of a clinical investigation, including medical notes. All source documents produced in this study will be maintained by the Investigator and made available for inspection. The original signed informed consent form for each patient will be retained by the Investigator and the second signed original given to the patient.

Source data include, but is not limited to, the following and will be identified in a source data location log:

- Screening/enrolment log
- Medical notes - which should be updated after each visit to include visit dates, medical history, diagnosis of COPD, concomitant medication, any clinically relevant findings of clinical examinations or clinically relevant adverse events/medication changes, SAEs and information on patient withdrawal

- Informed consent form
- 12-lead ECGs
- Laboratory reports
- Visit dates
- Study medication accountability/inventory forms

The study monitor will carry out source document verification at regular intervals. This is an essential element of quality control, as it allows the rectification of transcription errors and omissions.

8.3 Data Management and Coding

Data for each patient will be recorded in an eCRF. Data collection must be completed for each patient who signs an informed consent form and receives at least one dose of study medication.

eCRFs will be designed and produced by the Sponsor or designee and should be completed in accordance with instructions. The Investigator is responsible for maintaining adequate and accurate medical records from which accurate information will be transcribed directly into the eCRFs using a secure internet connection. The eCRFs should be filled out completely by the Investigator or designee as stated on the delegation of responsibilities form. The eCRF system will be Food and Drug Administration Code of Federal Regulations 21 Part 11 compliant.

The eCRFs must be reviewed, signed and dated by the Investigator.

Data entered into the eCRF will be validated as defined in the data validation plan. Validation includes, but is not limited to, validity checks (e.g. range checks), consistency checks and customised checks (logical checks between variables to ensure that study data are accurately reported) for eCRF data and external data. A majority of edit checks will be triggered during data entry and will therefore facilitate efficient 'point of entry' data cleaning.

Data management personnel will perform both manual eCRF review and review of additional electronic edit checks to ensure that the data are complete, consistent and reasonable. The electronic edit checks will run continually throughout the course of the study and the issues will be reviewed manually online to determine what action needs to be taken.

Manual queries may be added to the system by clinical data management or study monitor. Clinical data managers and study monitors are able to remotely and proactively monitor the patient eCRFs to improve data quality.

External data (laboratory safety, 12-lead ECG and PK data) will be transferred electronically into the study database. Discrepancies will be queried to the study centre and/or the laboratory until the electronic data and the database are reconciled.

All updates to queried data will be made by authorised study centre personnel only and all modifications to the database will be recorded in an audit trail. Once all the queries have been resolved, eCRFs will be locked by password protection. Any changes to locked eCRFs will be approved by the Investigator.

Once the full set of eCRFs have been completed and locked, the Sponsor will authorise database lock and all electronic data will be sent to the designated statistician for analysis. Subsequent changes to the database will then only be made only by written agreement of the Sponsor. A copy of the eCRFs for each patient will be provided to the Investigator in uneditable format at the end of the study.

Adverse events will be coded from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be coded according to the World Health Organisation drug code. An independent coding review will be performed by the Sponsor.

The clinical database (in Statistical Analysis System [SAS] format) will be transferred to the Sponsor at the end of the study.

9 STATISTICAL METHODS

9.1 Statistical and Analytical Plans

This section presents a summary of the planned statistical analyses. A detailed plan describing the analyses to be conducted will be defined before the last patient is completed and will include the determination of rules for major and minor protocol deviations. Any deviation from the analysis specified in the protocol or the statistical analysis plan will be detailed and justified in the clinical study report.

9.2 Populations to be Analysed

Allocation of patients to the analysis populations (and whether any patients or specific data from a patient will be excluded) will be determined at the pre-database lock meeting.

Part A:

The full analysis set will consist of all randomised patients with sufficient data collected after intake of study treatment to compute the efficacy/pharmacodynamic parameters.

The safety set will consist of all randomised and treated patients.

The PK data set will consist of all randomised patients with blood sampling performed after an RPL554 treatment and with data sufficient to calculate PK parameters.

Part B:

The full analysis set will consist of all randomised patients with sufficient data collected after intake of study treatment to compute the efficacy/pharmacodynamic parameters on at least two treatment periods.

The completer analysis set will consist of all randomised patients that complete all treatment periods.

The safety set will consist of all randomised patients who took at least one dose of study treatment during at least one period.

The PK data set will consist of all randomised patients with blood sampling performed after at least one dose of RPL554 and with data sufficient to calculate PK parameters.

9.3 Study Endpoints

9.3.1 Part A

9.3.1.1 Primary Endpoint

The primary endpoints in Part A are the pharmacokinetic parameters $AUC_{0\text{-}12}$ and $AUC_{0\text{-}t}$ maximum concentration (C_{max}), time to maximum concentration (t_{max}) and half-life.

9.3.1.2 Secondary Endpoints

- Safety and tolerability:
  - Continuous monitoring of adverse events
  - Laboratory safety tests [haematology, blood chemistry and urinalysis]

  - 12-lead ECG (including QTcF and heart rate), supine vital signs (blood pressure and pulse rate)
- Change from baseline in average FEV_1 $AUC_{0\text{-}4h}$ measured after single dose
- Change from baseline in average FEV_1 $AUC_{0\text{-}12h}$ measured after single dose
- Change from baseline in peak FEV_1 measured after single dose
- Change from baseline in peak pulse and peak heart rate measured after single dose

9.3.2 Part B

9.3.2.1 Primary Endpoint

The primary endpoint in Part B is change from baseline in peak FEV_1 measured after morning dosing on Day 7.

9.3.2.2 Secondary Endpoints

- Safety and tolerability:
  - Continuous monitoring of adverse events
  - Laboratory safety tests [haematology, blood chemistry and urinalysis]
  - 12-lead ECG (including QTcF and heart rate), supine vital signs (blood pressure and pulse rate)
- Change from baseline in (morning) trough FEV_1 measured prior to morning dosing on Day 7
- Change from baseline in peak FEV_1 measured after first dose
- Change from baseline in average FEV_1 $AUC_{0\text{-}4h}$ measured after morning dosing on Day 7
- Change from baseline in average FEV_1 $AUC_{0\text{-}12h}$ measured after first dose and after morning dosing on Day 7
- Determination of onset of action (>10% increase in FEV_1 from pre- to post- first dose, censored at 120 minutes) after first dose
- RPL554 steady state pharmacokinetics ($AUC_{0\text{-}12h}$, C_{max}, t_{max}, accumulation ratio) after dose 13 on Day 7
- Change from baseline in peak pulse after first dose on Day 1 and after morning dosing on Day 7
- Change from baseline in, average FEV_1 $AUC_{0\text{-}4h}$ and average FEV_1 $AUC_{0\text{-}12h}$ on Day 1
- Change from baseline in rescue medication use

9.3.2.3 Exploratory Endpoint

- Evaluation of dose response of RPL554 on peak and average FEV1 $AUC_{0\text{-}12h}$ after morning dose on Day 7, and morning trough FEV_1 prior to the last dose on Day 7
- Change from baseline in Likert dyspnoea scale measured after single dose and after morning dose on Day 7

9.4 Statistical Methods

In general, unless stated otherwise, continuous variables will be summarised using descriptive statistics (number of patients, mean, standard deviation, median, minimum and maximum values) and for categorical (nominal) variables, the number and percentage of patients will be used.

All hypothesis testing will be done using two-sided alternative hypotheses. P-values less than 5% will be considered statistically significant.

9.4.1 Patient Disposition

The number of patients enrolled, randomised, completed or withdrawn (with reason for withdrawal) will be summarised.

9.4.2 Protocol Deviations

All protocol deviations collected will be divided into critical, major or minor categories. Prior to database lock protocol deviations will be reviewed and consequences for inclusion of patients in various analysis population sets determined and documented.

9.4.3 Demographics and Other Baseline Characteristics

Demographics and baseline characteristics (including pre- and post-bronchodilator FEV_1 [both in litres and in percentage of predicted normal], post-bronchodilator FEV_1/FVC, FEV_1 reversibility, duration of COPD [time since diagnosis], smoking habits including number of pack-years, number of patients taking COPD medications by therapeutic class including ICS, LABA, LAMA or combinations thereof) will be listed and summarised appropriately.

Medical history, prior and concomitant medications, viral serology results, pregnancy test results from females and chest X-ray findings will be listed.

9.4.4 Extent of Exposure and Treatment Compliance

For Part A, all administration of study medication will be performed at the clinic under supervision of the study staff; therefore, no formal analysis of compliance will be performed.

For Part B, compliance will be assessed based on: 1) patient-reported missed doses, and 2) the weights of pMDI units dispensed and returned. Total exposure will be based on the patient-reported missed doses.

9.4.5 Efficacy/Pharmacodynamics

FEV_1 and FVC will be summarised as actual value and change from baseline using descriptive statistics over time for all treatments and both study parts.

The peak effect on FEV_1 during these time intervals will be computed as the maximum value in the 4 hours after dosing. The average effect (average FEV_1 AUC_{0-t}) will be calculated as the AUC divided by the length of the time interval of interest. For analysis of the peak, average and trough FEV_1, the change from baseline will be expressed as the parameter divided by the pre-dose Day 1 baseline value.

In Part A, computed efficacy/pharmacodynamic parameters for FEV_1 will be compared between the treatments using analysis of covariance models with fixed factor treatment, and

using the pre-dose baseline value as a covariate. In Part B, computed efficacy/pharmacodynamic parameters (peak, AUC_{0-4}, AUC_{0-12} and trough) for FEV_1 will be compared between the treatments using analysis of covariance models adjusting for treatment period and patient, and using the pre-dose Day 1 baseline value as a covariate. FEV_1 will be analysed using multiplicative models, which means that data (dependent and baseline) are logged prior to analysis and the result then transformed back to the linear scale giving treatment differences as ratios of geometric means.

Primarily, active treatments will be compared to placebo. For RPL554 pMDI, the high dose will first be compared to placebo, and if found statistically significant then the next lower dose will be compared to placebo, and if found statistically significant then the subsequent lower dose will be compared to placebo, and this procedure repeated for all doses. Secondarily, the different doses of RPL554 pMDI will be compared. Results of the comparisons will be expressed as the mean geometric ratio with 95% confidence intervals and associated, 2-sided, p-value.

Onset of action will be calculated and summarised by treatment. In Part B, a Kaplan-Meier plot illustrating time to onset will be constructed and from the survival curves the median time to onset will be estimated. Placebo will not be included in summaries of onset of action.

In Part B, the average use of rescue medication during the treatment periods will be summarised by treatment group. In addition, all rescue medication used during the treatment visits (Day 1 in Part A and Days 1 and 7 in Part B) will be listed to assess the accuracy of the FEV_1 recordings.

In Part B, change in Likert dyspnoea scale to each time point will be compared between the treatments using analysis of covariance models adjusting for factors for treatment, period and patient, and using the pre-dose Day 1 baseline value as a covariate. Additive models will be used for dyspnoea.

9.4.6 Pharmacokinetics

The following PK parameters will be calculated from plasma concentrations of RPL554 using standard non-compartmental methods.

- Part A: AUC_{0-t} represents the area under the plasma concentration curve from time 0 to last observed value above the lower limit of quantification
- Part A: Half-life=$\ln(2)/\lambda_z$
- Parts A and B: AUC_{0-12h} represents the area under the plasma concentration curve from time 0 to 12 hours. The AUC_{0-12h} value after dose 13 in Part B is considered an appropriate estimate of the AUC at steady state.
- C_{max} denotes the highest plasma concentration measured
- t_{max} denotes the time point corresponding to C_{max}

PK parameters will be summarised by dose level using descriptive statistics (n, geometric mean, coefficient of variation [CV], minimum, maximum and median for AUC parameters, C_{max}, n, arithmetic mean, standard deviation, minimum, maximum and median for t_{max}).

In Part A, proportionality for AUC_{0-12h} and C_{max} will be investigated by fitting a power model to data using linear regression on the log(parameter)-log(dose) scale. In Part B, dose-normalised AUC_{0-12h} and C_{max} will be compared using analysis of covariance models adjusting for factors treatment, period and patient 90% confidence intervals will be constructed for the geometric mean ratios. If appropriate, AUC_{0-12h} data from Parts A and B belonging to

the same patient and the same dose of RPL554 may be combined to compute the accumulation index (repeat dose/single dose ratio).

9.4.7 Safety

Safety data including laboratory safety tests, 12-lead ECG, vital signs and physical examinations, will be summarised by treatment group and timepoint of collection, when appropriate, for each of the two parts separately. For continuous variables, the change from baseline (pre-dose at each treatment period) to each post-dose time point will also be calculated and summarised. Data will further be illustrated by shift tables (showing changes from low/normal/high) and shift plots for selected time points. Separate listings will be generated of abnormal values occurring after the first dose of study medication.

In Part A, change from baseline in peak pulse and peak heart rate will be compared between the treatments using analysis of covariance models with fixed factor treatment, and using the pre-dose baseline value as a covariate. In Part B, change from baseline in peak pulse will be compared between the treatments using analysis of covariance models with fixed factors for treatment, period and patient, and using the pre-dose Day 1 baseline value as a covariate. Additive model will be used for pulse and heart rate.

Coded adverse event terms will be presented by system organ class (SOC) and preferred term and summarised by treatment group for each part. Summary tables by treatment group with total number and number of patients with adverse events, SAEs, adverse events leading to discontinuation of study treatment, causally related adverse events and severe adverse events will be produced. Further SAEs, causally related adverse events and adverse events of each intensity will be summarised by SOC and preferred term.

9.4.8 Handling of Withdrawals or Missing Data

In Part B, patients withdrawn after only one treatment period will not be included in the efficacy/pharmacodynamic and PK analyses of parameters that can be computed in all planned treatment periods. Imputation of data for calculation of average (AUC) effects for FEV_1 will be described in the statistical analysis plan. No other imputation of missing data will be performed.

All available data from all dosed patients who have received study treatment will be listed and summarised. Any unscheduled or unplanned readings will be presented within the patient listings, but only the scheduled readings will be used in any summaries. If a visit is rescheduled due to variability in FEV_1 or other reason, the rescheduled visit will be listed and summarised as the valid visit.

9.4.9 Interim Analyses

No formal interim analysis is currently planned. This study will consist of two separate and independent analyses. To avoid possible effects of the unblinding of data from Part A on the blinding in Part B, only aggregated data (i.e. treatment level, without individual patient identifiers) will be revealed at the time of the analysis of the Part A data.

9.5 Determination of Sample Size

The sample size is determined for Part B. This is a complete block crossover study. Assuming a residual CV of 6% for peak FEV_1, 30 patients will give an 80% power to detect a pairwise difference in peak FEV_1 of 4.6%. Assuming a mean baseline FEV_1 of 1.5 L this will correspond

to a difference of about 70 mL. To account for withdrawals, 36 patients will be randomised to Part A.

10 ETHICAL CONSIDERATIONS

10.1 Guidelines

The study will be performed in accordance with ICH GCP guidelines, the principles outlined in the Declaration of Helsinki (1996), the protocol and applicable regulatory requirements.

10.2 Ethics and Regulatory Approval

The Sponsor will supply all background data necessary to enable submission to the appropriate IECs and regulatory authorities. The study will not commence before formal ethical and regulatory approvals have been granted.

All changes or revisions of this protocol will be documented. The reason for the amendment will be stated. The Sponsor will ensure ethical and regulatory approval is obtained for all substantial amendments to the original approved documents.

10.3 Informed Consent Process

It is the responsibility of the Investigator to obtain written informed consent from patients. All consent documentation must be in accordance with applicable regulations and ICH GCP. Each patient is requested to sign and date the informed consent form after (s)he has received and read the patient information sheet and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences and the patient's rights and responsibilities. Patients will be given adequate time to evaluate the information given to them before signing the informed consent form.

One original of the signed informed consent form must remain on file and must be available for verification by the study monitor at any time. A second original of the informed consent form plus the patient information sheet must be given to the patient or the patient's legally authorised representative.

10.4 Patient Confidentiality

Data collected during this study may be used to support the development, registration or marketing of the study medication. The Sponsor will control all data collected during the study and will abide by the European Union Directive on Data Privacy concerning the processing and use of patient's personal data. For the purpose of data privacy legislation, the Sponsor will be the data controller.

After patients have consented to take part in the study, their medical records and the data collected during the study will be reviewed by the Sponsor and/or its representatives. These records and data may, in addition, be reviewed by the following: independent auditors who validate the data on behalf of the Sponsor; regulatory authorities and the IEC which gave its approval for this study to proceed.

Although patients will be known by a unique number, their initials will also be collected and used to assist the Investigator to reconcile data clarification forms, for example, that the results of study assessments are assigned to the correct patient. The results of this study containing the unique number, but not the patient's initials and relevant medical information may be recorded and transferred to and used in other countries throughout the world, which may not afford the same level of protection that applies within the European Union. The purpose of any such transfer would be to support regulatory submissions made by the Sponsor in such countries.

10.5 Record Maintenance/Retention

The Investigator will retain the originals of all source documents generated at the location where the study is being conducted, either: 1) until after regulatory agency approval is obtained for the study medication in the country/countries in which the results of this study comprise the submission dossier, or 2) for a period of 2 years after the report of the study has been finalised, in the absence of a regulatory approval. After that time, all study-related documents will be archived according to ICH GCP regulations.

11 FINANCE AND INSURANCE

Financial arrangements are detailed in the Investigator Agreement between the Sponsor and Investigator.

The Sponsor will arrange clinical study insurance to compensate patients for any potential injury or death caused by the study.

12 PUBLICATION POLICY

The publication policy is detailed in the Investigator Agreement between the Sponsor and Investigator.

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14 APPENDICES

14.1 Birth Control Methods For Women of Childbearing Potential Which May Be Considered As Highly Effective

(Adapted from the Clinical Trial Facilitation Group, Heads of Medicines Agencies, 2014)

I. Definitions

Woman of Childbearing Potential
A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered women of childbearing potential:

1. Premenopausal female with one of the following:
- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

   Note: Documentation can come from the study centre staff's: review of participant's medical records, medical examination, or medical history interview.

2. Premenarchal

3. Postmenopausal female

   Females who are postmenopausal (age-related amenorrhea ≥ 12 consecutive months and increased FSH >40 mIU/mL), or who have undergone hysterectomy or bilateral oophorectomy are exempt from pregnancy testing. If necessary to confirm postmenopausal status, an FSH will be drawn at Screening.

   Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

II. Methods

For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
  - Oral

  - Injectable
  - Implantable[1]
- Intrauterine device[1]
- Intrauterine hormone-releasing system[1]
- Bilateral tubal occlusion[1]
- Vasectomised partner[1,2]
- Sexual abstinence[3]

[1] Contraception methods that in the context of this guidance are considered to have low user dependency

[2] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success

[3] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient

14.2 Interpreting Adverse Event Causality

The following factors should be considered when deciding if there is a “reasonable possibility” that an adverse event may have been caused by the study medication.

- Time Course. Exposure to suspect study medication. Has the patient actually received the suspect study medication? Did the adverse event occur in a reasonable temporal relationship to the administration of the suspect study medication?
- Consistency with known study medication profile. Was the adverse event consistent with the previous knowledge of the suspect study medication (pharmacology and toxicology) or drugs of the same pharmacological class? OR Could the adverse event be anticipated from its pharmacological properties?
- Dechallenge experience. Did the adverse event resolve or improve on stopping or reducing the dose of the suspect study medication?
- No alternative cause. The adverse event cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors
- Rechallenge experience. Did the adverse event reoccur if the suspected study medication was reintroduced after having been stopped Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an adverse event where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course, but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the adverse events.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the study medication?
- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.