Verona Pharma

CLINICAL STUDY PROTOCOL

A PHASE II, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, THREE WAY CROSSOVER STUDY TO ASSESS THE BRONCHODILATOR EFFECT OF RPL554 ADMINISTERED IN ADDITION TO OPEN LABEL TIOTROPIUM/OLODATEROL IN PATIENTS WITH COPD

STUDY NO. RPL554-CO-204

Version:	**1.0**
Date:	**28 May 2018**
Phase:	**II**
Investigational Medicinal Product:	**RPL554**
EudraCT Number:	**2018-001037-41**
IND Number:	**133146**

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

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Jan-Anders Karlsson, PhD Chief Executive Officer		27 May 2018

INVESTIGATOR SIGNATURE PAGE

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

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

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DETAIL OF AMENDMENTS SINCE THE PREVIOUS VERSION

This is the first version of the protocol.

SYNOPSIS

Title of Study:	A Phase II, randomized, double blind, placebo controlled, three-way crossover study to assess the bronchodilator effect of RPL554 administered in addition to open label tiotropium/olodaterol in patients with COPD
Protocol Number:	RPL554-CO-204
EudraCT Number:	2018-001037-41
IND Number:	133146
Phase:	II
Sponsor:	Verona Pharma plc
Coordinating Investigator:	Prof S Dave Singh
Study Centre(s):	Up to four sites total, in US and UK
Planned Study Period:	Estimated: June to December 2018
Objectives:	**Primary Objective** To investigate the bronchodilator effect on peak forced expired volume in 1 second (FEV_1) (measured in the first 4 hours after dosing) of nebulized RPL554 dosed twice daily for 3 days, as compared to placebo, when administered in addition to once daily tiotropium/olodaterol. The peak FEV_1 is measured after the morning dose on Day 3. **Secondary Objectives** • To assess the bronchodilator effect on peak FEV_1 (measured in the first 4 hours after dosing) and average (measured as the area under the curve [AUC]) FEV_1 over 12 hours of nebulized RPL554 after the first dose on Day 1 as compared to placebo, when administered in addition to tiotropium/olodaterol • To investigate the effect of twice daily nebulized doses of RPL554, as compared to placebo, when administered in addition to tiotropium/olodaterol on morning trough FEV_1 (mean of values 11 and 12 hours after last dose of RPL554) on Day 4 • To investigate the effect of twice daily nebulized doses of RPL554, as compared to placebo, when administered in addition to tiotropium/olodaterol on average (measured as AUC) FEV_1 over 4 and 12 hours after the morning dose on Day 3 • To assess the bronchodilator effect on peak FEV_1 measured within 4 hours after the evening dose of RPL554 on Day 3 • To analyze plasma concentrations and assess the steady state pharmacokinetics of RPL554 when administered in addition to tiotropium/olodaterol • To assess the tolerability and safety of twice daily nebulized doses of RPL554 in addition to tiotropium/olodaterol • To determine the onset of action of RPL554 when administered with tiotropium/olodaterol (after the first dose) • To investigate the effects of RPL554 on specific airway conductance (sG_{aw}) and lung volumes (residual volume [RV], functional residual capacity [FRC]) when administered in addition to tiotropium/olodaterol **Exploratory Objectives** • To assess the dose response of RPL554 on peak and average (measured as AUC over 12 hours) on Day 3, and morning trough FEV_1 (mean of values at 11 and 12 hours after last dose of RPL554) on Day 4, when dosed in addition to tiotropium/olodaterol • To examine the effect of RPL554 on top of tiotropium/olodaterol on average (measured as AUC) FEV_1 over 24 hours after 3 days of dosing

	• To examine the effect of RPL554 on top of tiotropium/olodaterol on a Likert dyspnea scale
Study Design and Methodology:	This is a Phase II, randomized, double blind, placebo controlled, complete block three-way crossover study to investigate combination treatment with nebulized RPL554 and tiotropium/olodaterol Respimat® in patients with moderate to severe chronic obstructive pulmonary disease (COPD). It is planned to randomize approximately 70 patients at up to four study centers. Patients will be screened for eligibility, including a reversibility test with salbutamol/albuterol and ipratropium between 7 and 14 days before the first dose of study treatment. Eligible patients will then attend three separate treatment periods (Treatment Periods 1 to 3), with each lasting 3 days and separated by a 7 to 14-day washout period. During each treatment period, patients will be present at the study center from the morning of Day 1 until the morning of Day 4. Patients will be randomized pre-dose on Day 1 of Treatment Period 1. At Screening, patients will be assessed for eligibility into the study, including Holter monitoring, and reversibility testing with two puffs of salbutamol/albuterol followed by two puffs of ipratropium. Eligible patients will have all prior COPD medications discontinued, with the exception of inhaled corticosteroids, and placed on ipratropium and salbutamol/albuterol to use on a regular or as-needed basis (as per Investigator) throughout the study except during the treatment periods. During each treatment period, patients will be dosed with tiotropium/olodaterol Respimat® once daily each morning (Day 1 to Day 3) and either RPL554 or placebo twice daily (in the morning and evening) for total of six doses of RPL554 or placebo in each treatment period. The pre-dose FEV_1 at Day 1 of Treatment Period 2 and Day 1 of Treatment Period 3 must be within ±20% of the pre-dose FEV_1 at Day 1 of Treatment Period 1, in order to ensure consistent baseline FEV_1 for each study treatment. The following provides a brief overview of the major procedures to be performed during each treatment period. The following will be performed at Day 1: • Measurements of lung function (FEV_1 and forced vital capacity [FVC]) by spirometry pre-dose and up to 12 hours post-dose • 12-lead electrocardiogram (ECG) pre-dose and at 2 and 4 hours post-dose and vital sign (supine) measurements pre-dose and up to 12 hours post-dose • Measurement of lung volumes by whole body plethysmography pre-dose and 1.25 hours post-dose The following will be performed on Day 2 of each treatment period: • Measurement of lung function (FEV_1 and FVC) by spirometry pre-dose and for up to 12 hours post-dose • 12-lead ECG pre-dose and at 2 hours post dose and vital sign (supine) measurements pre-dose and up to 12 hours post-dose The following will be performed at Day 3 of each treatment period: • Measurements of lung function (FEV_1 and FVC) by spirometry pre-dose and up to 24 hours post dose • 12-lead ECG measurements pre-dose, 2 hours post-dose and 24 hours post- dose. • Measurement of lung volumes by whole body plethysmography pre-dose and at 1.25 hours, 8.25 and 12.25 hours post-dose • Vital signs (supine) done pre-dose, up to 8 hours post dose and 24 hours post- dose • Pharmacokinetic blood sampling pre-dose and up to 12 hours post dose • 24-hour Holter monitor placed

Study Procedures:	• Laboratory safety tests (hematology and biochemistry) at 24 hours post-dose The final assessments and Holter removal will be performed prior to discharge from the study center on Day 4. Adverse events and concomitant medications/therapies will be recorded throughout the study.
Number of Patients Planned:	Approximately 70 evaluable patients
Main Criteria for Eligibility:	***Inclusion Criteria*** Male and female patients with moderate to severe COPD, with a post-bronchodilator FEV_1 of 30 to 70% of predicted. They must have a baseline increase in FEV_1 of $\geq$150 mL after use of two puffs each of salbutamol/albuterol and ipratropium. They must have at least a 10 pack-year smoking history, and may be a former smoker or current smoker. ***Exclusion Criteria*** Patients must be clinically stable without recent COPD exacerbations or hospitalizations. They must not have uncontrolled disease or chronic heart failure.
Study Treatments:	All study treatments will be administered using the inhaled route. Patients will receive the following three dose treatment combinations in a randomized sequence during Treatment Periods 1 to 3: Tiotropium/olodaterol 5 µg /5 µg once daily + RPL554 6 mg twice daily Tiotropium/olodaterol 5 µg /5 µg once daily + Placebo twice daily Tiotropium/olodaterol 5 µg /5 µg once daily + RPL554 1.5 mg twice daily Each morning during each 3-day period, the tiotropium/olodaterol will be administered first followed immediately (starting within 2 minutes) by the nebulized study medication (RPL554 or placebo). The study medication only will be repeated in the evening on Day 1, Day 2, and 3, 12 hours after the morning dose. The tiotropium/olodaterol will be administered open label and the study medication will be administered double blind. The study medication will be administered using a standard Jet nebulizer and compressor. The RPL554 formulation is a sterile suspension supplied in a 2.5 mL dose in amber glass vials containing sterile micronized RPL554 in pH 7 phosphate buffered saline, and containing surfactants to aid suspension. The placebo is the same as the RPL554 suspension except that the active RPL554 ingredient is omitted, i.e. it consists of pH 7 phosphate buffered saline and surfactants only.
Duration of Treatment:	The approximate planned duration of participation for each patient will be up to 61 days: 7 to 14-day screening period, up to 9 days treatment (three treatment periods of 3 days each separated by 7 to 14 days) and an end of study visit 4 to 10 days after the last treatment visit (Day 4 of Treatment Period 3).
Statistical Methods:	Treatments will be compared using analysis of covariance adjusting for treatment, period, patient and baseline. Multiplicative models will be used for FEV_1 and outcome from whole body plethysmography and additive models for blood pressure, pulse rate and ECG heart rate. RPL554 doses will first be compared to placebo using a closed test procedure starting with the highest dose of RPL554.
Sample Size:	This is a complete block three-way crossover study. Assuming a residual coefficient of variation of 6% for peak FEV_1, 70 patients will give an 80% power to detect a pairwise difference in FEV_1 of 50 mL.

TABLE OF CONTENTS AND LIST OF TABLES AND FIGURES

Table of Contents

List of Tables and Figures

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ANCOVA	Analysis of covariance
ATS	American Thoracic Society
AUC	Area under the curve
BMI	Body mass index
C_{max}	Maximum concentration
COPD	Chronic obstructive pulmonary disease
CI	Confidence interval
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
ERS	European Respiratory Society
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
FEV_1	Forced expired volume in 1 second
FRC	Functional residual capacity
FVC	Forced vital capacity
HRT	Hormone replacement therapy
ICH	International Conference on Harmonisation
IUPAC	International Union of Pure and Applied Chemistry
LABA	Long acting beta2-agonists
LAMA	Long acting muscarinic antagonists
LPS	Lipopolysaccharide
MedDRA	Medical Dictionary for Regulatory Activities
NHANES	National Health and Nutrition Examination Survey
PC_{20}MCh	Provocative concentration of methacholine chloride causing a fall in FEV_1 of 20% from placebo
PDE	Phosphodiesterase
pMDI	Pressurized metered dose inhaler
QTcF	QT interval corrected for heart rate using Fridericia's formula
RV	Residual volume
SAE	Serious adverse event
SAS	Statistical analysis software
sG_{aw}	Specific airway conductance
SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected, unexpected serious adverse reaction
t_{max}	Time to maximum concentration

1 INTRODUCTION

1.1 Disease and Study Medication Review

RPL554, a small molecule isoquinolone derivative, is a dual inhibitor of two isoforms (type 3 and 4) of the phosphodiesterase (PDE) family of enzymes. PDE3 and PDE4 are known to have a role in modulating the inflammatory airway response in respiratory diseases, including chronic obstructive pulmonary disease (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 and there is also evidence to suggest that combined inhibition of PDE3 and PDE4 can have additive or synergistic anti-inflammatory and bronchodilator effects (reviewed by 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 unfavorable gastrointestinal side effects such as nausea, emesis, diarrhea, 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 inhibitors (administered by inhalation) have exhibited both bronchodilator and anti-inflammatory actions, with a more favorable 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 antimuscarinic agents, as well as additive properties with βa_2-agonists (Calzetta et al, 2013; Calzetta et al, 2015).

The safety, bronchodilator, bronchoprotective and anti-inflammatory activities of RPL554 have been evaluated in clinical studies involving over 730 subjects. Initially, five studies were done in healthy subjects, patients with mild-moderate persistent asthma and those with allergic rhinitis and COPD, using a nebulized solution in citrate/phosphate buffered saline at pH 3.2 (Franciosi et al, 2013; summarized in the Investigator's Brochure). Systemic exposure following inhalation using this solution formulation was low and somewhat variable, with maximum concentration (C_{max}) values ranging from about 0.9 ng/mL following administration at 0.018 mg/kg to about 4 ng/mL at 0.072 mg/kg. Area under the curve $(AUC)_{0-t}$ values ranged from about 1.5 ng.h/mL to 11 ng.h/mL over the same dose range. Mean half-life values ranged from approximately 3 to 7 hours.

RPL554 delivered as a nebulized solution was well tolerated. Adverse events were generally mild and generally of equal frequency between placebo and active treatment groups. RPL554 produced a rapid bronchodilation in both COPD and asthmatic patients and increased the provocative concentration of methacholine chloride causing a fall in FEV_1 of 20% from placebo (PC_{20}MCh) by 1.5 doubling doses compared with placebo (95% confidence interval [CI]: 0.63-2.28; p=0.004). In healthy subjects, RPL554 also produced a significant inhibition of the lipopolysaccharide (LPS)-induced recruitment of the total number of inflammatory cells to the airways, measured in the sputum (p=0.002), as well as an inhibition of the absolute numbers of neutrophils (p=0.002), eosinophils (p=0.001), lymphocytes (p=0.001) and macrophages (p=0.04) in sputum.

RPL554 has subsequently been re-formulated in a neutral pH phosphate buffered suspension formulation for nebulization. This formulation has been tested in seven completed clinical studies:

1. Study RPL554-007-2014 was a Phase I study in which single and multiple ascending doses up to 24 mg were administered to healthy subjects and COPD patients (RPL554-007-2014 Clinical Study Report, 2016). No maximum tolerated dose of RPL554 could be determined and there was a large bronchodilator response observed. Pharmacokinetics demonstrated a terminal serum half-life of about 10 to 12 hours.
2. Study RPL554-008-2014 was a Phase II crossover study that enrolled patients with mild to moderate chronic asthma who received four single doses of RPL554 (0.4 mg, 1.5 mg, 6 mg and 24 mg), two doses of nebulized salbutamol/albuterol (2.5 mg and 7.5 mg) and placebo. RPL554 produced a dose-dependent bronchodilation with a magnitude that was comparable to a maximal dose of salbutamol/albuterol, but with fewer of the well described salbutamol/albuterol side effects (e.g. hypokalemia, tachycardia, tremor and palpitations) (Bjermer et al, 2016).
3. Study RPL554-009-2015 was a Phase II crossover study in moderate to severe COPD patients who received salbutamol/albuterol (200 µg), ipratropium (40 µg) or placebo using a pressurized metered dose inhaler (pMDI) followed immediately by nebulized RPL554 (6 mg) or placebo. RPL554 alone was as effective as standard of care bronchodilators, and importantly produced significant additive bronchodilation. Indeed, there was an approximately 60% additional increase in peak forced expired volume in 1 second (FEV_1) in COPD patients administered RPPL554 in addition to either salbutamol/albuterol or ipratropium (RPL554-009-2015 Clinical Study Report, 2017).
4. Study RPL554-PK-101 was a Phase I study of the oral bioavailability of RPL554 in healthy subjects. Subjects were randomized to RPL554 6 mg given with, or without, a charcoal block. The study demonstrated a low oral bioavailability of 10.6% and a terminal half-life of 11.9 hours (RPL554-PK-101 Clinical Study Report, 2017).
5. Study RPL554-CO-202 was a Phase II crossover study in patients with moderate to severe COPD who received tiotropium 18 µg once daily, plus RPL554 1.5 mg, RPL554 6 mg or placebo twice daily for 3 days. This study demonstrated a significant increase in peak FEV_1 (103 mL and 127 mL for RPL554 1.5 mg and 6 mg, respectively) as compared to tiotropium + placebo. There was also significant improvement in both trough FEV_1 and lung volumes, including residual volume (RV) and functional residual capacity (FRC). The time of onset of RPL554 + tiotropium was dramatically faster than with tiotropium alone (4.2 versus 37 minutes) (Clinical Study Report pending).
6. Study RPL554-CO-203 was a Phase II parallel group study in 403 patients with COPD who were administered either placebo or RPL554 at doses ranging from 0.75 mg to 6 mg over 4 weeks. Clinically and statistically significant improvements in peak FEV_1 compared to placebo were observed in all active dose groups at all time points. Secondary endpoints of average FEV_1, COPD symptoms and quality of life were also met (Clinical Study Report pending).
7. Study RPL554-010-2015 was a Phase II crossover study in adult patients with cystic fibrosis. Patients received a single dose of RPL554, 1.5 mg, 6 mg, or placebo. This study demonstrated a significant increase (6.6%) in peak FEV_1, as well as demonstrating pharmacokinetic levels that were similar to that seen in patients with COPD. RPL554 was well tolerated in these patients (Clinical Study Report pending).

RPL554 was well tolerated in all seven studies, with adverse event rates that were similar to the subjects treated with placebo.

All clinical studies with the solution formulation, and with the first three studies above for the suspension, are described in the Investigator's Brochure.

This study is intended to examine the dose ranging effect of RPL554 when dosed on top of the combination of a long acting anti-muscarinic receptor antagonist (tiotropium) and a long acting β2-agonist (olodaterol) whilst dosing the RPL554 to steady state blood levels.

1.2 Summary of Risks and Benefits

Data from non-clinical studies suggested a potential for hypotension and tachycardia. However, in the clinical studies to date RPL554 has been well tolerated in moderate to severe COPD patients, healthy subjects, asthmatics and allergic rhinitics. The most common adverse events that have been reported at least twice in subjects who have received single or multiple doses of the nebulized suspension of RPL554 were generally mild and in descending order of frequency are headache, cough, dizziness, and palpitations. Adverse events for single and multiple dose studies are summarized in Investigator's Brochure Section 6.3.

The suspension formulation of RPL554 is pH balanced, and has favorable non-clinical toxicology and pharmacokinetic data.

There has been no evidence of significant adverse events related to the cardiovascular or gastrointestinal systems, except associated with an increase in heart rate at high doses (12 mg to 24 mg). These small increases in heart rate may relate to the PDE3 inhibitory activity of the compound. In single dose studies there appears to be an increase in the rate of headache, which is most pronounced at doses over 6 mg. There was no other apparent dose related adverse events, with the exception of palpitations in patients dosed at 24 mg. In particular, Holter findings have indicated no arrhythmogenic potential in the completed studies. Results from multiple dose data in patients with COPD suggests a transient increase in dizziness, the majority of which occurred during spirometry or dosing; otherwise, the rate of adverse events was similar in RPL554 and placebo treated patients. There was an apparent increase in mild adverse events in healthy subjects treated with high doses of RPL554, which may be associated with the higher serum levels in healthy subjects than in those with obstructive lung disease.

As RPL554 is planned in this study to be administered for only 6 days (12 doses) over two treatment periods (placebo is administered in the third treatment period), any benefit to the patients will be restricted to the immediate short-term.

2 OBJECTIVES

2.1 Primary Objective

To investigate the bronchodilator effect on peak FEV_1 (measured in first 4 hours after dosing) of nebulized RPL554 dosed twice daily for 3 days, as compared to placebo, when administered in addition to once daily tiotropium/olodaterol. The peak FEV_1 is measured after the morning dose on Day 3.

2.2 Secondary Objectives

- To assess the bronchodilator effect on peak FEV_1 (measured in the first 4 hours after dosing) and average (measured as the AUC) FEV_1 over 12 hours of nebulized RPL554 after the first dose (on Day 1) as compared to placebo, when administered in addition to tiotropium/olodaterol
- To investigate the effect of twice daily nebulized doses of RPL554, as compared to placebo, when administered in addition to tiotropium/olodaterol on morning trough FEV_1 (mean of values 11 and 12 hours after last dose of RPL554) on Day 4
- To investigate the effect of twice daily nebulized doses of RPL554, as compared to placebo, when administered in addition to tiotropium/olodaterol on average (measured as AUC) FEV_1 over 4, 8 and 12 hours after morning dosing on Day 3
- To assess the bronchodilator effect on peak FEV_1 measured within 4 hours after the evening dosing of RPL554 on Day 3
- To analyze plasma concentrations and assess the steady state pharmacokinetics of RPL554 when administered in addition to tiotropium/olodaterol
- To assess the tolerability and safety of twice daily nebulized doses of RPL554 in addition to tiotropium/olodaterol
- To determine the onset of action of RPL554 when administered with tiotropium/olodaterol (after the first dose)
- To investigate the effects of RPL554 on specific airway conductance (sG_{aw}) and lung volumes (RV, FRC) when administered in addition to tiotropium/olodaterol

2.3 Exploratory Objectives

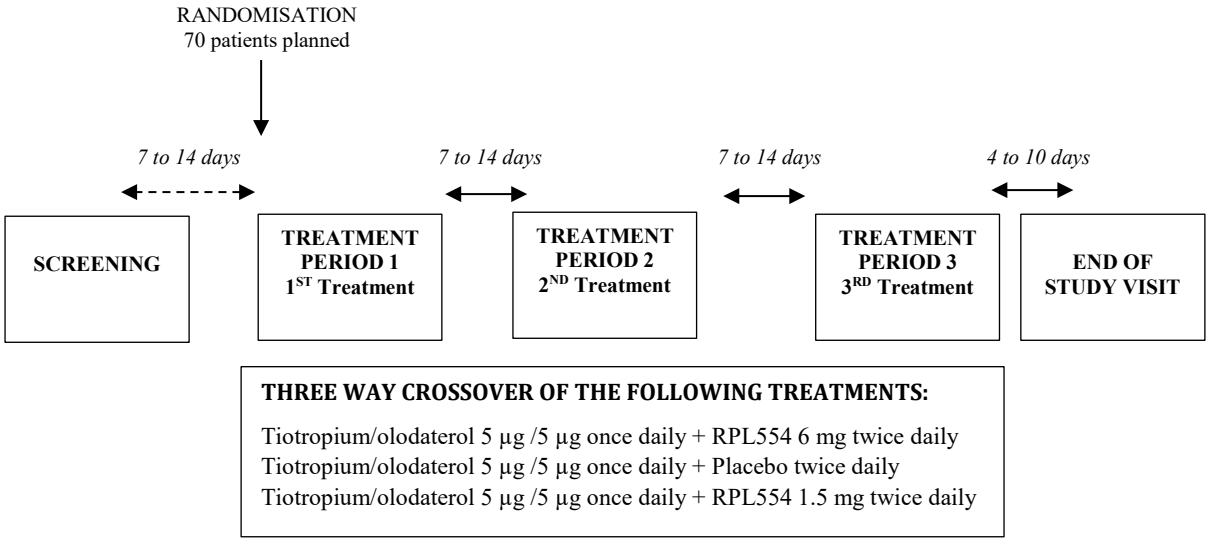
- To assess the dose response of RPL554 on peak and average (measured as AUC over 12 hours) after morning dose on Day 3, and morning trough FEV_1 (mean of values at 11 and 12 hours after last dose of RPL554) on Day 4, when dosed in addition to tiotropium/olodaterol
- To examine the effect of RPL554 on top of tiotropium/olodaterol on average (measured as AUC) FEV_1 over 24 hours after 3 days of dosing
- To examine the effect of RPL554 on top of tiotropium/olodaterol on a Likert dyspnea scale

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan Description

This is a Phase II, randomized, double blind, placebo controlled, complete block three-way crossover study to investigate treatment with nebulized RPL554 and tiotropium/olodaterol Respimat® in patients with moderate to severe COPD. It is planned to randomize approximately 70 patients at up to four study centers. The study comprises the following, as shown in Figure 1: Screening, three treatment periods each lasting 3 days and an end of study visit. The procedures performed at each visit are summarized in Section 6 and the study assessments are described in Section 7.

Figure 1 Study Flow Chart



Patients will be screened for eligibility, including a reversibility test with salbutamol (in UK) /albuterol (in US) and ipratropium between 7 and 14 days before the first dose of study treatment.

Eligible patients will then attend the clinic for three separate treatment periods (Treatment Periods 1 to 3), with each lasting 3 days and separated by a 7 to 14-day washout period (taken from last dose of study medication). Patients will be randomized pre-dose on Day 1 of Treatment Period 1. During each treatment period, patients will be present at the study center from the morning of Day 1 until the morning of Day 4.

In each treatment period, patients will receive an open label dose of tiotropium/olodaterol from a Respimat® device followed immediately (starting within 2 minutes) by a double-blind dose of either RPL554 or placebo (depending on treatment sequence) from a nebulizer in the morning on Day 1, Day 2 and Day 3. The dose of RPL554 or placebo will be repeated in the evening on Day 1, Day 2 and Day 3.

The assessments performed in each treatment period will be the same. Lung function (FEV_1 and forced vital capacity [FVC]) will be measured by spirometry pre-dose and up to 12 hours post-dose on Days 1 and 2 and up to 24 hours post-morning dose on Day 3 (i.e. Day 4). Whole body plethysmography will be performed pre-dose and 1.25 hours post-dose on Day 1, and pre-dose and 1.25, 8.25 and 12.25 hours post-dose on Day 3. Vital signs will be measured pre-dose and up to 12 hours post-dose on Day 1, up to 12 hours post-dose on Day 2 and up to 24 hours post-dose on Day 3 (i.e. Day 4). Electrocardiograms (ECG) assessments will be performed pre-dose and up to 4 hours post-dose on Day 1, at 2 hours post-dose on Day 2 and

up to 24 hours post-dose on Day 3 (i.e. Day 4). Adverse events and concomitant medications will be recorded throughout the study.

Patients will be discharged from the study center on the morning of Day 4, and after Treatment Period 3 will then attend an end of study visit between 4 and 10 days later.

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

The purpose of the study is to investigate if RPL554 has an additive bronchodilator effect when administered in combination with a commonly used anticholinergic/β-agonist combination medication, tiotropium/olodaterol, in this patient population.

A total of approximately 70 male or female COPD patients aged 40 to 80 years (inclusive) will be randomized. All patients will receive three combinations of study medication (1.5 mg RPL554, 6 mg RPL554 and placebo) in a randomized, crossover design; therefore, each patient will act as his or her own control in the study. This design makes it possible to obtain unbiased inferences about differences between treatments, based on intra-patient differences. Study medication will be administered double blind to minimize any potential bias in the overall assessment of treatment effect and safety.

The washout period between the three treatment periods has been selected based upon the available pharmacokinetics of RPL554 in healthy volunteers, and patients with asthma or COPD. Five half-lives is considered as the time for elimination of RPL554t from the body. In this study, a washout period of 7 to 14 days from the last dose of study medications has been deemed adequate to ensure there was no overlap between the pharmacokinetic profiles of treatments with RPL554 in consecutive treatment periods. Whilst tiotropium has a prolonged terminal half-life of 5 to 6 days, the clinical bronchodilator effects are gone before this timepoint. As such, and in the absence of measuring pharmacokinetic levels of tiotropium, this was felt to be an adequate washout between treatment periods.

Study treatment administration, pharmacodynamics, safety and tolerability assessments will be performed whilst patients are resident at the study center. This is to ensure standardized conditions for dosing and other study procedures. The pre-dose FEV_1 on Day 1 of both Treatment Period 2 and Treatment Period 3 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 is greater than 20% different then the start of the treatment period must be rescheduled.

3.3 Planned Duration of the Study

The approximate planned duration for each patient could be up to 61 days: 7 to 14 days screening, up to 9 days treatment (three treatment periods of 3 days each separated by 7 to 14 days) and an end of study visit 4 to 10 days after the last treatment visit (Day 4 of Treatment Period 3). 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 in the study.

4 SELECTION OF STUDY POPULATION

The population to be recruited into this study is stable patients with moderate to severe COPD and 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. If male: must agree to meet the following from the first dose up to 1 month after the last dose of study medication:
    - 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 ECG recording at Screening and pre-dose in Treatment Period 1 showing the following:
    - Heart rate between 45 and 90 beats per minute
    - 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, atrio-ventricular nodal dysfunction, ST segment abnormalities consistent with ischemia)
5. Have a Screening Holter report with a minimum of 18 hours recording that is able to be evaluated for rhythm analysis showing no abnormality which indicates a significant impairment of patient safety or which may significantly impair interpretation, including:
    - Significant arrhythmias including atrial flutter, atrial fibrillation, ventricular tachycardia
    - Any symptomatic arrhythmia (except isolated extra systoles)
    - Any sustained second or third-degree heart block
6. Capable of complying with all study restrictions and procedures including ability to use the study nebulizer and Respimat® correctly.
7. Body mass index (BMI) between 18 and 36 kg/m^2 (inclusive) with a minimum weight of 45 kg.
8. 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.

9. Post-bronchodilator (two puffs of salbutamol/albuterol followed by two puffs of ipratropium) spirometry at Screening:
    - Post-bronchodilator FEV_1/FVC ratio of ≤0.70
    - Post-bronchodilator FEV_1 ≥30 % and ≤70% of predicted normal
    - Demonstrates ≥150 mL increase from pre-bronchodilator FEV_1
10. Clinically stable COPD in the 4 weeks prior to Screening and Randomization (pre-dose in Treatment Period 1).
11. A chest X-ray (posterior-anterior) at Screening, or in the 12 months prior to Screening showing no abnormalities, which are both clinically significant and unrelated to COPD.
12. Meet the concomitant medication restrictions 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 8 hours prior to dosing.

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, in the 3 months prior to Screening or Randomization (pre-dose in Treatment Period 1).
3. A history of one or more hospitalizations for COPD in the 12 months prior to Screening or Randomization (pre-dose in Treatment Period 1).
4. Intolerance or hypersensitivity to tiotropium, olodaterol, ipratropium, or RPL554.
5. Evidence of cor pulmonale or clinically significant pulmonary hypertension.
6. Other respiratory disorders: Patients with a current diagnosis of asthma, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, interstitial lung diseases, sleep apnea, known alpha-1 antitrypsin deficiency or other active pulmonary diseases.
7. Previous lung resection or lung reduction surgery.
8. Use of oral COPD medications, except mucolytics, in the 3 months prior to Screening or Randomization.
9. Pulmonary rehabilitation, unless such treatment has been stable from 4 weeks prior to Screening and remains stable during the study.
10. History of, or reason to believe a patient has, drug or alcohol abuse within the past 5 years.
11. Inability to perform acceptable spirometry or whole body plethysmography (at Screening or pre-dose in Treatment Period 1).
12. Received an experimental drug within 30 days or five half-lives, whichever is longer.
13. Patients with uncontrolled disease including, but not limited to, endocrine, active hyperthyroidism, neurological, hepatic, gastrointestinal, renal, hematological, urological, immunological, psychiatric, or ophthalmic diseases that the Investigator believes are clinically significant. This includes any hepatic disease, or an alanine aminotransferase or aspartate aminotransferase>2 x ULN.

14. Documented cardiovascular disease: arrhythmias, angina, recent (<1 year) or suspected myocardial infarction, congestive heart failure, unstable or uncontrolled hypertension, or diagnosis of hypertension in the 3 months prior to Screening or Randomization.
15. Use of non-selective oral β-blockers.
16. Major surgery (requiring general anesthesia) in the 6 weeks prior to Screening or Randomization (pre-dose in Treatment Period 1), or will not have fully recovered from surgery, or planned surgery through the end of the study.
17. A disclosed history or one known to the Investigator, of significant non-compliance in previous investigational studies or with prescribed medications.
18. Required use of oxygen therapy, even on an occasional basis.
19. Symptomatic prostatic hyperplasia or bladder-neck obstruction or with narrow-angle glaucoma.
20. History of malignancy of any organ system within 5 years, with the exception of localized skin cancers (basal or squamous cell).
21. Clinically significant abnormal values for safety laboratory tests (hematology, biochemistry, virology or urinalysis) at Screening, as determined by the Investigator (see Section 7.1.4).
22. 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 jeopardizing 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 treatment, 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 Randomization, every attempt should be made to contact the patient to determine the reason for withdrawal and to complete the recording of any available efficacy 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 Conference 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 ethics committee 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 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 ethics committee 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 ethics committees are notified.

4.3.4 Replacement Policy

It is planned to have 70 evaluable patients (i.e., completing at least two treatment periods). Withdrawn patients may need to be replaced to meet this target.

5 STUDY TREATMENTS

5.1 Study Treatments Administered

Patients will receive the three treatment combinations shown in Table 1 in a randomized sequence during Treatment Periods 1 to 3. All study treatments will be administered using the inhaled route. In each case, the Respimat® medication will be administered first, followed immediately (within 2 minutes) by the study medication (RPL554 or placebo). The Respimat® medication will be open label and the study medication will be double blind.

Table 1 Treatment Combinations in RPL554-CO-204

Treatment Combination	Respimat® Medication	Study Medication
1	Tiotropium/olodaterol 5 µg /5 µg qd	RPL554 6 mg bid
2	Tiotropium/olodaterol 5 µg /5 µg qd	Placebo bid
3	Tiotropium/olodaterol 5 µg /5 µg qd	RPL554 1.5 mg bid
Abbreviation: bid=twice daily; qd=once daily		

5.2 Identity of Study Treatments

5.2.1 RPL554 and Placebo

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 composition of the nebulized RPL554 and placebo formulations is shown in Table 2.

Table 2 Composition of Nebulized RPL554 and Placebo Formulations

Constituent	Concentration (mg/mL)
RPL554 (micronized)	0 (=placebo), 0.6 or 2.4
Polysorbate 20 (Tween 20)	0.5
Sorbitan Monolaurate (Span 20)	0.05
Monosodium Phosphate Dihydrate	7.44
Disodium Phosphate Dihydrate	8.53
Sodium Chloride	4.80
Water	N/A

RPL554 and placebo are manufactured using aseptic manufacturing techniques in accordance with Good Manufacturing Practice (GMP) guidelines.

RPL554 is supplied as a sterile, micronized suspension in pH 7 phosphate buffered saline with surfactants to aid suspension. Two concentrations of RPL554 (0.6 mg/mL and 2.4 mg/mL) and a placebo will be provided as a nominal 2.5 mL fill in amber glass vials sealed with an ethylene tetrafluoroethylene coated rubber stopper and flip tear-up cap. The placebo is the same as the RPL554 suspension except that the active RPL554 ingredient is omitted.

5.2.2 Tiotropium/olodaterol Respimat®

Tiotropium/olodaterol (Stiolto® in US, Spiolto® in UK) Respimat® (Boehringer Ingelheim International GmbH; Anatomic Therapeutic Chemical Code R03BB04) is a marketed

anticholinergic and β_2-agonist combination for the treatment of COPD (see Section 14.2). This medication will be provided by the study center.

5.3 Preparation and Labelling

5.3.1 Nebulized RPL554 and Placebo

Vials of RPL554 and placebo will be packed as patient kits, one kit per period, each containing six vials, and labelled in compliance with GMP, released by a qualified person, where appropriate, and then shipped to the study center.

RPL554 and placebo are a unit dose 2.5 mL volume and will be prepared (poured into a nebulizer cup) by an unblinded individual who will not disclose the nature (appearance) of study treatment to the blinded Investigator and study center staff. The dose will be poured into a nebulizer cup, with is covered with tape to mask the color of the content.

5.3.2 Tiotropium/olodaterol

Each tiotropium/olodaterol Respimat® will be labelled by the site with the randomization number and in accordance with local regulations.

5.4 Selection of Doses, Dosing Schedule and Route of Administration

5.4.1 Selection of Doses in the Study

The dose of tiotropium/olodaterol, 5 µg /5 µg once daily (administered as two inhalations of 2.5 µg /2.5 µg each), is the approved dose for this medication.

The doses of RPL554 have been selected based on the results from prior studies investigating single and multiple ascending doses in healthy subjects, single doses in asthmatics, single/multiple ascending doses in COPD patients, and 3 days of dosing in COPD patients. These doses were demonstrated to be both effective as a bronchodilator and well tolerated.

5.4.2 Selection and Timing of Dose for each Patient

The first dose of each treatment period (Day 1) should be given at approximately the same time of day (±1 hour). All subsequent doses should be given at 12-hour intervals (±30 minutes) relative to the Day 1 first dose. The first dose should be given between 7 and 11 am.

For each morning dose, the tiotropium/olodaterol will be given first, followed immediately (starting within 2 minutes) by nebulized RPL554 or placebo. The evening dose (RPL554 or placebo only) is given 12 hours (±30 minutes) after the morning dose.

5.4.2.1 Nebulized RPL554 and Placebo

RPL554 and placebo will be administered by inhalation of an aerosol generated by a reusable PARI LC Sprint® jet nebulizer, with an exhalation filter, attached to a compressor (PARI TurboBOY® SX in the UK or a PARI VIOS Pro® in the US). Wherever possible, the same compressor unit should be used for each dose for a given a patient.

The dosing cup on each nebulizer will be obscured with opaque tape by study center personnel to visually blind the study medication.

The end time of nebulization (sputtering) will be considered Time 0 for the purposes of scheduling all post-dose study procedures. Nebulization time should be approximately 5 minutes and may not exceed 10 minutes. Patients must wear a protective gown on Day 3

during the dosing procedure to prevent contamination of the cannula for pharmacokinetic samples. Patients should be dosed in a well-ventilated environment, and away from other patients.

The following must be recorded in the eCRF:

- Compressor unit number
- Start and end times of nebulization (times will be rounded down to the nearest minute)
- The volume of residual product at the end of nebulization

5.4.2.2 Tiotropium/olodaterol Respimat®

Prior to use of the Respimat®, patients will be instructed in the proper use of the device, including the requirement to inhale slowly through their mouth (see instructions in Section 14.2). They will be instructed to hold their breath for 10 seconds, or as long as comfortable. A second inhalation is required to get the entire dose. The time of dosing will be recorded in the eCRF. The tiotropium/olodaterol is administered as two inhalations.

5.4.3 Route of Administration

All study treatments will be dosed via inhalation. RPL554 is administered as a nebulized suspension. Tiotropium/olodaterol uses the Respimat® Soft Mist™ inhaler.

5.5 Storage

RPL554 and placebo should be stored below 25°C (77°F) and should not be frozen. The expiry date will be indicated on the carton label.

Tiotropium/olodaterol Respimat® should be at room temperature, 20°C to25°C (68°F to 77°F) (see Section 14.2).

Temperature logs should be maintained in areas where study treatment is stored. If temperature conditions have been seriously compromised or any study treatment has not been stored appropriately, this should be documented, and the study treatment quarantined until the Sponsor has been notified and confirmed whether it may be used.

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

5.6 Accountability

The Investigator will be responsible for the dispensing, inventory and accountability of study treatment, exercising accepted medical and pharmaceutical practices and ensuring that an accurate, timely record of the disposition is maintained. The study treatment supplies and inventory must be available for inspection by the designated representatives of the Sponsor upon request.

Upon receipt of the study medication (RPL554 and placebo), 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 center to their final removal from the center.

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 authorization has been provided by the Sponsor.

5.7 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 center number and YYY is the patient number (001, 002, etc.).

Patients will receive three different treatment combinations in the study (See Section 5.1). Patients will be equally randomized to one of six treatment sequences (using a Latin Square design with the three different potential treatment combinations) before the first study treatment administration in Treatment Period 1.

5.8 Blinding

Tiotropium/olodaterol will be used in trade dress and will not be blinded.

RPL554 and placebo will be administered double blind. The placebo is the same as the active medication (RPL554) except for the omission of the active ingredient. Because a visually matching placebo could not be developed, the dosing cup on each nebulizer administered at the study center will be obscured with opaque tape to visually blind the study medication.

The study personnel pouring the RPL554 and placebo into the nebulizer will therefore not be blinded to the study medication identity. This individual needs to be separate from other study center staff participating in the study, and may not reveal the appearance of the nebulizer contents to the patient or the blinded study staff. To ensure proper blinding, the Sponsor, Investigator (defined as Principal Investigator and all study physicians), all patients and all other research personnel (except bioanalytical personnel performing the pharmacokinetic assays and the unblinded study staff) will therefore be blinded to the treatment allocation.

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 investigational product 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 site and must be kept in a secure access area.

5.9 Prior and Concomitant Therapies and Medications

5.9.1 Prior and Concomitant COPD Medications

All prior therapies for COPD taken in the 3 months prior to the first study treatment 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.

The following therapies are restricted or prohibited during the study as indicated:

- Oral therapies for COPD (e.g. oral steroids, theophylline, and roflumilast) are not allowed in the 3 months prior to Screening and throughout the study. Inhaled steroids may continue during the study at a maintenance dose
- Terbutaline is not allowed beginning the day prior to Screening
- 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 #9
- 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
- All long acting (once or twice daily) bronchodilators (long acting muscarinic antagonists [LAMA], long acting β_2-agonists [LABA], or combinations with an inhaled steroid) are to be discontinued prior to the Screening visit and are not allowed during the study. The withhold period prior to Screening is as follows:
  - Once daily bronchodilators – at least 48 hours prior
  - Twice daily bronchodilators – at least 24 hours prior
- Patients taking LAMAs and LABAs should be placed on short acting bronchodilators (e.g. salbutamol/albuterol, ipratropium or Combivent®) as per the discretion of the Investigator. These can be dosed on a regularly scheduled basis or as needed.
- Patients taking inhaled corticosteroids may continue their medication only if the dose is stable from at least 4 weeks prior to Screening and is expected to remain stable.
- Patients taking LABA/inhaled steroid combination products should be prescribed the inhaled steroid at the same or equivalent dose contained in the combination product to allow continuation of steroid use regularly throughout the study whilst stopping the LABA component. Inhaled steroid medication should be procured via prescription for patients requiring its use; it will not be supplied by the Sponsor.
- No scheduled use of salbutamol/albuterol or ipratropium is allowed during the 3-day treatment periods; but may be used as a rescue medication (see Section 5.10). Salbutamol/albuterol and ipratropium (or Combivent®) must be withheld for at least 8 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:
  - 8 hours prior to pre-reversibility spirometry for Screening
  - 8 hours prior to pre-dose spirometry for Day 1, Day 2 and Day 3
  - Post dose:
    - Day 1 until after +12 hours spirometry
    - Day 2 until after + 12 hours spirometry
    - Day 3 until after + 24 hours spirometry (Day 4 morning)

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

5.9.2 Other (non-COPD) Prior and Concomitant Medications

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

All concomitant medications must also be documented on the eCRF.

5.10 Rescue Medications

Short acting bronchodilators may be used as rescue medication. Rescue medication will be sourced by the study center and dispensed at the Screening visit. Rescue medication use during each treatment period must be separately documented on the eCRF (medication, dose, route, date and time of each administration). Protocol procedures must still continue even if rescue medication has been taken. Salbutamol/albuterol is to be used for primary rescue use.

5.11 Treatment Compliance

Study treatment administration will take place at the study center and will be administered by the Investigator or designated and trained study center personnel. The precise date and time of administrations shall 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 treatment administration. Screening procedures may be performed as a single visit or more than one visit. Since the Holter monitor is to be removed after 24 hours, patients will return one day after placement.
- Three treatment periods, each 3 days in duration and separated by 7 to 14 days (from last dose of study medication on Day 3 of each treatment period)
- An end of study visit between 4 and 10 days after the completion of Treatment Period 3

Eligible patients may be re-screened at the discretion of the Investigator.

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

The overall schedule of assessments at each visit is shown in Table 3 and the schedule of assessments on each day of each treatment period is shown in Table 4. Assessments are listed by visit in Section 1.1 to Section 6.4 and are described in Section 7.

Post-dose assessments should be performed in the following order: 1) ECG, 2) vital signs, 3) pharmacokinetic blood sample, 4) spirometry (prioritized on the timepoint).

Table 3 Overall Schedule of Assessments at Each Visit in RPL554-CO-204

Procedures	Screening	Treatment Periods 1 to 3 (7 to 14 days between Treatment Periods)				End of Study
	14 to 7 days before Randomization	Day 1	Day 2	Day 3	Day 4	4 – 10 days after Day 4 of Treatment Period 3
Informed consent	X					
Demographics including height and weight	X					
Medical/surgical and disease history	X					
Eligibility criteria	X	X[a]				
Physical examination	X (Full)	X (Brief)			X (Brief)	X (Full)
Vital signs	X	X	X	X	X	X
Safety laboratory tests: hematology and biochemistry	X				X	X
Safety laboratory tests: urinalysis	X					X
Viral serology	X					
Alcohol breath test	X					
Serum pregnancy test (females of childbearing potential)	X					
Urine pregnancy test (females of childbearing potential)	X	X				X
Chest X-ray (or in last 12 months)	X					
12-lead ECG	X	X	X	X	X	X
24-hour Holter monitoring	X			X		
Spirometry: Reversibility test	X					
Spirometry: Study measurements		X	X	X	X	X
Whole body plethysmography training	X					
Whole body plethysmography		X		X		
Inhalation training (nebulizer and Respimat®)	X	X				
Randomization		X[a]				
Tiotropium/olodaterol and RPL554 or placebo dosing		X	X	X		
Pharmacokinetic sampling				X		
Dyspnea scale		X		X	X	
Prior/concomitant medications and therapies	Throughout the study					
Adverse events	Throughout the study					

Abbreviations: ECG=electrocardiogram
[a] Treatment Period 1 only

Table 4 Pre-dose and Post-dose Assessments on Each Day of Treatment Periods 1 to 3 in RPL554-CO-204

Procedures	**Day 1**												
	Pre-dose	**0**	**5m**	**15m**	**30m**	**1h**	**1.25h**	**1.5h**	**2h**	**4h**	**6h**	**8h**	**12h**[a]
Tiotropium/olodaterol dosing by Respimat®		X											
RPL554 or placebo dosing by nebulization		X											X
Brief physical examination	X												
Vital signs	X				X	X			X	X	X	X	X
12-lead ECG	X								X	X			
Spirometry	X[c]		X	X	X	X		X	X	X	X	X	X
Inhalation training	X												
Whole body plethysmography	X						X						
Randomization [b]	X												
Urine pregnancy test (females of childbearing potential)	X												
Dyspnea scale	X		X	X	X								
Adverse events		Throughout											

Abbreviations: ECG=electrocardiogram; h=hours (post-dose); m=minutes (post-dose)

[a] Post-dose measurements will be taken in relation to the morning dose of tiotropium/olodaterol and RPL554 or placebo. The 12-hour procedures will therefore be performed pre-dose before the evening dose of RPL554 or placebo

[b] Treatment Period 1 only

[c] Performed at 1 hour and immediately pre-dose

NOTE: Table 4 (Days 2 through 4) continues on next two pages.

Procedures	**Day 2**									
	Pre-	**0**	**15m**	**30m**	**1h**	**1.25h**	**2h**	**3h**	**4h**	**12h**[a]
Tiotropium/olodaterol dosing by Respimat®		X								
RPL554 or placebo dosing by nebulization		X								X
Vital signs	X			X	X		X	X	X	X
12-lead ECG	X						X			
Spirometry	X		X	X	X		X	X	X	X
Adverse events	Throughout									

Abbreviations: ECG=electrocardiogram; h=hour; m=minutes

[a] Post-dose samples will be taken in relation to the morning dose of tiotropium/olodaterol and RPL554 or placebo. The 12-hour procedures will therefore be performed pre-dose before the evening dose of RPL554 or placebo.

Procedures	**Day 3**																			**Day 4** [a]
	Pre-	**0**	**5 m**	**15m**	**30m**	**45m**	**1h**	**1.25h**	**1.5h**	**2h**	**4h**	**6h**	**8h**	**8.25h**	**12h**	**12.25h**	**13 h**	**14h**	**16 h**	**23 h**	**24 h**
Tiotropium/olodaterol dosing by Respimat®		X																			
RPL554 or placebo dosing by nebulization		X													X						
Brief physical examination																					X[b]
Vital signs	X				X		X			X	X	X	X								X
12-lead ECG	X									X											X
24-hour Holter monitor placed	X																				
Spirometry	X		X	X	X		X		X	X	X	X	X		X		X	X	X	X	X
Whole body plethysmography	X							X						X		X					
Pharmacokinetic samples	X		X		X	X	X		X	X	X		X		X[c]						
Hematology and biochemistry																					X
Dyspnea scale	X		X	X	X																X
Adverse events	Throughout																				

Abbreviations: ECG=electrocardiogram; h=hour; m=minutes

[a] Procedures performed prior to discharge from the study center on the morning of Day 4, 12 hours after final RPL554 dosing on Day 3
[b] Can be performed any time prior to discharge
[c] Perform pharmacokinetic sample prior to dosing

6.1 Pre-visit Restrictions

The following restrictions in relation to dosing should be adhered to:

- Patients should refrain, where possible, from xanthine (chocolate, caffeine containing drinks and food), for at least 24 hours before and during all visits. Decaffeinated beverages are permitted
- Patients should refrain from alcohol for 24 hours before and during all 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
- Patients should refrain from smoking from 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 all study 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 5.9). 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 treatment. There are no fasting requirements for the Screening visit. Patients must observe the medication restrictions described in Section 5.9.1, and other restrictions described in Section 1.1To 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
- Vital signs
- Full physical examination (see Section 7.4.5)
- Alcohol breath test
- 12-lead ECG
- Chest X-ray (unless historical X-ray performed in last 12 months is available)
- Whole body plethysmography training and assessment of capacity to perform procedure (may be performed more than once as required)
- Pre-reversibility spirometry
- Reversibility test (two puffs salbutamol/albuterol followed by two puffs ipratropium)
- Post-reversibility spirometry (20 to 30 minutes after administration)
- Place 24-hour Holter monitor; patients will be instructed to return the next day for removal of the Holter monitor

- Blood and urine samples for laboratory safety tests (hematology, biochemistry, urinalysis), pregnancy tests (female patients of childbearing potential only), and viral serology. The urine pregnancy test result should be obtained prior to chest X-ray for females of childbearing potential.
- Instruct patients to stop all long acting bronchodilators for the duration of the study
- Inhalation training for use of nebulizer and Respimat®. This will be verbal instruction and demonstration of the device
- Questioning for adverse events

If the patient meets all of the Inclusion and none of the Exclusion Criteria, he/she will be instructed to return in 7 to 14 days for Treatment Period 1, Day 1.

6.3 Treatment Periods 1 through 3

Each treatment period is approximately 72 hours in duration. Patients will stay at the study center for the duration of each treatment period.

Patients must withhold long acting bronchodilators, ipratropium and salbutamol/albuterol (or Combivent®) prior to the start of the treatment period as defined in Section 5.9.1. If not, the start of the treatment period must be rescheduled so as to occur within the permitted windows. All restrictions defined in Section 1.1 should also be adhered to.

At the start of Treatment Period 1, patients will be evaluated to ascertain if the Inclusion and Exclusion Criteria are still met. If so, patients will receive a randomization number.

6.3.1 Day 1

6.3.1.1 Pre-Dose Assessments

The following assessments will be performed prior to dosing:

- Confirm that respiratory medications were withheld as required
- Questioning for adverse events
- Urine pregnancy test (females of childbearing potential only)
- 12-lead ECG
- Dyspnea scale
- Vital signs
- Brief physical examination (see Section 7.4.5)
- Spirometry; 1 hour (±5 minutes) and immediately prior to study treatment administration
- Whole body plethysmography
- Inhalation training

6.3.1.2 Study Treatment Administration

Patients will be dosed with open label tiotropium/olodaterol 5/5 µg (two inhalations, each containing 2.5 µg /2.5 µg), followed immediately (within 2 minutes) with either blinded RPL554 or placebo using a nebulizer according to randomization scheme. At 12 hours (±30 minutes) after the morning dose, the second dose of RPL554 or placebo will be administered by nebulization.

6.3.1.3 Post-Dose Assessments (after morning doses only)

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

- Spirometry at 5 (±1) minutes, 15 (±5) minutes, 30 minutes and 1, 1.5, 2, 4, 6, 8 and 12 hours (the latter assessments all ±10 minutes)
- Whole body plethysmography at 1.25 hours (±10 minutes)
- Vital signs at 30 minutes and 1, 2, 4, 6, 8 and 12 hours (±10 minutes)
- 12-lead ECGs at 2 and 4 hours (±10 minutes)
- Dyspnea scale administered at 5 (±1), 15 (±5), and 30 (±10) minutes
- Questioning for adverse events

6.3.2 Day 2

6.3.2.1 Pre-Dose Assessments

The following assessments will be performed prior to dosing:

- Questioning for adverse events
- 12-lead ECG
- Vital signs
- Spirometry

6.3.2.2 Study Treatment Administration

Patients will be dosed with open label tiotropium/olodaterol 5 µg /5 µg (two inhalations, each containing 2.5 µg /2.5 µg) followed immediately (within 2 minutes) with either blinded RPL554 or placebo using a nebulizer according to the randomization scheme. At 12 hours (±30 minutes) after the morning dose, the second dose of RPL554 or placebo will be administered by nebulization.

6.3.2.3 Post-Dose Assessments (after morning dose only)

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

- 12-lead ECGs at 2 hours (±10 minutes)
- Vital signs at 30 minutes and 1, 2, 3, 4, 8 and 12 hours (±10 minutes)
- Spirometry at 15 (±5) and 30 minutes and 1, 2, 3, 4 and 12 hours (the latter assessments all ±10 minutes)
- Questioning for adverse events

6.3.3 Days 3 to 4

6.3.3.1 Pre-Dose Assessments

The following assessments will be performed prior to dosing:

- Questioning for adverse events
- 12-lead ECG
- Vital signs

- Spirometry
- Whole body plethysmography
- 24-hour Holter monitor placed
- Dyspnea scale
- Blood sample for pharmacokinetics

6.3.3.2 Study Treatment Administration

Patients will be dosed with open label tiotropium/olodaterol 5 µg /5 µg (two inhalations, each containing 2.5 µg /2.5 µg) followed immediately (within 2 minutes) with either blinded RPL554 or placebo using a nebulizer according to the randomization scheme. At 12 hours (±30 minutes) after the morning dose, the second dose of RPL554 or placebo will be administered by nebulization.

6.3.3.3 Post-Dose Assessments

- 12-lead ECGs at 2 and 24 hours (±10 minutes)
- Vital signs at 30 minutes and 1, 2, 4, 6, 8 and 24 hours (±10 minutes)
- Spirometry at 5 (±1), 15 (±5) and 30 minutes and 1, 1.5, 2, 4, 6, 8, 12, 13, 14, 16, 23 and 24 hours after the morning dose (the latter assessments all ±10 minutes)
- Whole body plethysmography at 1.25, 8.25 and 12.25 hours (±10 minutes)
- Dyspnea scale at 5 (±1), 15 (±5), and 30 (±10) minutes and 24 hours (±10 minutes)
- Questioning for adverse events
- Blood samples for pharmacokinetics at 5 (±1), 30 and 45 minutes and 1, 1.5, 2, 4, 8 and 12 hours (the latter assessments all ±10 minutes)
- Blood sample for laboratory safety tests (hematology and biochemistry) at 24 hours (±10 minutes)
- Brief physical examination prior to discharge (Day 4)

The 24-hour assessments will be performed in the morning on Day 4 prior to discharge from the study center.

Patients will be instructed to return in 7 to 14 days (taken from last dose of study medication on Day 3) for the next visit, or if Treatment Period 3, to return in 4 to 10 days (from Day 4) for the end of study visit. Early terminated patients should have an End of Study Visit.

6.4 End of Study Visit

The following will be performed:

- Full physical examination
- Vital signs
- Spirometry
- Blood and urine samples for laboratory safety tests (hematology, biochemistry, urinalysis)
- Urine pregnancy test (females of childbearing potential)
- 12-lead ECG
- Questioning for adverse events

7 STUDY METHODOLOGY

7.1 Demographics, Baseline Characteristics and Eligibility Assessments

Safety assessments (laboratory safety assessments, vital signs, 12-lead ECG and physical examination) will be performed at Screening as part of the eligibility assessment as described in Section 7.1.1 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/albuterol will be assessed at Screening as an eligibility measure. Spirometry (FEV_1 and FVC) assessment before and after two puffs (200 µg) of salbutamol/albuterol and two puffs (40 µg) of ipratropium, each 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 ≥30 % and ≤70% 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

At Screening, blood samples will be taken and tested at the laboratory for human immunodeficiency virus, hepatitis B and hepatitis C serology. Note: 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.

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

An alcohol breath test will be performed by the study center at Screening.

Unscheduled and/or repeat testing may be performed at the discretion of the Investigator.

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 5.9.1.

Other prior medications will be separately recorded at Screening and concomitant use during the study recorded as described in Section 5.9.2.

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 Treatment Period 1.

7.2 Efficacy/Pharmacodynamic Assessments

7.2.1 Pulmonary Function Tests

Spirometry (FEV_1 and FVC) will be performed at Screening, the end of study visit and the following time points in each treatment period:

- Day 1: 1 hour and immediately pre-dose; 5, 15 and 30 minutes and 1, 1.5, 2, 4, 6, 8 and 12 hours post-dose
- Day 2: pre-dose; 15 and 30 minutes and 1, 2, 3 4 hours and 12 hours post-dose
- Day 3: pre-dose; 5, 15 and 30 minutes and 1, 1.5, 2, 4, 6, 8, 12, 13, 14, 16, 23 and 24 hours post-dose.

Post-dose measurements will be taken in relation to the morning dose of tiotropium/olodaterol and RPL554 or placebo. The 12-hour measurement will therefore be taken pre-dose before the evening dose of RPL554 or placebo. The 24-hour measurement on Day 3 will be taken in the morning on Day 4 prior to discharge from the study center.

Spirometry assessments will be made in accordance with ATS/ERS guidelines (Miller et al, 2005). At all timepoints, three technically acceptable measurements should 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.

7.2.2 Whole Body Plethysmography

Whole body plethysmography training and assessment for ability to perform the procedure will be conducted at Screening.

Whole body plethysmography will be performed pre-dose and 1.25 hours post-dose on Day 1, and pre-dose and 1.25, 8.25 and 12.25 hours post-dose on Day 3 of each treatment period. Assessments will be made in accordance with ATS/ERS guidelines, including the use of appropriate quality control measures to minimize data variability and error (Wanger et al, 2005; see Quality Control section for plethysmography on pp. 514-515).

Patients will be placed on a body box for plethysmographic determination of lung volumes, to include RV and FRC. Additionally, measurements will be made of sG_{aw}.

7.2.3 Dyspnea Scale

An 11-point Likert scale will be utilized, which will be anchored from 0: “no shortness of breath” to 10: “the worst shortness of breath that you can imagine” (Davis et al., 2006). This

scale will be an instantaneous measurement of their dyspnea at that moment, and not reflective. It will be administered on Day 1 pre-dose and 5, 15, and 30 minutes post-dose; and on Day 3 pre-dose and 5, 15, 30 minutes and 24 hours post-dose.

7.3 Pharmacokinetic Assessments

Pharmacokinetic analysis will be performed on samples taken from patients on Day 3 of each treatment period. Blood samples (4 mL at each time point) will be collected at the following timepoints: pre-dose, 5, 30 and 45 minutes and 1, 1.5, 2, 4, 8, and 12 hours post-dose.

Samples will be collected by venipuncture 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 hospitalization, 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 hospitalization or prolongation of existing hospitalization
- 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 hospitalization may be considered a SAE when, based on appropriate medical judgement, they may jeopardize 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

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 14.3.

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, hospitalization, 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 drug must also be reported

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

SAEs will be reported to the ethics committee(s)/institutional review board(s) and regulatory authority(is) 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

All female patients of childbearing potential will have a serum pregnancy test at Screening. Samples will be taken and handled according to the laboratory manual and analyzed at an approved central laboratory.

Urine pregnancy tests will also be performed by the study center at Screening (confirmed to be negative prior to the chest X-ray), on Day 1 of each treatment period and at the end of study visit.

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 Safety Assessments

In addition to the laboratory tests detailed in Section 7.4.3.1 to Section 7.4.3.3, 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 by manually annotating a print out of the results.

Samples will be taken and handled according to the laboratory manual and analyzed at an approved central laboratory.

7.4.3.1 Hematology

The following will be measured at Screening, on Day 4 of each treatment period and at the end of study visit: Hemoglobin, hematocrit, total white cell count, leukocyte differential count and platelet count.

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

7.4.3.2 Biochemistry

The following will be measured at Screening, on Day 4 of each treatment period and at the end of study visit: creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine transaminase, gamma-GT, lactate dehydrogenase, creatine kinase, thyroid stimulating hormone, triiodothyronine and thyroxine, glucose, potassium, sodium and calcium. Additionally, follicle-stimulating hormone (FSH) will be measured at Screening, where appropriate, to confirm post-menopausal status.

At each timepoint, 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 at Screening and at the end of study visit. The following will be tested: leucocytes, blood, ketones, bilirubin, urobilinogen, protein and glucose.

If urinalysis on Dipstick is positive for leucocytes and/or blood/hemoglobin, a microscopic examination including erythrocytes, leucocytes, bacteria, casts, epithelial cells and crystals will be performed.

7.4.4 Vital Signs

Blood pressure and pulse rate will be measured at Screening, the end of study visit and the following time points in each treatment period:

- Day 1: pre-dose; 30 minutes and 1, 2, 4, 6, 8 and 12 hours post-dose
- Day 2: pre-dose; 30 minutes and 1, 2, 3, 4 and 12 hours post-dose
- Day 3; pre-dose; 30 minutes and 1, 2, 4, 6, 8 and 24 hours post-dose

Post-dose measurements will be taken in relation to the morning dose of tiotropium/olodaterol and RPL554 or placebo. The 12-hour measurement will therefore be taken pre-dose before the evening dose of RPL554 or placebo. The 24-hour measurement on Day 3 will be taken in the morning on Day 4 prior to discharge from the study center.

At each timepoint, supine vital signs will be assessed whilst 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 on Day 1 and prior to discharge from the study center on Day 4.

7.4.6 12-Lead ECG

12-lead ECGs will be performed at Screening, the end of study visit and the following time points in each treatment period:

- Day 1: pre-dose and 2 and 4 hours post-dose
- Day 2: pre-dose and 2 hours post-dose
- Day 3: pre-dose and 2 and 24 hours post-morning dose

Post-dose measurements will be taken in relation to the morning dose of tiotropium/olodaterol and RPL554 or placebo. The 24-hour measurement at the end of each treatment period will be taken in the morning on Day 4 prior to discharge from the study center.

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.

Each 12-lead ECG recording will be sent to a central vendor for interpretation.

7.4.7 Holter Monitoring

12-lead Holter monitors will be used to perform 24-hour Holter monitoring. A Holter monitor will be placed at Screening. Monitoring will be ambulatory and will be recorded as an outpatient and the monitor will be removed at the study center after 24 hours. The Screening Holter report must have a minimum of 18 hours recording that is evaluable for rhythm analysis and the report must be reviewed to assess Inclusion criteria prior to Randomization.

A Holter monitor will also be placed at least 30 minutes pre-dose on Day 3 of each treatment period and removed on Day 4.

Holter readings will be sent to a central vendor for interpretation.

8 QUALITY ASSURANCE AND QUALITY CONTROL

The study will be conducted in accordance with the current approved protocol, standard operating procedures (SOPs) 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 ethics committee, 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 customized 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, Holter, 12-lead ECG and pharmacokinetic data) will be transferred electronically into the study database. Discrepancies will be queried to the site and/or the laboratory until the electronic data and the database are reconciled.

All updates to queried data will be made by authorized study center 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 authorize 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.

Adverse events will be coded from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA) ([specify version] or later). 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 first patient is enrolled 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 Analyzed

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.

The full analysis set will consist of all randomized patients with sufficient data collected after intake of study treatment to compute the pharmacodynamic parameters on at least two treatment periods. A completer analysis set will consist of all randomized patients that complete all treatment periods.

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

The pharmacokinetic data set will consist of all randomized patients with blood sampling performed after at least one dose of RPL544 and with data sufficient to calculate pharmacokinetic parameters.

9.3 Study Endpoints

9.3.1 Primary Endpoint

The primary endpoint is peak FEV_1 (measured in first 4 hours after morning dosing). This will be measured after dosing on Day 3.

The primary comparisons are RPL554 6mg + tiotropium/olodaterol vs RPL554 placebo + tiotropium/olodaterol, followed by RPL554 1.5 mg + tiotropium/olodaterol vs RPL554 placebo + tiotropium/olodaterol.

9.3.2 Secondary Endpoints

- Change from baseline in trough FEV_1 on Day 4 (mean of -1 and 0 time prior to dosing)
- Determination of $AUC_{0\text{-}4h}$ FEV_1 after morning dosing on Day 3
- Peak FEV_1 (measured in first 4 hours after dosing) and $AUC_{0\text{-}12h}$ FEV_1. These will be measured after dosing on Day 1
- Change from baseline in $AUC_{0\text{-}12h}$ FEV_1 measured on Day 3
- Change from pre-evening dose FEV_1 on Day 3 (peak over 4 hours)
- Determination of onset of action (>10% increase in FEV_1, from pre-first dose, censored at 120 minutes) on Day 1
- RV, FRC and sG_{aw} at 1.25 hours on Day 1 and 1.25, 8.25 and 12.25 hours after dosing on Day 3
- RPL554 steady state pharmacokinetics (AUC, C_{max}, time to maximum concentration [t_{max}])

- Safety and tolerability:
  - Continuous monitoring of adverse events
  - Laboratory safety tests [hematology, biochemistry and urinalysis]
  - 12-lead ECG (including QTcF and heart rate), supine vital signs [blood pressure and pulse rate]
  - Peak (measured in first 4 hours after dosing) and AUC_{0-4h} pulse rate for each treatment period.
  - Holter monitor results

9.3.3 Exploratory Endpoints

- AUC_{0-24h} FEV_1 on Day 3
- Change from baseline in Likert dyspnea scale

9.4 Statistical Methods

In general, unless stated otherwise, continuous variables will be summarized 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, randomized, completed or withdrawn (with reason for withdrawal) will be summarized.

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 liters 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) will be listed and summarized appropriately.

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

9.4.4 Extent of Exposure and Treatment Compliance

All administration of study treatment will be done at the clinic under supervision of the study staff; therefore, no formal analysis of compliance will be performed. The RPL554 exposure will be estimated based on residual volume in the nebulizer cup.

9.4.5 Efficacy/Pharmacodynamics

FEV_1 and FVC will be summarized as actual and change from baseline using descriptive statistics over time.

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 will be calculated as the AUC divided by the length of the time interval of interest. For analysis, the peak, average and trough FEV_1 will be divided by the pre-dose Day 1 baseline value.

Computed pharmacodynamic parameters for FEV_1 will be compared between the three study treatments using analysis of covariance (ANCOVA) models with fixed factors for treatment, period and patient, and using the pre-dose Day 1 baseline value as a covariate. FEV_1 will be analyzed 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 the combination RPL554+tiotropium/olodaterol will be compared to tiotropium/ olodaterol alone for each of the two doses of RPL554. 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 summarized by treatment and a Kaplan-Meier plot illustrating time to onset constructed.

Outcomes from the whole body plethysmography at 1.25 hours post-dose on Day 1 and 1.25, 8.25 and 12.25 hours post-dose on Day 3 will be compared in the same way as FEV_1 using multiplicative ANOVA models. The baseline of the visit (pre-first dose in a treatment period) will be used as covariate in these models.

The use of rescue medication during the study visits will be summarized by treatment, and, if appropriate, a Kaplan-Meier plot illustrating time to first use of rescue constructed.

9.4.6 Pharmacokinetics

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

- $AUC_{0\text{-}12h}$ represents the area under the plasma concentration curve from time 0 to 12 hours after dose on Day 3. The $AUC_{0\text{-}12h}$ value in indicative of the steady state AUC_T for a twice daily dosage regimen of RPL554 for the study cohort
- C_{max} denotes the highest plasma concentration measured
- t_{max} denotes the time point corresponding to C_{max}

Pharmacokinetic parameters will be summarized 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}).

9.4.7 Safety

Safety data including safety laboratory tests, 12-lead ECG and Holter parameters, vital signs and physical examinations, will be summarized by treatment group and time point of collection, when appropriate. For continuous variables, the change from baseline (pre-dose at each treatment period) to each post-dose time point will also be calculated and summarized. 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 treatment.

Coded adverse event terms will be presented by system organ class (SOC) and preferred term and summarized by treatment group. A summary table 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 event of each intensity will be summarized by SOC and preferred term.

9.4.8 Handling of Withdrawals or Missing Data

Patients withdrawn after only one treatment period will not be included in the efficacy analyses. 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 summarized. 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 summarized as the valid visit.

9.4.9 Interim Analyses

No formal interim analysis is planned for the study.

9.5 Determination of Sample Size

This is a complete block three-way crossover study. Assuming a residual CV of 6% for peak FEV_1, 70 patients will give an 80% power to detect a pairwise difference in peak FEV_1 of 5.1%. Assuming a mean baseline FEV_1 of 1.3 liters this will correspond to a difference of about 50 mL.

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 ethics committees 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 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 authorized 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 ethics committee 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 finalized, in the absence of a regulatory approval. After that time, all study-related documents will be archived according to 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.

13 REFERENCES

Abbott-Banner KH, Page CP. Dual PDE3/4 and PDE4 inhibitors: novel treatments for COPD and other inflammatory airway diseases. Basic Clin Pharmacol Toxicol. 2014 May;114(5):365-376. Doi: 10.1111/bcpt.12209. Epub 2014 Mar 6.

Bjermer L, Stewart J, Abbott-Banner KH et al. RPL554, a first-in-class dual PDE3/4 inhibitor is equi-effective as a bronchodilator to maximal doses of salbutamol in asthmatics but with fewer adverse events. Am J Resp Crit Care Med 2016;193:A7770.

Calverley PM, Sanchez-Toril F, McIvor A et al. Effect of 1-year treatment with roflumilast in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2007; 176(2):154-161.

Calzetta L, Page CP, Spina D, et al. The effect of the mixed phosphodiesterase 3/4 inhibitor RPL554 on human isolated bronchial smooth muscle tone. J Pharmacol Exp Ther 2013; 346: 414–423.

Calzetta L, Cazzola M, Page CP, et al. Pharmacological characterization of the interaction between the dual phosphodiesterase (PDE) 3/4 inhibitor RPL554 and glycopyrronium on human isolated bronchi and small airways. Pulm Pharmacol Ther 2015 Apr 18. pii: S1094-5539(15)00042-5.

Celli BR, MacNee W, ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J, 2004; 2:932-946.

Compton CH, Gubb J, Nieman R et al. Cilomilast, a selective phosphodiesterase-4 inhibitor for treatment of patients with chronic obstructive pulmonary disease: a randomized, dose-ranging study. Lancet 2001; 358(9278):265-270.

Davis AH, Carrieri-Kohlman V, Janson SL et al. Effects of treatment on two types of self-efficacy in people with chronic obstructive pulmonary disease. J Pain Symptom Manage 2006; 32(1):60-70.

EU Directive 95/46/EC: The Data Protection Directive.

Franciosi LG, Diamant Z, Banner KH, et al. Efficacy and safety of RPL554, a dual PDE3 and PDE4 inhibitor, in healthy volunteers and in patients with asthma or chronic obstructive pulmonary disease: findings from four clinical trials. Lancet Respiratory Medicine 2013; 1(9):714-727.

Gamble E, Grootendorst DC, Brightling CE et al. Anti-inflammatory effects of the phosphodiesterase-4 inhibitor cilomilast (Ariflo) in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2003; 168(8):976-982.

Grootendorst D, Gauw SA, Verhoosel RM, et al. Reduction in sputum neutrophil and eosinophil numbers by the PDE4 inhibitor roflumilast in patients with COPD. Thorax 2007; 62(12); 1081-1087.

Hankinson JL, Odencrantz JR, Fedan KB. Spirometry reference values from a sample of the general U.S. Population. Am J Respir Crit Care 1999;159:179-187.

Harbinson PL, MacLeod D, Hawksworth R et al. The effect of a novel orally active selective PDE4 isoenzyme inhibitor (CDP840) on allergen-induced responses in asthmatic subjects. Eur Respir J 1997;10(5):1008-1014.

International Conference on Harmonisation Topic E6. ICH Harmonised Tripartite Guideline. Good Clinical Practice.

Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26(2):319-338.

Rabe KF, Bateman ED, O'Donnell D, et al. Roflumilast--an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomized controlled trial. Lancet 2005; 366(9485):563-571.

Recommendations related to contraception and pregnancy testing in clinical trials. Clinical Trial Facilitation Group, Heads of Medicines Agencies, 2014. Downloaded from: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf.

Rennard SI, Schachter N, Strek M, et al. Cilomilast for COPD: results of a 6-month placebo controlled study of a potent, selective inhibitor of phosphodiesterase 4. Chest 2006;129(1):56-66.

Turner MJ, Matthes E, Billet A, et al. The dual phosphodiesterase 3 and 4 inhibitor RPL554 stimulates CFTR in ciliary beating in primary cultures of bronchial epithelia. Am J Physiol Lung Cell Mol Physiol 2016;310:L59-L70.

Ukena D, Rentz K, Reiber C, et al. Effects of the mixed phophodiesterase III/IV inhibitor, zardaverine, on airway function in patients with chronic airflow obstruction. Respir Med 1995;89 (6):441-444.

van Schalkwyk E, Strydom K, Williams Z et al. Roflumilast, an oral, once-daily phosphodiesterase 4 inhibitor, attenuates allergen-induced asthmatic reactions. J Allergy Clin Immunol 2005;116 (2):292-298.

Verona Pharma plc RPL554 Investigator Brochure, February 2017.

Verona Pharma plc RPL554 Investigational Medicinal Product Dossier current version.

Verona Pharma plc. RPL554-007-2014 Clinical Study Report, August 2016.

Verona Pharma plc. RPL554-009-2015 Clinical Study Report (February 2017).

Verona Pharma plc. RPL554-010-2015 Clinical Study Report (in preparation).

Verona Pharma plc. RPL554-PK-101 Clinical Study Report (December 2017).

Verona Pharma plc. RPL554-CO-202 Clinical Study Report (in preparation).

Verona Pharma plc. RPL554-CO-203 Clinical Study Report (in preparation).

Wanger J, Clausen JL, Coates A et al. Standardisation of the measurement of lung volumes. Eur Respir J 2005;26:511–522

World Medical Association, Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 48th World Medical Association General Assembly, Somerset West, 1996.

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 sterilization 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 center 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 enrollment.

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]
- Vasectomized 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 vasectomized 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 Tiotropium/Olodaterol Prescribing Highlights and Instructions for Use

Note: The information below is excerpted from the US package insert for tiotropium/ olodaterol. Full prescribing information in the US is available at:

http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Stiolto%20Respimat/stiolto.pdf

Full prescribing information in the UK is available at:

http://www.spioltorespimatpi.uk

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use STIOLTO RESPIMAT safely and effectively. See full prescribing information for STIOLTO RESPIMAT.

STIOLTO® RESPIMAT® (tiotropium bromide and olodaterol) inhalation spray, for oral inhalation use
Initial U.S. Approval: 2015

WARNING: ASTHMA-RELATED DEATH
See full prescribing information for complete boxed warning.

- **Long-acting beta$_2$-adrenergic agonists (LABA) such as olodaterol, one of the active ingredients in STIOLTO RESPIMAT, increase the risk of asthma-related death. (5.1)**
- **A placebo-controlled study with another long-acting beta$_2$-adrenergic agonist (salmeterol) showed an increase in asthma-related deaths in patients receiving salmeterol. (5.1)**
- **This finding of an increased risk of asthma-related death with salmeterol is considered a class effect of LABA, including olodaterol, one of the active ingredients in STIOLTO RESPIMAT. The safety and efficacy of STIOLTO RESPIMAT in patients with asthma have not been established. STIOLTO RESPIMAT is not indicated for the treatment of asthma. (4, 5.1)**

INDICATIONS AND USAGE

STIOLTO RESPIMAT is a combination of tiotropium, an anticholinergic and olodaterol, a long-acting beta$_2$-adrenergic agonist (LABA) indicated for:
The long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) (1.1)

Important limitations:
- STIOLTO RESPIMAT is NOT indicated to treat acute deterioration of COPD. (1.2)
- STIOLTO RESPIMAT is NOT indicated to treat asthma. (1.2)

DOSAGE AND ADMINISTRATION
- For oral inhalation only.
- Two inhalations of STIOLTO RESPIMAT once-daily at the same time of day. (2)

DOSAGE FORMS AND STRENGTHS

Inhalation spray: Each actuation from the mouthpiece contains 3.124 mcg tiotropium bromide monohydrate, equivalent to 2.5 mcg tiotropium, and 2.736 mcg olodaterol hydrochloride, equivalent to 2.5 mcg olodaterol.

Two actuations equal one dose. (3)

CONTRAINDICATIONS
- All LABAs are contraindicated in patients with asthma without use of a long-term asthma control medication. (4) STIOLTO RESPIMAT is not indicated for the treatment of asthma. (1.2)
- Hypersensitivity to tiotropium, ipratropium, olodaterol, or any component of this product. (4)

WARNINGS AND PRECAUTIONS
- LABA increase the risk of asthma related death. (5.1)
- Do not initiate STIOLTO RESPIMAT in acutely deteriorating COPD patients. (5.2)
- Do not use for relief of acute symptoms. Concomitant short-acting beta$_2$-agonists can be used as needed for acute relief. (5.2)
- Do not exceed the recommended dose. Excessive use of STIOLTO RESPIMAT, or use in conjunction with other medications containing LABA can result in clinically significant cardiovascular effects and may be fatal. (5.3)
- Immediate hypersensitivity reactions: Discontinue STIOLTO RESPIMAT at once and consider alternatives if immediate hypersensitivity reactions, including angioedema, bronchospasm, or anaphylaxis, occur. (5.4)
- Life-threatening paradoxical bronchospasm can occur. Discontinue STIOLTO RESPIMAT immediately. (5.5)
- Use with caution in patients with cardiovascular or convulsive disorders, thyrotoxicosis, or sensitivity to sympathomimetic drugs. (5.6, 5.7)
- Worsening of narrow-angle glaucoma may occur. Use with caution in patients with narrow-angle glaucoma and instruct patients to consult a physician immediately if this occurs. (5.8)
- Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patients to consult a physician immediately if this occurs. (5.9)
- Be alert to hypokalemia and hyperglycemia. (5.11)

ADVERSE REACTIONS

The most common adverse reactions (>3% incidence and more than an active control) were nasopharyngitis, cough, and back pain.

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
- Other adrenergic drugs may potentiate effect. Use with caution. (5.3, 7.1)
- Xanthine derivatives, steroids, diuretics, or non-potassium sparing diuretics may potentiate hypokalemia or ECG changes. Use with caution. (7.2, 7.3)
- MAO inhibitors, tricyclic antidepressants, and drugs that prolong QTc interval may potentiate effect on cardiovascular system. Use with extreme caution. (7.4)
- Beta-blockers may decrease effectiveness. Use with caution and only when medically necessary. (7.5)
- Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administration of STIOLTO RESPIMAT with other anticholinergic-containing drugs. (7.6)

USE IN SPECIFIC POPULATIONS

Patients with moderate to severe renal impairment should be monitored closely for potential anticholinergic side effects. (2, 8.7)

See 17 for PATIENT COUNSELING INFORMATION, Medication Guide, and Instructions for Use.

Revised: 6/2016

Instructions for Use

Tiotropium bromide and olodaterol inhalation spray

In the US: **STIOLTO® RESPIMAT®** (sti-OL-to-RES peh mat)
(default name used below)

In the UK: **SPIOLTO® RESPIMAT®** (spi-OL-to-RES peh mat)

For Oral Inhalation Only

Do not spray STIOLTO RESPIMAT into your eyes.

Read these Instructions for Use before you start using STIOLTO RESPIMAT and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or your treatment.

You will need to use this inhaler ONCE A DAY, at the same time each day. Each time you use it take TWO PUFFS.

Do not turn the clear base before inserting the cartridge.

How to store your STIOLTO RESPIMAT inhaler

- Store STIOLTO RESPIMAT at room temperature 68°F to 77°F (20°C to 25°C).
- Do not freeze your STIOLTO RESPIMAT cartridge and inhaler.
- If STIOLTO RESPIMAT has not been used for more than 3 days, release 1 puff towards the ground.
- If STIOLTO RESPIMAT has not been used for more than 21 days, repeat steps 4 to 6 under the "Prepare for first use" until a mist is visible. Then repeat steps 4 to 6 three more times.
- Keep your STIOLTO RESPIMAT cartridge and inhaler out of the reach of children.

How to care for your STIOLTO RESPIMAT inhaler

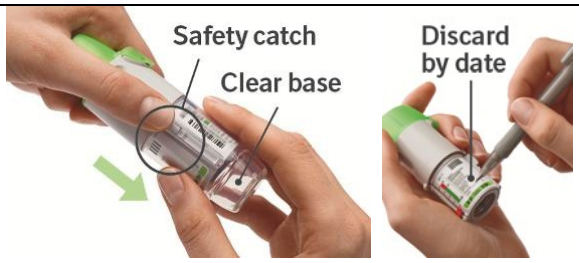
- Clean the mouthpiece, including the metal part inside the mouthpiece, with a damp cloth or tissue only, at least once a week. Any minor discoloration in the mouthpiece does not affect your STIOLTO RESPIMAT inhaler.

When to get a new STIOLTO RESPIMAT inhaler

- Your inhaler contains 60 puffs (30 doses) if used as indicated (2 puffs once daily). If you have a sample, your inhaler contains 28 puffs (14 doses) if used as indicated (2 puffs once daily).

- The dose indicator shows approximately how much medicine is left.
- When the dose indicator enters the red area of the scale you need to get a refill; there is approximately medicine for 7 days left (if you have a sample, there is approximately medicine for 3 days left).
- When the dose indicator reaches the end of the red scale, your STIOLTO RESPIMAT is empty and automatically locks. At this point, the clear base cannot be turned any further.
- Three months after insertion of cartridge, throw away the STIOLTO RESPIMAT even if it has not been used, or when the inhaler is locked, or when it expires, whichever comes first.

Prepare for first use

1. Remove clear base • Keep the cap closed. • Press the safety catch while firmly pulling off the clear base with your other hand. Be careful not to touch the piercing element. • Write the discard by date on the label (3 months from the date the cartridge is inserted).	
2. Insert cartridge • Insert the narrow end of the cartridge into the inhaler. • Place the inhaler on a firm surface and push down firmly until it clicks into place.	
3. Replace clear base • Put the clear base back into place until it clicks. • Do not remove the clear base or the cartridge after it has been put together.	
4. Turn • Keep the cap closed. • Turn the clear base in the direction of the arrows on the label until it clicks (half a turn).	
5. Open • Open the cap until it snaps fully open.	

6. Press • Point the inhaler toward the ground. • Press the dose-release button. • Close the cap. • If you do not see a mist, repeat steps 4 to 6 until a mist is seen. • After a mist is seen, repeat steps 4 to 6 three more times. • After complete preparation of your inhaler, it will be ready to deliver the number of puffs on the label.	

Daily use (T O P)

Turn • Keep the cap closed. • **Turn** the clear base in the direction of the arrows on the label until it clicks (half a turn).	
Open • **Open** the cap until it snaps fully open.	
Press • Breathe out slowly and fully. • Close your lips around the mouthpiece without covering the air vents. • Point the inhaler to the back of your throat. • While taking a slow, deep breath through your mouth, **Press** the dose-release button and continue to breathe in. • Hold your breath for 10 seconds or for as long as comfortable. • Repeat **T**urn, **O**pen, **P**ress (TOP) for a total of 2 puffs. • Close the cap until you use your inhaler again.	

Answers to Common Questions

It is difficult to insert the cartridge deep enough:

Did you accidentally turn the clear base before inserting the cartridge? Open the cap, press the dose-release button, then insert the cartridge.

Did you insert the cartridge with the wide end first? Insert the cartridge with the narrow end first.

I cannot press the dose-release button:

Did you turn the clear base? If not, turn the clear base in a continuous movement until it clicks (half a turn).

Is the dose indicator on the STIOLTO RESPIMAT pointing to zero? The STIOLTO RESPIMAT inhaler is locked after 60 puffs (30 doses). If you have a sample, the STIOLTO RESPIMAT inhaler is locked after 28 puffs (14 doses). Prepare and use your new STIOLTO RESPIMAT inhaler.

I cannot turn the clear base:

Did you turn the clear base already? If the clear base has already been turned, follow steps "Open" and "Press" under "Daily use" to get your medicine.

Is the dose indicator on the STIOLTO RESPIMAT pointing to zero? The STIOLTO RESPIMAT inhaler is locked after 60 puffs (30 doses). If you have a sample, the STIOLTO RESPIMAT inhaler is locked after 28 puffs (14 doses). Prepare and use your new STIOLTO RESPIMAT inhaler.

The dose indicator on the STIOLTO RESPIMAT reaches zero too soon:

Did you use STIOLTO RESPIMAT as indicated (2 puffs once daily)? STIOLTO RESPIMAT will deliver 60 puffs and last 30 days if used at 2 puffs once daily. If you have a sample, STIOLTO RESPIMAT will deliver 28 puffs and last 14 days if used at 2 puffs once daily.

Did you turn the clear base before you inserted the cartridge? The dose indicator counts each turn of the clear base regardless whether a cartridge has been inserted or not.

Did you spray in the air often to check whether the STIOLTO RESPIMAT is working?

Once you have prepared STIOLTO RESPIMAT, no test-spraying is required if used daily.

Did you insert the cartridge into a used STIOLTO RESPIMAT? Always insert a new cartridge into a **NEW** STIOLTO RESPIMAT.

My STIOLTO RESPIMAT sprays automatically:

Was the cap open when you turned the clear base? Close the cap, then turn the clear base.

Did you press the dose-release button when turning the clear base? Close the cap, so the dose-release button is covered, then turn the clear base.

Did you stop when turning the clear base before it clicked? Turn the clear base in a continuous movement until it clicks (half a turn).

My STIOLTO RESPIMAT doesn't spray:

Did you insert a cartridge? If not, insert a cartridge.

Did you repeat Turn, Open, Press (TOP) less than three times after inserting the cartridge? Repeat Turn, Open, Press (TOP) three times after inserting the cartridge as shown in steps 4 to 6 under "Prepare for first use".

Is the dose indicator on the STIOLTO RESPIMAT pointing to 0? You have used up all your medicine and the inhaler is locked.

For more information about STIOLTO RESPIMAT or a video demonstration on how to use STIOLTO RESPIMAT, go to www.stiolto.com. You may also call 1-800- 542-6257 or (TTY) 1-800-459-9906 for further information about STIOLTO RESPIMAT.

This Medication Guide and Instructions for Use has been approved by the U.S. Food and Drug Administration.

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14.3 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 subject 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 etiology 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 recognized 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.