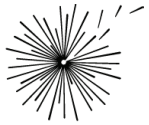

Verona Pharma

CLINICAL STUDY PROTOCOL

A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED DOSE RANGING STUDY TO ASSESS THE EFFECT OF RPL554 ADDED ON TO TIOTROPIUM IN PATIENTS WITH COPD

STUDY NO. RPL554-CO-205

Version:	**5.0**
Date:	**22 July 2019**
Phase:	**II**
Investigational Medicinal Product:	**RPL554**
IND Number:	**133146**

SPONSOR SIGNATURE PAGE

[redacted]

INVESTIGATOR SIGNATURE PAGE

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

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

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

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

Name and Title	Signature	Date

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CONTACT LIST

Sponsor	[redacted]
Contract Research Organization	

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

DETAIL OF AMENDMENTS SINCE THE PREVIOUS VERSION

Section 4.1, Inclusion Criteria

Inclusion Criterion 4 has been modified to state that ECG tracing must show none of the abnormalities that are now listed in Section 14.2.

Section 4.2, Exclusion Criteria

Exclusion Criterion 14 has been modified to specify additional clinically significant cardiovascular findings that would render patients ineligible for enrollment.

Exclusion Criterion 19 has been modified to specify additional hepatitis test findings, and their respective eligibility characteristics.

Section 14.2, ECG Requirement for Inclusion

This section has been added.

SYNOPSIS

Title of Study:	A Phase II, randomized, double-blind, placebo controlled, dose ranging study to assess the effect of RPL554 added on to tiotropium in patients with COPD
Protocol Number:	RPL554-CO-205
IND Number:	133146
Phase:	II
Sponsor:	Verona Pharma plc
Number of Patients Planned:	Approximately 400 randomized
Study Center(s):	Approximately 50
Planned Study Period:	May 2019 to November 2019
Objectives:	**Primary Objective** To investigate the bronchodilator effect of different doses of RPL554 administered by nebulizer on change from baseline in peak forced expiratory volume in 1 second (FEV_1) (maximum over 3 hours following dosing) at the final study visit (i.e., Visit 6, after 4 weeks of treatment) when administered twice daily to patients with moderate to severe Chronic Obstructive Pulmonary Disease (COPD) on a background of once-daily tiotropium. **Secondary Objectives** ● To investigate the bronchodilator effect of RPL554 administered by nebulizer on average area under the curve $(AUC)_{0\text{-}3h}$ FEV1 at Visit 6 ● To investigate the bronchodilator effect of RPL554 administered by nebulizer on average $AUC_{0\text{-}12h}$ FEV_1 at Visit 6 ● To investigate the effect of RPL554 administered by nebulizer on change from baseline in morning trough FEV_1 at Visit 6 ● To investigate the effects of RPL554 on COPD symptoms, as measured by daily diary (Evaluating Respiratory Symptoms for COPD [E-RS™:COPD], St. George's Respiratory Questionnaire for COPD patients (SGRQ-C), Baseline Dyspnea Index (BDI)/Transition Dyspnea Index (TDI), and patient global assessment of change (PGAC) ● To investigate the bronchodilator effect of RPL554 administered by nebulizer on peak FEV_1, trough FEV_1 and average $AUC_{0\text{-}3h}$ FEV_1 at Visits 3, 4 and 5 (i.e., after 1, 2 and 3 weeks of treatment) ● To investigate the effect of RPL554 administered by nebulizer on peak FEV_1, average $AUC_{0\text{-}3h}$ FEV_1 and $AUC_{0\text{-}12h}$ FEV_1 at Visit 2 ● To investigate the safety of RPL554 when administered for 4 weeks in patients with COPD, as measured by adverse events, laboratory tests, 12-lead electrocardiograms (ECGs) and vital signs ● To investigate the effect of RPL554 on rescue albuterol use ● To investigate the bronchodilator effect of RPL554 administered by nebulizer on peak and average $AUC_{0\text{-}3h}$ forced vital capacity (FVC) at Visits 2 to 6, in average $AUC_{0\text{-}12h}$ FVC at Visits 2 and 6 and in morning trough FVC at Visits 3 to 6 ● To evaluate the steady state exposure of RPL554 ● To evaluate the effect of RPL554 on tiotropium steady state exposure

	Exploratory Objectives ● To assess peak and average $AUC_{0\text{-}12h}$ FEV_1 at Visit 6 compared to Visit 2 ● To investigate the effect of RPL554 or placebo on inspiratory capacity (IC) at Visits 2 and 6 ● To investigate the effects of RPL554 on COPD symptoms, as measured by the COPD Assessment Test (CAT) ● To assess the effect of RPL554 on morning symptoms and activity limitation
Study Design and Methodology:	This is a Phase IIb, randomized, double-blind, placebo controlled, multiple dose, parallel group study to investigate the effects of 4 weeks of treatment with nebulized RPL554 (at different dose levels) compared to placebo in patients with moderate to severe COPD on a stable background therapy of open-label tiotropium. The study comprises seven visits: Pre-screening (Visit 0), Screening (Visit 1) and then a Treatment Period consisting of Randomization (Visit 2), and weekly visits for 4 weeks (Visit 3 to Visit 6). Visit 0 will be conducted for the patient to sign the informed consent form and receive a patient identification number prior to initiating any study-related procedures (including medication washout). Patients will be screened for eligibility (Visit 1) following at least a 48-hour washout of all long-acting bronchodilators, and assessed for reversibility to albuterol. Eligible patients will enter a 14-day Run-in taking open-label tiotropium (as Spiriva® Respimat®) once daily in the morning, and dispensed an electronic diary (e-diary) for recording daily symptoms and activity, rescue medication use and confirming proper use of study treatment. At Visit 1, patients will also be instructed on the use of tiotropium. Patients will be dispensed rescue medication to be used as needed for increased pulmonary symptoms during the screening, run-in and treatment periods.
Study Procedures:	At Visit 2, patients will be re-assessed for eligibility, including the assessment of the Randomization Criteria. Eligible patients will be stratified 1:1 based on reversibility to albuterol as determined at Screening ("reversible" defined as ≥12% and ≥200 mL increase in FEV_1, and "non-reversible" defined as <12% or <200 mL)). Each reversibility stratum will be capped at 50% of patients. Patients will then be randomized equally across the five possible treatment arms (four doses of RPL554 and placebo) within each reversibility stratum. Following randomization, patients will be dispensed double-blind study medication and instructed on the use of the nebulizer. Patients will first receive their tiotropium dose followed within 2 minutes by double-blind study medication. The patient will take the second (evening) dose of study medication in the clinic following completion of spirometry efforts. Between clinic visits, patients will self-administer both tiotropium and study medication every morning at home, while only study medication will be taken in the evening. Patients will be instructed to withhold all study treatments (including tiotropium) and rescue albuterol prior to all study visits, and to bring their e-diary, open-label tiotropium and nebulized study medication to all study visits. Assessments performed at Visit 2 will include: ● Randomization criteria ● SGRQ-C, BDI and CAT questionnaires

	● Pre-dose pharmacokinetic sampling ● Pre- and 2-hours post-dose IC (via slow maneuver) ● Spirometry pre-dose and up to 12 hours post-dose ● 12-lead ECG pre-dose and 2 hours post dose Assessments performed at Visits 3 through 5 will include: ● Visit 3 only: 12-lead ECG pre-dose and 2 hours post-dose ● Visit 4 only: pre-dose pharmacokinetic sampling, SGRQ-C, TDI, CAT and PGAC questionnaires ● Spirometry pre-dose and up to 3 hours post-dose Assessments performed at Visit 6 will include: ● SGRQ-C, TDI, CAT and PGAC questionnaires ● Pre- and 2-hours post-dose IC (via slow maneuver) ● Spirometry pre-dose and up to 12 hours post-dose ● 12-lead ECG at pre-dose and 2 hours post dose A follow-up telephone contact will be made approximately 1 week after Visit 6. Adverse events will be recorded from the time informed consent is provided until the telephone call.
Main Criteria for Eligibility:	Male and female patients 40 to 80 years old with moderate to severe COPD, with a post-bronchodilator FEV_1 of 30 to 70% of predicted and FEV_1/FVC ratio of ≤0.70. Patients must have a minimum score of 2 on the modified Medical Research Council (mMRC) dyspnea scale. They must have at least a 10 pack-year smoking history, and may be a former smoker or current smoker. At randomization, patients must continue to have a minimum score of 2 on the mMRC, demonstrate pre-dose FEV_1 of 30 to 70% of predicted and be compliant with e-diary and tiotropium use during the 14 days between Visits 1 and 2. Patients must be clinically stable without recent COPD exacerbations or hospitalizations. They must not have uncontrolled disease or chronic heart failure.
Study Treatments:	Patients will be randomized to one of the following treatment arms: ● RPL554 0.375 mg twice daily ● RPL554 0.75 mg twice daily ● RPL554 1.5 mg twice daily ● RPL554 3.0 mg twice daily ● Placebo twice daily All eligible patients will take open-label tiotropium provided by the study centers during the run-in and treatment periods.
Duration of Treatment:	The approximate planned duration for each completed patient will be 14 days of run-in and 28 days of treatment with study medication.
Statistical Methods:	Treatments will be compared using mixed model for repeated measures (MMRM) adjusting for treatment, visit and treatment by visit interaction. Each RPL554 nebulized formulation treatment will first be compared to placebo using a closed test procedure starting with the highest dose of RPL554. With an FEV_1 standard deviation estimated at 200 mL, a 2-sided test at a 5% significance and 73 evaluable patients per group, there will be an 80% power to detect a true difference of 93 mL between treatments. Assuming approximately a 10% early withdrawal rate, 80 patients per group are planned to be randomized.

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LIST OF ABBREVIATIONS

ANCOVA	Analysis of covariance
Anti-HBc	Hepatitis B core antibody
Anti-HBs	Hepatitis B surface antibody
ATS	American Thoracic Society
AUC	Area under the curve
BDI	Baseline Dyspnea Index
BMI	Body mass index
CAT	COPD Assessment Test
COPD	Chronic obstructive pulmonary disease
ECG	Electrocardiogram
eCRF	Electronic case report form
E-RS™:COPD	Evaluating Respiratory Symptoms for COPD
EDTA	Ethylenediaminetetraacetic acid
ERS	European Respiratory Society
FAS	Full analysis set
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
IC	Inspiratory capacity
ICH	International Council on Harmonization
ICS	Inhaled corticosteroid
INN	International Nonproprietary Name
IRT	Interactive Response Technology (system)
IUPAC	International Union of Pure and Applied Chemistry
LABA	Long acting β_2-agonists
LAMA	Long acting muscarinic antagonists
mMRC	Modified Medical Research Council (dyspnea scale)
MMRM	Mixed model for repeated measures
NHANES	National Health and Nutrition Examination Survey
NYHA	New York Heart Association
PDE	Phosphodiesterase

PGAC	Patient global assessment of change
PK	Pharmacokinetics
PPS	Per protocol set
pMDI	Pressurized metered dose inhaler
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SAS	Statistical analysis software
SGRQ-C	St. George's Respiratory Questionnaire for COPD Patients
SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected, unexpected serious adverse reaction
TDI	Transition Dyspnea Index
TSH	Thyroid stimulating hormone

1 INTRODUCTION

1.1 Disease and Study Medication Review

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

Current standard of care treatments include inhaled short- and long-acting bronchodilators, inhaled corticosteroids (ICS) and, more recently, the phosphodiesterase (PDE) 4 inhibitor roflumilast. These therapies have little or no effect on disease progression or mortality, although there is evidence to suggest that they can reduce exacerbation rates and improve quality of life (Rabe et al, 2005; Calverley et al, 2007; Rennard et al, 2011, Singh et al, 2015). Approximately 30% to 40% of moderate to severe COPD patients on triple inhaled therapy (ICS/long-acting muscarinic antagonists [LAMA]/long-acting β_2 agonists [LABA]) remain uncontrolled and continue to experience airway obstruction, COPD symptoms and exacerbations (Vestbo et al, 2017). Thus, there is an urgent unmet medical need for drugs with novel mechanisms of action that can be used by these patients in addition to current therapies.

RPL554, a small molecule isoquinolone derivative, is a dual inhibitor of two isoforms (type 3 and 4) of the PDE family of enzymes. PDE3 and PDE4 are known to have a role in modulating the inflammatory airway response in respiratory diseases, including COPD, allergic asthma and allergic rhinitis. In general, PDE3 inhibitors act as bronchodilators (through interaction with smooth muscle cells), while PDE4 inhibitors have anti-inflammatory properties. There is also evidence to suggest that combined inhibition of PDE3 and PDE4 can have additive or synergistic anti-inflammatory and bronchodilator effects (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 β_2-agonists (Calzetta et al, 2013; Calzetta et al, 2015). RPL554, therefore, has the potential to benefit patients not satisfactorily treated with existing medicines.

The safety, bronchodilator, bronchoprotective and anti-inflammatory activities of RPL554 have been evaluated in 13 completed clinical studies involving over 800 subjects. Initially, five studies

were conducted in healthy subjects, patients with mild-moderate persistent asthma and those with allergic rhinitis and COPD, using a nebulized solution [redacted] (Franciosi et al, 2013; summarized in the Investigator's Brochure).

RPL554 was subsequently re-formulated [redacted]

This formulation has been tested in eight 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 (PK) 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 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 albuterol, but with fewer of the well described 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 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 expiratory volume in 1 second (FEV_1) in COPD patients administered RPPL554 in addition to either 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 and functional residual capacity. The time of onset of RPL554 + tiotropium was significantly 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 PK levels that were similar to that seen in patients with COPD (Clinical Study Report pending).

8. Study RPL554-CO-204 was a Phase II crossover study in patients with moderate to severe COPD who received tiotropium/olodaterol (Stiolto®) once daily, plus RPL554 1.5 mg, RPL554 6 mg or placebo twice daily for 3 days. This study demonstrated a non-significant but consistent increase in peak and average area under the curve $(AUC)_{0\text{-}4h}$ FEV_1 (approximately 34 mL to 62 mL for RPL554 1.5 mg and approximately -11 mL to 47 mL for RPL554 6 mg) as compared to tiotropium + placebo. There was a significant improvement in evening peak FEV_1 and residual volume following the evening dose of RPL554 (Clinical Study Report pending).

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

The purpose of this study is to investigate the dose response of RPL554 in patients with moderate to severe COPD that are still symptomatic despite treatment with a stable background of tiotropium over 4 weeks of treatment. This study is intended to support optimal dose selection for a Phase III program evaluating RPL554 as an add-on treatment to standard of care therapy.

1.2 Summary of Risks and Benefits

Data from non-clinical studies had suggested a potential for hypotension and tachycardia. However, in the clinical studies to date, overall, RPL554 has been well tolerated in healthy subjects as well as patients with moderate to severe COPD, asthma and allergic rhinitis. The most common adverse events that were reported at least twice in subjects who received single or multiple doses of RPL554 were considered generally mild. In descending order of frequency, they included headache, cough, dizziness, and palpitations. Adverse events for single and multiple dose studies are summarized in the Investigator's Brochure.

There has been no evidence of clinically significant adverse events related to the cardiovascular or gastrointestinal systems. A small and transient increase in heart rate at 6 mg and 12 mg doses were reported; however, they were not considered clinically significant. Holter findings in completed studies did not show any arrhythmogenic potential.

In single dose studies, there was an increase in the rate of headache that was most pronounced at doses over 6 mg. Results from multiple dose data in patients with COPD suggested a transient increase in dizziness, the majority of which occurred during spirometry or dosing; otherwise, the rate of adverse events was comparable for RPL554 and placebo treated patients. There was an increase in mild adverse events reported for healthy subjects treated with higher doses of RPL554 (up to 24 mg) that were considered related to the higher serum levels of RPL554 achieved in healthy subjects than in those with COPD.

2 OBJECTIVES

2.1 Primary Objective

To investigate the bronchodilator effect of different doses of RPL554 administered by nebulizer on change from baseline in peak FEV_1 (maximum over 3 hours following dosing) at the final study visit (i.e., Visit 6, after 4 weeks of treatment) when administered twice daily to patients with moderate to severe COPD on a background of once-daily tiotropium.

2.2 Secondary Objectives

- To investigate the bronchodilator effect of RPL554 administered by nebulizer on average $AUC_{0\text{-}3h}$ FEV_1 at Visit 6
- To investigate the bronchodilator effect of RPL554 administered by nebulizer on average $AUC_{0\text{-}12h}$ FEV_1 at Visit 6
- To investigate the effect of RPL554 administered by nebulizer on change from baseline in morning trough FEV_1 at Visit 6
- To investigate the effects of RPL554 on COPD symptoms, as measured by daily diary (Evaluating Respiratory Symptoms for COPD [E-RS™:COPD], St. George's Respiratory Questionnaire for COPD patients (SGRQ-C), Baseline Dyspnea Index (BDI)/Transition Dyspnea Index (TDI) and patient global assessment of change (PGAC)
- To investigate the bronchodilator effect of RPL554 administered by nebulizer on peak FEV_1, trough FEV_1 and average $AUC_{0\text{-}3h}$ FEV_1 at Visits 3, 4 and 5 (i.e., after 1, 2 and 3 weeks of treatment)
- To investigate the bronchodilator effect of RPL554 administered by nebulizer on peak FEV_1, average $AUC_{0\text{-}3h}$ FEV_1 and average $AUC_{0\text{-}12h}$ FEV_1 at Visit 2
- To investigate the safety of RPL554 when administered for 4 weeks in patients with COPD, as measured by adverse events, laboratory tests, 12-lead electrocardiograms (ECGs) and vital signs
- To investigate the effect of RPL554 on rescue albuterol use
- To investigate the bronchodilator effect of RPL554 administered by nebulizer on peak and average $AUC_{0\text{-}3h}$ forced vital capacity (FVC) at Visits 2 to 6, in average $AUC_{0\text{-}12h}$ FVC at Visits 2 and 6 and in morning trough FVC at Visits 3 to 6.
- To evaluate the steady state exposure of RPL554
- To evaluate the effect of RPL554 on tiotropium steady state exposure

2.3 Exploratory Objectives

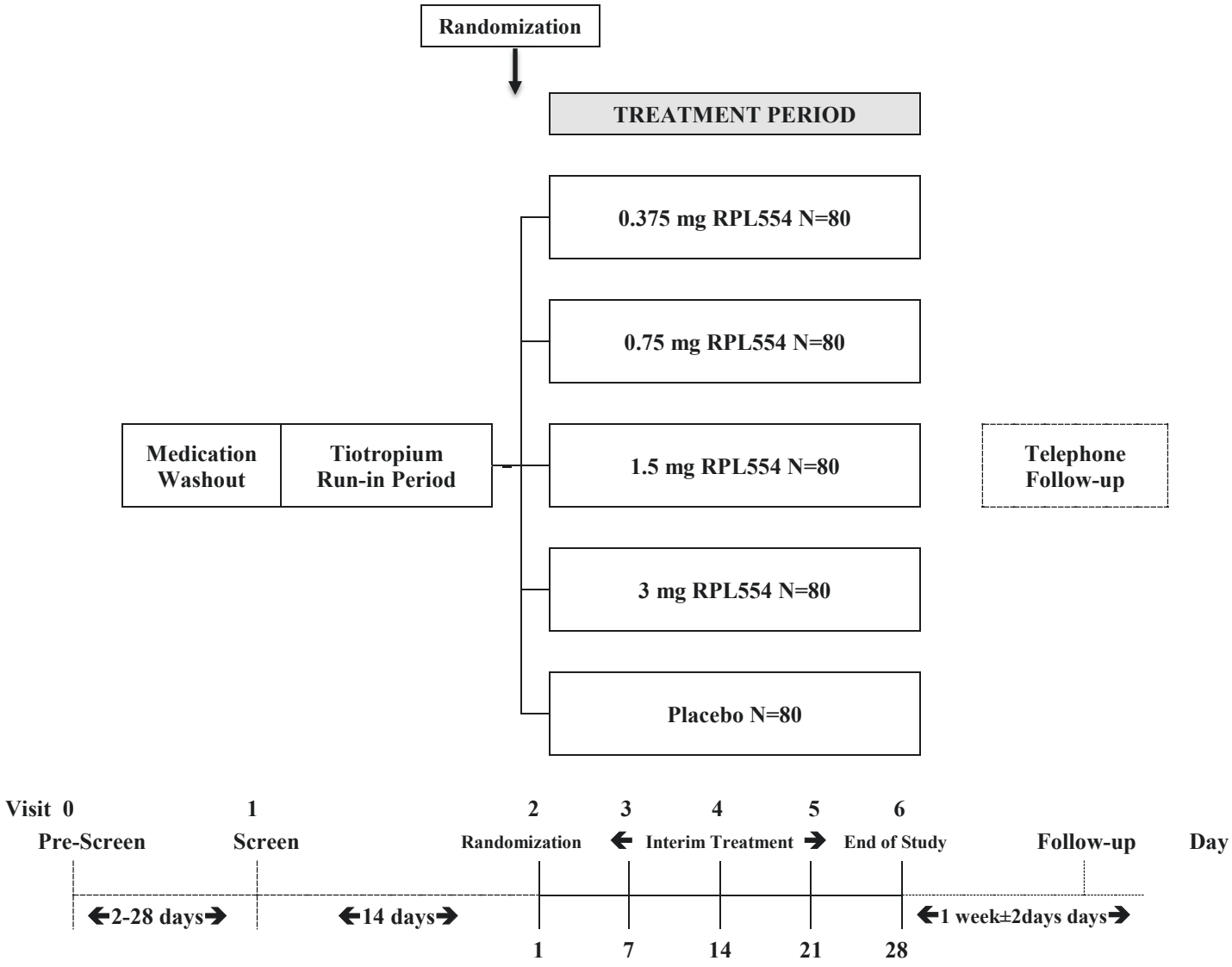
- To assess peak and average $AUC_{0\text{-}12h}$ FEV_1 at Visit 6 compared to Visit 2
- To investigate the effect of RPL554 on inspiratory capacity (IC) at Visits 2 and 6
- To investigate the effects of RPL554 on COPD symptoms, as measured by the COPD Assessment Test (CAT)
- To assess the effect of RPL554 on morning symptoms and activity limitation

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan Description

This is a Phase IIb, randomized, double-blind, placebo-controlled, multiple dose, parallel group study. A flow chart illustrating the key components of the study is provided in Figure 1.

Figure 1 Study Flow Chart



The study comprises seven visits: Pre-screening (Visit 0), Screening (Visit 1) and then a Treatment Period consisting of Randomization (Visit 2), and weekly visits for 4 weeks (Visit 3 to Visit 6):

The Pre-screening visit (Visit 0) will be conducted for the patient to sign the informed consent, receive a patient identification number and commence washout of prohibited medications. Patients

will be dispensed rescue medication to be used as needed for increased pulmonary symptoms during the Screening, Run-in and Treatment Period.

At Visit 1, screening procedures will be performed following at least a 48-hour washout of all long-acting bronchodilators, and patients will be assessed for reversibility to albuterol.

Eligible patients will then enter a 14-day Run-in, taking open-label tiotropium as Spiriva® Respimat® once daily in the morning starting the day after Visit 1, and dispensed an electronic diary (e-diary) for recording daily symptoms and activity, rescue medication use and confirming administration of tiotropium during run-in.

Patients will then enter the Treatment Period lasting 4 weeks. At Visit 2, patients will be re-assessed for eligibility according to the randomization criteria. Eligible patients will be stratified based on reversibility to albuterol as determined at Screening ("reversible" defined as ≥12% and ≥200 mL increase in FEV_1, and "non-reversible" defined as ≤12% or <200 mL). Each reversibility stratum will be capped at 50%. Patients will then be randomized equally across the five possible treatment arms (four doses of RPL554 and placebo) within each reversibility stratum. Following randomization, patients will do the following:

1) Be dispensed twice daily nebulized study medication
2) Take their tiotropium dose followed within 2 minutes by double-blind study medication (see Section 5.3)
3) Undergo serial spirometry and other assessments over 12 hours
4) Be instructed by unblinded study staff in the use of the nebulizer, and demonstrate their ability when taking their second dose
5) Take the second (evening) dose of study treatment prior to clinic discharge

Between clinic visits, patients will self-administer both tiotropium and study medication every morning at home in the same order as described above, while only study medication treatment will be taken in the evening.

Patients will be instructed to withhold study treatments (including tiotropium) and rescue albuterol prior to all study visits, and to bring their e-diary, open-label tiotropium and nebulized study medication to all study visits. Patients will be instructed to withhold albuterol for at least 6 hours prior to all visits.

Patients will return for three interim, weekly visits (Visits 3, 4 and 5), where they will return used and unused double-blind study medication and receive new study medication from the unblinded study staff. The first dose of the newly dispensed study medication will be administered in the clinic with spirometry performed for 3 hours after dosing. Questionnaires, safety assessments, study treatment compliance (including tiotropium) and e-diary review will be conducted at Visits 2 through 5. Blood samples for PK analysis will be collected pre-dose at Visits 2 and 4.

At the End of Study visit (Visit 6) (after 4 weeks of treatment, or early termination), patients will take their last dose of tiotropium and study medication, and will be resident at the study center from the morning until at least 12 hours after dosing to allow for monitoring of lung function and study closeout procedures. A phone call will occur approximately 1 week after the final visit as a safety follow-up.

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

This study aims to determine the effect of RPL554 on the lung function, symptom improvement and safety measures on symptomatic patients with COPD on a stable background of tiotropium.

Twice daily nebulized doses of RPL554 or placebo will be administered for 4 weeks on top of open-label tiotropium. Prior studies have demonstrated that twice daily dosing is appropriate given sustained bronchodilation observed over 12 hours. The treatment duration should allow for evaluation of RPL554 as a maintenance bronchodilator, including peak FEV_1, and the anti-inflammatory response associated with the PDE3/4 dual mechanism of action, as measured by trough FEV_1 and improvement in symptoms. An equal number of reversible and non-reversible patients is planned in order to enrich the population with patients expected to be more responsive to bronchodilator treatment to support optimal dose selection.

A parallel group placebo-controlled design is used to allow for an examination of any dose dependent effects on efficacy and safety compared to placebo. This design makes it possible to obtain unbiased inferences about differences between treatments. Treatments will be administered double-blind with the Investigator and patient unaware of the treatment identity to further minimize any potential bias in the overall assessment of treatment effect and safety.

An eight-fold dose range has been selected in order to show a separation between efficacious and sub-optimal doses.

3.3 Planned Duration of the Study

The approximate planned duration for each patient (including the screening, run-in and treatment periods as well as the follow-up phone contact) will be between 44 and 83 days, as determined by adding the minimum and maximum time windows shown in Table 4. The total study duration, from screening of the first enrolled patient to completion of the last one, is expected to be approximately 6 months.

3.4 Definition of the End of the Study

The end of the study is defined as the date of the follow-up phone call, 1 week (±2 days) after the End of Study visit of the last patient to complete the study. Consequently, any patient who for whatever reason does not have a follow-up phone call will be recorded as having early terminated in the electronic case report form (eCRF).

4 SELECTION OF STUDY POPULATION

The population to be recruited into this study is stable patients with moderate to severe COPD, who continue to have symptoms and impaired lung function after 2-weeks of tiotropium maintenance therapy and without significant heart disease.

Specific criteria are as follows:

4.1 Inclusion Criteria at Screening

1. Sign an informed consent document indicating they understand the purpose of and procedures required for the study and are willing to participate in the study.
2. Male or female aged between 40 and 80 years inclusive, at the time of informed consent.

3. Must agree to meet the following from the first dose up to 1 month after the last dose of study medication:

   If male:

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

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

   If female: be of non-childbearing potential or use a highly effective form of contraception as defined in Section 14.1.
4. Have a 12-lead ECG recording at Screening showing none of the abnormalities listed in Section 14.2.
5. Capable of complying with study restrictions and procedures, including ability to use the nebulizer correctly.
6. Body mass index (BMI) between 18 and 35 kg/m^2 (inclusive) with a minimum weight of 45 kg.
7. COPD diagnosis: Patients with a diagnosis of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (Celli and MacNee, 2004) with symptoms compatible with COPD for at least 1 year prior to Screening.
8. Ability to perform acceptable and reproducible spirometry.
9. Post-bronchodilator (four puffs of albuterol) spirometry at Screening demonstrating the following:
   - FEV_1/ FVC ratio of ≤0.70
   - FEV_1 ≥30% and ≤70% of predicted normal*

   *National Health and Nutrition Examination Survey (NHANES) III (Hankinson et al, 1999) will be used as the reference for normal predicted values.
10. Clinically stable COPD in the 4 weeks prior to Screening (Visit 1) and during the period between Visits 1 and 2.
11. A score of ≥2 on the modified Medical Research Council (mMRC) dyspnea scale at Screening.
12. A chest X-ray (posterior-anterior) at Screening, or in the 12 months prior to Screening showing no clinically significant abnormalities unrelated to COPD.
13. Meet the concomitant medication restrictions (within the time intervals defined in Section 5.9.1) and be expected to do so for the rest of the study.
14. Current and former smokers with smoking history of ≥10 pack years.
15. Capable of withdrawing from long acting bronchodilators (other than tiotropium) for the duration of the study, and short acting bronchodilators for 6 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, within 3 months of Screening or prior to the first treatment.
3. A history of one or more hospitalizations for COPD or pneumonia within 6 months of Screening or prior to the first treatment.
4. Intolerance or hypersensitivity to albuterol, tiotropium or other muscarinic receptor antagonists.
5. Other respiratory disorders: Patients with a current diagnosis of asthma, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, interstitial lung diseases, uncontrolled or unstable sleep apnea, known alpha-1 antitrypsin deficiency, core pulmonale, clinically significant pulmonary hypertension or other active pulmonary diseases.
6. Previous lung resection or lung reduction surgery.
7. Pulmonary rehabilitation, unless such treatment has been stable from 4 weeks prior to Screening and remains stable during the study.
8. Oral therapies for COPD (e.g. oral steroids, theophylline, and roflumilast) or antibiotics within 3 months prior to Screening, or ICS therapy within 4 weeks prior to Screening (additional prohibited medications, with shorter washout periods than those above, are shown in Table 3.)
9. Prior exposure to RPL554.
10. History of, or reason to believe a patient has, drug or alcohol abuse within the past 5 years.
11. Received an experimental drug within 30 days or five half-lives, whichever is longer.
12. Women who are pregnant or breast-feeding.
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 moderate to severe renal impairment.
14. Patients with historical or current evidence of clinically significant cardiovascular disease. Significant is defined as any disease that in the opinion of the investigator would put the safety of the subject at risk through participation or which could affect the efficacy or safety analysis if the disease/condition were to exacerbate during the study. In particular, the following are excluded:
    - Myocardial infarction or unstable angina within 6 months prior to Screening
    - Unstable or life threatening cardiac arrythmia requiring intervention within 3 months prior to Screening
    - Diagnosis of NYHA class III and IV heart disease
15. Use of non-selective oral β-blockers.
16. Major surgery (requiring general anesthesia) within 6 weeks prior to Screening, lack of full recovery from surgery at Screening, or planned surgery through the end of the study.
17. Required use of oxygen therapy, even on an occasional basis.

18. History of malignancy of any organ system within 5 years, with the exception of localized skin cancers (basal or squamous cell).
19. Clinically significant abnormal values for laboratory safety tests (hematology, blood chemistry, viral serology or urinalysis) at Screening, as determined by the Investigator (see Section 7.1.5). Please note the following:
    - Alanine aminotransferase or aspartate aminotransferase cannot be more than twice the upper limit of normal.
    - A positive test at Screening for HIV, and/or active hepatitis C infection (anti-HCV reactive), are also exclusionary.
    - The following apply to hepatitis B findings:
        - Patients who are positive for both HBsAg and anti-HBc are excluded, as this indicates acute or chronic infection.
        - Patients who are negative for HBsAg and anti-HBs but positive for anti-HBc are excluded, as this may indicate current or resolving infection
        - Patients who are positive for anti-HBc and anti-HBs but negative to HBsAg are not excluded, as this indicates immunity due to natural infection.
        - Patients who are positive for anti-HBs but negative for HBsAg and anti-HBc are not excluded, as this indicates immunity due to hepatitis B vaccination
20. Patients receiving immunotherapy (e.g., azathioprine, cyclophosphamide) whose effects could impact the PDE4 inhibition of RPL554.
21. Patients with conditions which are sensitive to antimuscarinic effects such as narrow angle glaucoma, urinary retention, prostatic hypertrophy, or bladder neck obstruction.
22. Current marijuana use (all forms).
23. A disclosed history or one known to the Investigator, of significant non-compliance in previous investigational studies or with prescribed medications.
24. Any other reason that the Investigator considers makes the patient unsuitable to participate.

4.3 Randomization Criteria (i.e. Additional Inclusion Criteria at Randomization)

1. Subjects must score ≥2 on the modified mMRC dyspnea scale at Visit 2.
2. Pre-dose FEV_1 ≥30 % and ≤70% of predicted normal at Visit 2.
3. E-diary compliance: Completion of the e-diary at least 5 of the last 7 days of the Run-in period.
4. Patient must be at least 75% compliant with once-daily open-label tiotropium (according to e-diary) during the Run-in period.
5. Patient must not have experienced a COPD exacerbation or lower respiratory tract infection between Visit 1 and Visit 2 (defined as use of any additional treatment other than current treatment and rescue medication and/or emergency department or hospital visit).

4.4 Removal of Patients from the Study

4.4.1 Screen Failures

All patients who provide informed consent but for whatever reason are not randomized will be considered a screen failure, and recorded as such in the Interactive Response Technology system (IRT).

The following information will be recorded in the IRT for screen failures:

- Date of Visit 0
- Date of Visit 1 and/or Visit 2 (depending on when the patient screen fails)
- Patient identification number
- Reason for screen failure

For all screen failures who experience an adverse event, and for those who perform at least one screening assessment at Visit 1, eCRFs will also be completed (the IRT system will provide a prompt for this purpose). The information to be recorded is as follows:

- Same information as entered into IRT (per above)
- Adverse events (if any)
- Demographic information including race, age and gender*
- COPD medications taken within 3 months prior to Visit 1*

*These items will only be collected for screen failures for whom at least one screening assessment is performed at Visit 1.

Patients will be stratified based on reversibility at Screening. Each stratum will be capped at 50% of total patients; therefore, when one of the reversibility strata is capped, additional patients meeting the criteria for that stratum will become ineligible for the study and will be considered screen failures.

Patients who screen fail may be considered for re-Screening upon consultation with the Medical Monitor. Re-Screening in the event of failure to meet lung function criteria will generally not be allowed unless extenuating circumstances exist. Repeat, rescheduled, and unscheduled visits and procedures are permitted at the discretion of the Investigator (rescheduled visits are subject to the ±1 day window mentioned above).

4.4.2 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

4.4.3 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 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 End of Study visit may be performed.

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

4.4.4 Study Discontinuation

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

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- The decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of RPL554
- Serious failure of the Investigator to comply with the International Council on Harmonization ICH) Guidelines on Good Clinical Practice (GCP) or local regulations
- Submission of knowingly false information from the research facility to the Sponsor, the institutional review board 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 institutional review board 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 institutional review board are notified.

4.4.5 Replacement Policy

It is planned to randomize approximately 400 patients; assuming a 10% early withdrawal rate, it is expected that approximately 360 patients will complete the study. Withdrawn patients may need to be replaced, depending on the actual discontinuation rate.

5 STUDY TREATMENTS

5.1 Study Treatments Administered

Patients will receive one of five possible different treatments as shown in Table 1, as determined by random assignment.

Table 1 Dose Levels and Concentrations of Study Medication

Substance	Dose Level (mg)	[redacted]
RPL554	0.375	
RPL554	0.75	
RPL554	1.5	
RPL554	3.0	
Placebo	N/A	
Abbreviations: N/A=not applicable		

5.2 Identity of Study Treatments

Note: For the purposes of this protocol, the term "study medication" refers to the nebulized, double-blind preparation of RPL554 or placebo, while "study treatment" refers collectively to both study medication and open label tiotropium.

5.2.1 Study Medication

The recommended International Non-proprietary Name (INN) for RPL554 is ensifentrine. The International Union of Pure and Applied Chemistry (IUPAC) name for RPL554 drug substance is N-[2-{(2E)-9,10-dimethoxy-4-oxo-2-[(2,4,6-trimethylphenyl)imino]-6,7-dihydro-2H-pyrimido[6,1-a]isoquinolin-3(4H)-yl]ethyl]urea. The composition of the RPL554 and placebo formulations is shown in Table 2.

Table 2 Composition of Study Medication

[redacted]	

The RPL554 suspension formulations and 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 actives are sterile, micronized suspensions with surfactants to aid suspension. The

placebo is the same as the active formulation, except that the active ingredient is omitted. The RPL554 active and placebo formulations are manufactured using aseptic manufacturing techniques in accordance with Good Manufacturing Practice (GMP) guidelines and will be provided to the sites as patient kits.

5.2.2 Tiotropium

Tiotropium is a commercially available LAMA that will be supplied by study centers in open label fashion. Each supply will provide 30 days of dosing; therefore, two will be required for the duration of the study and will be dispensed at Visits 1 and 2. Instructions for use are provided in Appendix 14.4.

5.3 Study Medication Preparation and Labelling

The vials and kits/cartons containing RPL554 and placebo will be labelled in compliance with GMP, released by a qualified person, where appropriate, and then shipped to the study center.

[redacted]

At Visits 2 to 5, patients will be dispensed 18 vials of study medication for twice daily dosing over 7 days (four vials provided as extras). For all visits, the first dose will be used for the in-clinic nebulization; for Visit 2 only the second dose will also be given in-clinic. The final dose administered in the morning at Visit 6 (final study visit) will be individually packaged. As such, the study medication administered in the clinic will always be stored only at the study center.

[redacted]

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 should be dosed in a well-ventilated environment, and away from other patients (i.e., in a separate location of the clinic).

For the in-clinic nebulizations, the following must be recorded in the eCRF:

- Start and end times of nebulization (times will be rounded down to the nearest minute)
- An estimation of the volume of residual product (in mL) at the end of nebulization

5.4 Selection of Doses and Dosing Schedule

5.4.1 Selection of Doses in the Study

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 up to 4 weeks of dosing in COPD patients. These twice daily doses were shown to be effective as a bronchodilator over a 12-hour dosing interval, and to provide improvement in COPD symptoms and, in general, considered safe and well tolerated.

5.4.2 Timing of Dose for Each Patient

Double-blind study medication is to be administered twice daily, first in the morning between 7 and 10 am, and then in the evening approximately 12 hours later. All doses for a given patient will be taken at approximately the same time each day (±1 hour). At each visit, study medication will be administered at the study center by unblinded personnel, and the precise time of administrations shall be documented in the eCRF.

Tiotropium will be administered once-daily in the morning at approximately the same time each day, just prior to dosing with study medication.

Patients will document whether each daily dose of all study treatments was taken in the e-diary.

5.5 Storage

Study medication (RPL554 and placebo) should be stored below 77°F (25°C) and should not be frozen. 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 medication 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.

Tiotropium is to be stored at room temperature 68°F to 77°F (20°C to 25°C).

5.6 Accountability

The Investigator will be responsible for the dispensing, inventory and accountability of all study treatments (i.e., double-blind study medication and open label tiotropium), 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, 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. Typically, study medication (including used vials) should be returned once final study medication accountability has been performed. If storage constraints require an earlier return of supplies, the study monitor should be contacted to make appropriate arrangements.

At the end of the study, the unused double-blind study medication vials will be returned to the Sponsor after accountability has been verified.

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 be stratified at randomization according to reversibility testing at Screening, such that all treatment groups will have approximately equal numbers of patients who are reversible to albuterol (≥12% and ≥200 mL increase in FEV_1) and those who are not. Each stratum will be capped at 50%. Within each stratum, patients will be equally randomized to one of the four doses or placebo before the first study medication administration at Visit 2. Medication identification numbers will be provided on the study medication kit.

5.8 Blinding

With the exception of specified unblinded site personnel (per next paragraph), the active formulations of RPL554 and placebo will be double-blind. The placebo is the same as the RPL554 active formulation, except that the active RPL554 ingredient is omitted [redacted] These unblinded individuals will 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 (except for designated individuals responsible for pharmacovigilance and clinical supplies), Investigator (defined as Principal Investigator and all study physicians), all patients and all other research personnel (except bioanalytical personnel performing the PK assays and the unblinded study center personnel) will, therefore, be blinded to the treatment allocation.

Note: Patients will also be aware of the appearance when pouring study medication into the nebulizer. Therefore, they should be instructed not to inform site personnel of the appearance of their study medication. Similarly, study personnel are not to discuss the appearance with patients. Patients will be instructed to seal the kit before returning it to the site at their next visit.

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

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 Visit 1 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.

Tiotropium use at a stable dose once daily will be administered during the Run-in and Treatment Periods, starting on the morning after Visit 1.

Upon providing informed consent, patients will discontinue COPD medications for the time periods described in Table 3 prior to the Screening visit and will remain off these medications for the duration of the study.

Table 3 Restrictions for COPD Medications Prior to Screening

Medication	Time Interval Prior to Screening Visit
Oral COPD therapies – e.g. oral steroids, theophylline, roflumilast (Oral mucolytics allowed)	3 months
Antibiotics	3 months
Terbutaline	1 day
Short-acting antimuscarinics (e.g., ipratropium)	1 day
Once or twice daily bronchodilators (LAMA, LABA or LAMA/LABA)	48 hours
Inhaled corticosteroids	4 weeks
Nebulized therapies (other than study medication)	1 week if a bronchodilator 4 weeks if an ICS
Abbreviations: COPD=chronic obstructive pulmonary disease; ICS=inhaed corticosteroids; LABA: long acting β2 agonist; LAMA=long acting muscarinic antagonist	

The following therapies are subject to restriction as indicated:

- Patients must continue to take their background tiotropium medication at the same dose and regimen throughout the Run-in and Treatment Periods. Starting or stopping tiotropium or changes in dosing is not allowed.
- Albuterol may be used as a rescue medication (see Section 5.10), but must be withheld for at least 6 hours prior to spirometry (per below), and this is to be confirmed in the spirometry system. 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:
  - 6 hours prior to pre-reversibility spirometry at Visit 1 for Screening
  - 6 hours prior to pre-dose spirometry for all subsequent visits
  - Until the completion of all spirometry assessments for all visits

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

- Pulmonary rehabilitation programs should not be started or completed during participation in the study, although an ongoing maintenance program is acceptable in accordance with Exclusion Criterion #7
- Oxygen therapy and non-selective oral β-blockers are Exclusion Criteria and are not to be used at any time during the study
- Oral mucolytics and ocular β-blockers are allowed

5.9.2 Other (non-COPD) Prior and Concomitant Medications

All concomitant medications must be documented on the eCRF, as well as any prior medications taken within 3 months of the Screening visit (Visit 1).

Patients may continue other prescribed non-respiratory therapies during the study that the Investigator considers to neither compromise patient safety nor affect study data. Such other prior prescription or non-prescription medications (medication, dose, route, treatment duration and indication) taken 3 months before Visit 1 must be recorded in order to confirm compliance with the Inclusion and Exclusion Criteria.

5.10 Rescue Medication

Albuterol is to be used for rescue use. Rescue medication will be sourced by the study center and dispensed at Visit 0. See Section 5.9.1 for withholding requirements prior to spirometry and rescheduled visit allowances.

Rescue albuterol use during each study visit, if required by the patient, must be separately documented by site staff on the eCRF (dose, route, and date and time of each administration). Rescue use between study visits will be documented by the patient daily in the e-diary (number of puffs).

5.11 Treatment after the End of Study

There are no plans to provide study medication for compassionate use following study completion.

At the end of the treatment period (Visit 6 or early termination), patients may resume conventional COPD therapy as prescribed by the investigator or other physician.

Medications initiated after Visit 6 should not be entered into the eCRF except for those given for a serious adverse event (SAE).

6 STUDY PROCEDURES AT EACH VISIT

The study will consist of seven visits:

- Pre-Screening (Visit 0), occurring between 2 and 28 days before Visit 1 (sufficient to allow for washout of prohibited medications)
- Screening (Visit 1), occurring 14 (±1) days prior to the first study treatment administration. Screening procedures ideally should occur over the course of a single day, but may be done over more than one day if necessary. All Screening procedures must be performed prior to initiation of the run-in (i.e., administration of open-label tiotropium)
- Five treatment visits (Visit 2 to Visit 6) each separated by 7 (±1) days

The schedule of assessments at each visit is shown in Table 4 and listed in Section 6.1 to Section 6.6. The study assessments are described in Section 7.

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

Table 4 Schedule of Assessments

Visit	Visit 0 Pre-Screen	Visit 1 Screening (Week -2 ±1 d)	Visit 2 Randomization	Visit 3 (Week 1 ±1 d)	Visit 4 (Week 2 ±1 d)	Visit 5 (Week 3 ±1 d)	Visit 6 End of Study (Week 4 ±1 d or ET)	Telephone Follow-up (1 week after Visit 6 ±2 d)
Informed consent	X							
Assign patient number	X							
Dispense albuterol[a]	X							
Prohibited medication washout	X							
Demographics		X						
Medical/surgical & disease history		X						
Inclusion/exclusion criteria		X	X					
Randomization criteria			X					
Prior/concomitant medications/therapies		X	X	X	X	X	X	
Physical examination		X					X	
Height and body weight		X					X[b]	
mMRC questionnaire		X	X					
12-lead ECG (QTcF and heart rate)		X	X[c]	X[c]			X[c]	
Vital signs (blood pressure, pulse)		X	X[d]	X[e]	X[e]	X[e]	X[d]	
Laboratory safety tests		X					X	
Urinalysis		X					X	
Viral serology		X						
Pregnancy test[f]		X	X				X	
Reversibility test		X						
Chest X-ray (if needed)		X						
Adverse event questioning		X	X	X	X	X	X	X
Slow spirometry (inspiratory capacity) - 30 min & +2 hours[g]			X				X	
Forced spirometry -30 min to +12 hours[h]			X				X	
Forced spirometry -30 min to +3 hours[i]				X	X	X		

Visit	Visit 0 Pre-Screen	Visit 1 Screening (Week -2 ±1 d)	Visit 2 Randomiza-tion	Visit 3 (Week 1 ±1 d)	Visit 4 (Week 2 ±1 d)	Visit 5 (Week 3 ±1 d)	Visit 6 End of Study (Week 4 ±1 d or ET)	Telephone Follow-up (1 week after Visit 6 ±2 d)
Dispense tiotropium		X	X					
Dispense symptom e-diary		X						
Review symptom e-diary			X	X	X	X	X	
SGRQ-C, BDI/TDI & CAT questionnaires			X		X		X	
Pre-dose PK blood sample[(j)]			X		X			
Randomization			X					
Administer study treatments (tiotropium & double-blind study medication)[(k)]			X[(0]	X	X	X	X	
Nebulization inhalation training			X					
Dispense study medication & nebulizer			X	X	X	X		
Dispense compressor			X					
Collect study medication & nebulizer				X	X	X	X	
Study treatment compliance (including tiotropium)			X	X	X	X	X	
Administer PGAC questionnaire					X		X	
Collect compressor							X	
Collect symptom e-diary							X	

Abbreviations: BDI/TDI=Baseline Dyspnea Index/Transition Dyspnea Index; CAT=COPD assessment test; d=days; ECG=electrocardiogram; ET=early termination; mins=minutes; mMRC=modified Medical Research Council; QTcF=QT interval corrected using Fridericia's formula; PGAC=Patient Global Assessment of Change; PK=pharmacokinetics; SGRQ-C=St George's Respiratory Questionnaire-COPD specific

(a) A second canister of albuterol may be dispensed during the study if necessary
(b) Body weight only at Visit 6
(c) ECG at Visits 2, 3 and 6 is performed pre-dose and 2 hours post-dose
(d) Vital signs at Visits 2 and 6 are measured pre-dose and 30 minutes, 1, 2, 4, 6, 8 and 12 hours post-dose
(e) Vital signs at Visits 3, 4 and 5 are measured pre-dose and 30 minutes, 1, 2 and 3 hours post-dose
(f) Serum pregnancy test at Visit 1; urine pregnancy test at Visits 1, 2 and 6
(g) Inspiratory capacity is performed via slow maneuver prior to forced efforts at Visits 2 and 6, 30 minutes pre-dose and 2 hours post-dose.
(h) Forced efforts at Visits 2 and 6 are performed 30 minutes pre-dose (after inspiratory capacity), followed by 30 minutes and 1, 2, 3, 4, 6, 8 and 12 hours post-dose
(i) Spirometry at Visits 3, 4 and 5 is performed 30 minutes pre-dose, followed by 30 minutes and 1, 2 and 3 hours post-dose

Visit	Visit 0 Pre-Screen	Visit 1 Screening (Week -2 ±1 d)	Visit 2 Randomiza-tion	Visit 3 (Week 1 ±1 d)	Visit 4 (Week 2 ±1 d)	Visit 5 (Week 3 ±1 d)	Visit 6 End of Study (Week 4 ±1 d or ET)	Telephone Follow-up (1 week after Visit 6 ±2 d)
(j) Pre-dose samples are for assay of tiotropium steady state exposure prior to and following 14 days of treatment with RPL554. PK samples from Visit 4 will also be used for assay pf RPL554 concentrations (k) Study medication is to be dosed following administration of tiotropium (l) At Visit 2, study medication is to be administered twice; first, just after randomization and again 12 hours later once all assessments are complete								

6.1 Pre-visit Restrictions

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

- Patients should refrain, where possible, from xanthine (chocolate, caffeine containing drinks and food), for at least 24 hours before and during visits. Decaffeinated beverages are permitted
- Patients should refrain from alcohol for 24 hours before and during visits (including visits for laboratory safety tests) and until all procedures for that study visit are completed
- Patients must fast (water permitted) from 2 hours pre-dose until 1 hour post-dose (does **not** apply to Visits 0 or 1)
- 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 visits and should undertake no unaccustomed strenuous exercise between visits

6.2 Visit 0 (Pre-screening)

The following will be performed at the Pre-screening visit:

- Obtain written informed consent (see Section 10.3)
- Assign patient identification number (see Section 5.7)
- Dispense rescue albuterol and instruct patient to wash out of prohibited medications
- Instruct patient to return 2 to 28 days later (as required for medication washout) for Visit 1

6.3 Visit 1 (Screening)

Patients will be screened to determine eligibility against the Inclusion and Exclusion Criteria 14 days before the first dose of study treatment. Patients must observe the medication restrictions described in Section 5.9.1, and other restrictions described in Section 6.1. To account for diurnal variability in pulmonary function, the Screening visit is to take place in the morning.

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

- Demographic information, height and body weight
- Medical/surgical and disease history, including assessment of chronic bronchitis (see Section 7.1.2)
- Prior medications and therapies
- mMRC questionnaire
- 12-lead ECG
- Vital signs
- Physical examination
- Pre-albuterol spirometry
- Reversibility test (four puffs of albuterol)
- Post-albuterol spirometry (20 to 30 minutes after administration)
- Urinalysis

- Blood samples for laboratory safety tests (hematology and blood chemistry), viral serology and serum pregnancy (the latter for women of childbearing potential)
- Urine pregnancy test (for women of childbearing potential). The result should be obtained prior to chest X-ray for females of childbearing potential
- Chest X-ray (unless historical X-ray performed in last 12 months is available)
- Questioning for adverse events

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

- Dispensing of tiotropium and instructions on its use
- Dispensing of e-diary and instructions on its use. The patient will log into the electronic device and answer all of the questions to ensure comprehension (see Section 7.2.2)

The patient will be instructed on the following:

- Instruct patient to return in 14 days for Visit 2
- Observe the medication restrictions described in Section 5.9.1, and other restrictions described in Section 6.1
- Contact the site for any significant increase in COPD symptoms

6.4 Treatment Period: Visit 2 (Randomization)

Patients must withhold all medications described in Section 5.9 prior to treatment in accordance with the washout times provided. If not, the visit must be rescheduled so as to occur within the permitted windows. All restrictions defined in Section 6.1 should also be adhered to.

6.4.1 Pre-dose Assessments

- The following assessments will be performed prior to dosing: Inclusion/Exclusion Criteria, including randomization criteria (see Section 4.1 to Section 4.3)
- Concomitant medications; confirm that medications were withheld as required
- Review of e-diary to confirm compliance with the device
- Assessment of tiotropium compliance
- mMRC questionnaire
- Questioning for adverse events
- Urine pregnancy test (females of childbearing potential only)
- 12-lead ECG
- Vital signs
- SGRQ-C, BDI and CAT questionnaires
- Blood sample for tiotropium PK measurement
- Slow spirometry (to obtain inspiratory capacity), performed 30 (±10) minutes pre-dose
- Forced spirometry, performed following completion of slow maneuver
- Inhalation training
- Administration of tiotropium

6.4.2 Study Medication Administration

Patients will be administered either RPL554 or placebo by the unblinded study staff member according to the randomization scheme, and again approximately 12 hours later upon completion of the assessments listed below.

Note: If possible, the unblinded study staff member should administer both doses at Visit 2, but if this cannot be arranged for the evening dose it may be done by a blinded staff member provided that he/she does not directly observe the patient pouring the suspension into the nebulizer.

6.4.3 Post-dose Assessments

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

- 12-lead ECG at 2 hours (±10 minutes)
- Vital signs at 30 minutes and 1, 2, 4, 6, 8 and 12 hours (±10 minutes)
- Spirometry: Forced efforts at 30 (±10) minutes and 1, 2, 3, 4, 6, 8 and 12 hours (the latter assessments all ±15 minutes). At 2 hours post-dose, a slow IC maneuver will precede the forced efforts
- Questioning for adverse events

Patients completing the visit will be dispensed a compressor, nebulizer, open label tiotropium and a box of double-blind study medication. They will demonstrate their ability to use the study medication and nebulizer by administering the evening dose while in the clinic that day. They will be instructed/reminded of the following:

- Take tiotropium followed by study medication each morning (other than the morning of the next visit), and study medication each evening
- Use of the e-diary
- Return in 7 days (± 1 day) for Visit 3
- Observe the medication restrictions described in Section 5.9.1, and other restrictions described in Section 6.1
- Contact the site for any significant increase in COPD symptoms

6.5 Treatment Period: Visits 3 through 5 (Interim Treatment Visits)

Patients will return for study visits at 1, 2 and 3 weeks post-randomization. The visits shall be scheduled to begin in the morning, such that dosing occurs within 1 hour of the time of administration at Visit 2.

Patients must withhold all medications described in Section 5.9 prior to treatment in accordance with the washout times provided. If not, the visit must be rescheduled so as to occur within the permitted windows. All restrictions defined in Section 6.1 should also be adhered to.

6.5.1 Pre-dose Assessments

The following assessments will be performed prior to dosing:

- Concomitant medications; confirm that medications were withheld as required
- Unblinded study staff will collect nebulizer and any used/unused study medication

- Review compliance with study treatments (study medication and tiotropium), and nebulizer technique and maintenance
- Review of e-diary to confirm compliance with the device
- Assessment of tiotropium and study medication compliance
- Questioning for adverse events
- Visit 3 only: 12-lead ECG
- Vital signs
- Visit 4 only: PK measurement (tiotropium and RPL554)
- Visit 4 only: SGRQ-C, TDI, CAT and PGAC questionnaires
- Spirometry at 30 (± 10) minutes pre-dose (forced efforts only)
- Administration of tiotropium

6.5.2 Study Medication Administration

Patients will be administered either RPL554 or placebo by the unblinded study staff member according to the randomization scheme.

6.5.3 Post-dose Assessments

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

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

Patients completing the visit will be dispensed a new nebulizer and box of study medication, and will be instructed/reminded of the following:

- Use of the e-diary
- Withhold use of all long acting (once or twice daily) bronchodilators (except for tiotropium)
- Return in 7 days (± 1 day) for the next visit
- Observe the medication restrictions described in Section 5.9.1, and other restrictions described in Section 6.1
- Contact the site for any significant increase in COPD symptoms

6.6 Treatment Period: Visit 6 (End of Study [or Early Termination])

Patients will return for the final visit 4 weeks post-randomization. The visit shall be scheduled to begin in the morning, such that dosing occurs within 1 hour of the time of administration at Visit 2.

Patients must withhold all medications described in Section 5.9 prior to treatment in accordance with the washout times provided. If not, the visit must be rescheduled so as to occur within the permitted windows. All restrictions defined in Section 6.1 should also be adhered to.

6.6.1 Pre-dose Assessments

The following assessments will be performed prior to dosing:

- Concomitant medications; confirm that medications were withheld as required

- Unblinded study staff will collect nebulizer, compressor and any used/unused study medication
- Collect e-diary and review for compliance with the device
- Assessment of tiotropium and study medication compliance
- Questioning for adverse events
- Physical examination and body weight
- Blood samples for laboratory safety tests
- Urinalysis
- Urine pregnancy test (females of childbearing potential only)
- 12-lead ECG
- Vital signs
- SGRQ-C, TDI, CAT and PGAC questionnaires
- Slow spirometry (to obtain inspiratory capacity), performed 30 (± 10) minutes pre-dose
- Forced spirometry, performed following completion of slow maneuver
- Administration of tiotropium

6.6.2 Study Medication Administration

Patients (other than for whom this is an Early Termination visit) will be administered either RPL554 or placebo by the unblinded study staff member according to the randomization scheme. Study medication for Visit 6 is packaged separately, and is maintained on site throughout the patient's participation in the study.

6.6.3 Post-dose Assessments

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

- 12-lead ECG at 2 hours (±10 minutes)
- Vital signs at 30 minutes and 1, 2, 4, 6, 8 and 12 hours (±10 minutes)
- Spirometry: Forced efforts at 30 (±10) minutes and 1, 2, 3, 4, 6, 8 and 12 hours (the latter assessments all ±15 minutes). At 2 hours post-dose, a slow IC maneuver will precede the forced efforts
- Questioning for adverse events
- Scheduling of telephone follow-up, 1 week (±2 days) after Visit 6 to review adverse events

7 STUDY METHODOLOGY

7.1 Demographics, Baseline Characteristics and Eligibility Assessments

Safety assessments (pregnancy testing, laboratory safety assessments [hematology, blood chemistry and urinalysis], vital signs, 12-lead ECG and physical examination) will be performed at Screening as part of the eligibility assessment as described in Section 7.4.

7.1.1 Demographic Variables

Demographic variables, including date of birth, sex, height, 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. COPD disease history, including date of diagnosis will also be recorded. In addition, the patient will be assessed for the presence of chronic bronchitis, which is defined as follows: productive cough and sputum production on most days for three months in each of two consecutive years (Pauwels et al, 2001).

7.1.3 Reversibility Test

Reversibility in response to albuterol will be assessed at Screening as an eligibility measure. Spirometry (FEV_1 and FVC) assessment before and after four puffs (400 µg) of albuterol, administered using a pMDI, will be performed. Pre- and post-reversibility spirometry will be performed in accordance with the information in Section 7.2.1.

7.1.4 Modified Medical Research Council (mMRC) Questionnaire

The mMRC will be completed by patients at Visit 1, in accordance with Inclusion Criterion 11 in Section 4.1. It uses a simple grading system to assess a patient's level of breathlessness. It relates well to other health status measures and predicts future mortality risk (Pocket Guide to COPD Diagnosis, Management and Prevention, 2018).

7.1.5 Screening Laboratory Assessments and Chest X-ray

Blood samples will be taken and analyzed for viral serology (human immunodeficiency virus, hepatitis B and hepatitis C serology) as well as thyroid stimulating hormone (TSH), triiodothyronine and thyroxine at Screening only.

All female patients of childbearing potential will have a serum pregnancy test at Screening. Follicle-stimulating hormone (FSH) will be measured at Screening, where appropriate, to confirm post-menopausal status.

Samples will be taken and handled according to the manual provided by the central laboratory.

Safety laboratory assessments at Screening will be performed in accordance with the information in Section 7.4.3.

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

7.1.6 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.

7.2 Efficacy/Pharmacodynamic Assessments

7.2.1 Pulmonary Function Tests

Forced spirometry maneuvers (FEV_1 and FVC) will be performed at all study visits, and slow IC maneuvers will be performed at Visits 2 and 6, in accordance with the information in Section 6. These should be conducted as separate maneuvers and should not be linked (i.e. slow maneuver leading directly into a fast effort).

Post-dose measurements will be taken in relation to the morning dose of RPL554 or placebo. As noted in Section 5.3, all post-dose measurements will be relative to the end time of nebulization (sputtering).

Spirometry assessments will be made in accordance with ATS/ERS guidelines (Miller et al, 2005). At all time points, 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.

Inspiratory capacity (IC) is an indirect assessment of resting lung hyperinflation. IC maneuvers will be conducted according to ATS/ERS guidelines (Miller et al, 2005). At all time points where IC is collected, it will be performed prior to the forced maneuvers. Three technically acceptable measurements should be made and recorded. The average of at least three acceptable maneuvers will be reported. Patients should be asked to breathe regularly for several breaths (typically at least three tidal maneuvers) until end expiratory lung volume is stable, then urged to take a deep breath to total lung capacity with no hesitation.

Spirometry will be performed using equipment provided by the Sponsor and reviewed centrally, and sites will be instructed in proper use of the equipment prior to study initiation.

7.2.2 Electronic Diary

At Visit 1 an e-diary will be dispensed to the patients continuing in the study, who will use it twice daily in the morning and at bedtime. In addition to assessing use of tiotriopium, study medication and rescue use, the e-diary will collect symptom and activity information.

In the morning, patients will be prompted to answer the following questions:

- **Please rate your overall COPD symptom severity** in the early morning before your first dose of any COPD treatment. COPD symptoms include any of the following: cough,

wheezing, shortness of breath, tightness in chest, chest congestion, difficulty bringing up phlegm.
  - Rate your symptoms on a scale of 0 to 4: 0= no symptoms and 4= very severe symptoms

- **Please rate your early morning activity limitation** due to COPD symptoms before your first dose of any COPD medication.
  - Rate your ability to perform your daily activities in the morning upon awakening such as showering, making breakfast, dressing, etc.) on a scale of 0 to 4: 0= I do not have any difficulty in performing) to 4= I have great difficulty in performing.

In the evening, symptoms will be assessed using the E-RS™:COPD scale (EXACT-PRO® Initiative website, 2018). E-RS™:COPD uses the 11 respiratory symptom questions in the EXACT-PRO® instrument. Three subscales are used to assess breathlessness, cough/sputum and chest symptoms. The E-RS™:COPD has a scoring range of 0 to 40.

At Screening (Visit 1), study staff will train the patients on use of the e-diary as follows:

- Have patients log into the device using a password and read and answer all of the 14 questions to ensure comprehension
- Instruct patients to reflect on their day and answer the questions based on how they felt over the day
- Remind patients there are no right or wrong answers
- Remind patients that all 14 items are to be answered daily

7.2.3 St. George's Respiratory Questionnaire – COPD specific (SGRQ-C)

Patients will be asked to complete the SGRQ-C while they are at the study site at Visits 2, 4 and 6. The SRGQ-C is designed to measure impact on overall health, daily life, and perceived well-being in patients with COPD (Meguro et al, 2007). It is a revised version of the original SGRQ (Jones et al, 1991) in that it is intended only for COPD patients, is shorter in length and does not specify a recall period.

The study staff should explain to patients why they are completing it and ask them to complete it as honestly as possible, stressing that there are no right or wrong answers. It is important that the questionnaire is completed in a quiet area by patients on their own, and that a member of the study staff is available to give advice if required. It is appropriate to clarify a question, but not to provide an answer on behalf of the patient. It is designed to elicit the opinion of the patient, not someone else's; consequently, any family members or friends present should not influence the responses. Once the patient has completed the SRGQ-C it is important that a member of the study team check that a response has been given for every question and if this is not the case, that it is returned to the patient for completion.

7.2.4 Baseline and Transition Dyspnea Indexes (BDI and TDI)

The BDI will be performed at Visit 2 and the TDI at Visits 4 and 6. These questionnaires are interviewer administered ratings of dyspnea severity. It is based on three components that evoke dyspnea in activities of daily living. The BDI is scored from 0 to 12 and is only assessed at baseline. The lower the score the worse the dyspnea severity. The TDI measures the change in dyspnea

severity from the baseline as measured by the BDI. It is rated by seven grades ranging from -3 (major deterioration) to +3 (major improvement) (Mahler et al, 1984).

7.2.5 COPD Assessment Test (CAT)

Patients will complete the CAT at the same visits as the SGRQ. Given that the impact of COPD on patients goes beyond dyspnea, the CAT was developed as a more comprehensive assessment of symptoms (Pocket Guide to COPD Diagnosis, Management and Prevention, 2018).

Similar guidelines as indicated in Section 7.2.3 above apply to the CAT as well.

7.2.6 Patient Global Assessment of Change (PGAC)

At Visits 4 and 6, patients will be asked to respond to a PGAC question asking, "Compared with prior to the study start, how do you feel your breathing is?" on a scale of '1=much worse' to '5=much better', with '3=no change'.

7.2.7 Diary Compliance

Site staff will review compliance with e-diary entries at study visits. Patients who not at least 75% compliant should be re-educated on the importance of completing their e-diary twice daily; such non-compliance will be recorded as a deviation.

7.2.8 Tiotropium and Study Medication Compliance

Patients will return their tiotropium and study medication at each treatment visit. Patients who are not at least 75% compliant with study treatment administration should be re-educated on the importance of taking these study treatments as specified in the protocol; such non-compliance will be recorded as a protocol deviation.

7.3 Pharmacokinetic Assessments

Determination of plasma concentrations of tiotropium will be performed on blood samples taken pre-dose at Visit 2, and concentrations of tiotropium and RPL554 will be performed at Visit 4.

Blood samples of 4 mL will be collected by venipuncture in the forearm vein using a Vacuette® Blood Collection System into a lithium heparin tube and then into a K2 ethylenediaminetetraacetic acid (EDTA) tube. Once mixed by inversion, the samples will be promptly chilled in an 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 appropriately labelled screw capped polypropylene tubes. After each blood collection, the plasma will be dispensed into two aliquots for each analyte. 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. Additional handling and shipment instructions will be provided in the laboratory manual.

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.

Since (per Section 3.4) the follow-up phone call is defined as the End of Study, all adverse events occurring from the time of informed consent until the follow-up phone call are to be reported in the eCRF.

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 important 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 telephone follow-up. 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 medication must also be reported.

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

SAEs will be reported to the 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

Urine pregnancy tests will also be performed by the study center at Screening (confirmed to be negative prior to the chest X-ray) and pre-dose at Visits 2 and 6.

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

Samples will be taken and handled according to the manual provided by the central laboratory.

7.4.3.1 Hematology

The following will be measured: hemoglobin, hematocrit, total white cell count, leukocyte differential count and platelet count.

At each time point, a sample of venous blood will be collected in a collection tube containing EDTA.

7.4.3.2 Blood Chemistry

The following will be measured: creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine transaminase, gamma-glutamyl transferase, lactate dehydrogenase, creatine kinase, TSH, triiodothyronine, thyroxine, glucose, potassium, sodium and calcium. These assessments will be performed at the same times as for hematology. **Note:** TSH, triiodothyronine and thyroxine will be analyzed for samples obtained at Visit 1 only, to assess for hyperthyroidism, in accordance with Exclusion Criterion 10 and Section 7.1.5.

At each time point, 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 the same time points as hematology and blood chemistry. The following will be tested: leukocytes, blood, ketones, bilirubin, urobilinogen, protein and glucose. If urinalysis on Dipstick is positive for leukocytes and/or blood/hemoglobin, a microscopic examination including erythrocytes, leukocytes, bacteria, casts, epithelial cells and crystals will be performed.

7.4.4 Vital Signs

Blood pressure and pulse rate will be measured at each study visit in accordance with the information provided in Section 6. Post-dose measurements will be taken in relation to the morning dose of RPL554 or placebo.

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

7.4.5 Physical Examination

A full physical examination, covering major body systems (assessments of the nose, throat, skin, thyroid gland, neurological system, respiratory system, cardiovascular system, abdomen [liver and spleen], lymph nodes and extremities) will be performed at Screening (Visit 1) and End of Study (Visit 6). Results will be recorded in the eCRF as normal, abnormal not clinically significant or abnormal clinically significant and abnormal results described..

7.4.6 12-Lead ECG

12-lead ECGs will be performed at Visits 1, 2, 3 and 6 in accordance with the information provided in Section 6.

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. The ECGs will be centrally collected and analyzed.

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 institutional review board, 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, 12-lead ECG and PK 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. Prior and concomitant medications will be coded according to the World Health Organization 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 prior to database lock 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 (FAS) will consist of all randomized patients with sufficient data collected after intake of study treatment to compute the pharmacodynamic parameters based on FEV_1 on at least one occasion.

The per-protocol set (PPS) will consist of all patients in FAS without any major protocol deviations considered to influence the treatment effect of RPL554.

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

The PK data set will consist of all randomized patients with blood sampling performed and a quantitative value of tiotropium and/or RPL554 concentration determined.

9.3 Study Endpoints

9.3.1 Primary Endpoint

The primary endpoint is the change from baseline in peak FEV_1 (maximum value during 3 hours following dose) at Visit 6 (after 4 weeks of treatment).

9.3.2 Secondary Endpoints

- Change from baseline in average $AUC_{0\text{-}3h}$ FEV_1 at Visits 2 to 6
- Change from baseline in average $AUC_{0\text{-}12h}$ FEV_1 at Visits 2 and 6
- Change from baseline in peak FEV_1 at Visits 2 to 5
- Change from baseline in morning trough FEV_1 at Visits 3 to 6
- Change from baseline (i.e., mean over the last 7 days of Run-in) to the mean weekly values over weeks 1 to 4 in COPD symptoms, as measured by daily e-diary (E-RS™:COPD)
- Change from baseline in the SGRQ-C questionnaire at Visits 4 and 6
- TDI questionnaire at Visits 4 and 6
- PGAC questionnaire at Visits 4 and 6
- Change from baseline (i.e., mean over the last 7 days of Run-in) to the mean weekly values over weeks 1 to 4 in rescue medication use
- Change from baseline in peak and average $AUC_{0\text{-}3h}$ FVC at Visits 2 to 6, in average $AUC_{0\text{-}12h}$ FVC at Visits 2 and 6 and in morning trough FVC at Visits 3 to 6.

- Trough plasma concentration of tiotropium at Visits 2 and 4, and trough plasma concentration of RPL554 at Visit 4
- Safety and tolerability:
  - Continuous monitoring of adverse events
  - Laboratory safety tests (hematology, blood chemistry and urinalysis)
  - 12-lead ECG (including QTcF and heart rate), supine vital signs (blood pressure and pulse rate)

9.3.3 Exploratory Endpoints

- Change in peak and average $AUC_{0\text{-}12h}$ FEV_1 between Visits 2 and 6
- Change from baseline in IC after 4 weeks of treatment
- Change from baseline in the CAT questionnaire at Visits 4 and 6
- Change from baseline (i.e., mean over the last 7 days of Run-in) to the mean weekly values over weeks 1 to 4 in morning symptoms
- Change from baseline (i.e., mean over the last 7 days of Run-in) to the mean weekly values over weeks 1 to 4 in morning activity limitation

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 prior COPD medications by therapeutic class including ICS, LABA, LAMA or combinations thereof) will be listed and summarized appropriately.

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

9.4.4 Extent of Exposure and Treatment Compliance

Compliance will be calculated based on two parameters – the number of used and unused vials returned and the dosing recorded in the e-diary. Total exposure will be based on the compliance with dose and the dose group the subject was randomized into. For in-clinic dosing, the RPL554 exposure will be calculated based on the nominal dose.

9.4.5 Efficacy/Pharmacodynamics

The FAS will be the primary efficacy population; outcomes based on the PPS will be considered as a sensitivity analysis.

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

The peak effect on FEV_1 will be computed as the maximum value in the 3 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 included as the change from the pre-dose Day 1 baseline value.

Computed pharmacodynamic parameters based on FEV_1 will be compared between the treatments using a mixed model for repeated measures (MMRM) with fixed effects for treatment, visit and treatment by visit interaction, baseline as covariate, patient as random and covariance structure by visit.

RPL554 treatments will be compared to placebo using a closed testing procedure. The highest dose (3 mg) will first be compared to placebo, and if found statistically significant then the next dose (1.5 mg) will be compared to placebo, and so on. Secondarily, doses will be compared pairwise. Results of the comparisons will be expressed as the mean effect difference with 95% confidence intervals and associated, 2-sided, p-value.

Pharmacodynamic parameters based on FVC, average daily use of rescue medication, average weekly E-RS™:COPD means, SGRQ-C, TDI, CAT and PGAC scores will be compared between the treatments using similar MMRM models as for the primary variable. Subdomain scores of the E-RS™:COPD, SGRQ-C and weekly morning symptoms and activity limitation will be summarized and subjected to exploratory analyses.

The number of COPD exacerbations will be summarized by treatment group.

As a sensitivity analysis the primary endpoint (peak FEV_1 at Visit 6), the average $AUC_{0\text{-}12h}$ FEV_1 at Visit 6 and the total E-RS™:COPD score at week 4 will also be compared using analysis of covariance (ANCOVA) models with fixed factors for treatment, reversibility strata and the pre-dose baseline value as a covariate.

9.4.6 Pharmacokinetics

Plasma concentrations of tiotropium and RPL554 will be summarized by dose level using descriptive statistics (n, geometric mean, coefficient of variation, arithmetic mean, standard deviation, minimum, maximum and median).

9.4.7 Safety

Safety data including laboratory safety tests, 12-lead ECG, vital signs and physical examinations, will be summarized by treatment group and time point of collection, when appropriate, for each of the two parts separately. For continuous variables, the change from baseline (pre-dose at Visit 2) 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 for each part. Summary tables by treatment group with total number and number of patients with adverse events, SAEs, adverse events leading to discontinuation of study treatment, causally related adverse events and severe adverse events will be produced. Further SAEs, causally related adverse events and adverse events of each intensity will be summarized by SOC and preferred term.

9.4.8 Handling of Withdrawals or Missing Data

Imputation of data for calculation of average (AUC) effects for FEV_1 and FVC will be described in the statistical analysis plan. No other imputation of missing data will be performed for the parameter computations. For the sensitivity ANCOVA analyses, missing data will be imputed using the last observation carried forward method prior to analysis.

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.

9.4.9 Interim Analyses

No formal, unblinded interim analysis is planned for the study. To assess the plausibility of the assumptions in the sample size calculation, an estimate of the standard deviation of peak and $AUC_{0\text{-}3h}$ FEV_1 will be made based on blinded data after completion of 125 patients. If the estimated standard deviations are markedly higher than the 200 mL assumed (>20%), a revised sample size estimation using the new standard and the previously used detectable difference (89) will be made. If the outcome is an increase of the sample size, an amendment will be submitted for approval.

9.5 Determination of Sample Size

The standard deviation for peak FEV_1 is estimated to be 200 mL. With a 2-sided test at a 5% significance level and 73 evaluable patients per group, there will be 80% power to detect a true difference of 93 mL between any two treatments. This detectable limit has been considered sufficient to identify an effective dose of RPL554. Assuming a 10% early withdrawal rate, 80 patients per group will be randomized.

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 Institutional Review Board and Regulatory Approval

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

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

10.3 Informed Consent Process

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

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

11 FINANCE AND INSURANCE

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

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

12 PUBLICATION POLICY

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

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14 APPENDICES

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

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

I. Definitions

Woman of Childbearing Potential
A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent 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 (estrogen 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] Vasectomized 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 12-lead ECG Requirement for Inclusion

The ECG obtained at Screening must be free from any of the following abnormalities:

- Sinus tachycardia ≥110bpm (Sinus tachycardia ≥110bpm should be confirmed by 2 additional readings at least 5 minutes apart.)
- Sinus bradycardia < 45bpm (Sinus bradycardia < 45bpm should be confirmed by 2 additional readings at least 5 minutes apart)
- Multifocal atrial tachycardia
- Junctional (heart rate > 100bpm)
- Junctional escape complexes
- Supraventricular tachycardia (> 100bpm)
- Ventricular tachycardia
- Atrial fibrillation with rapid ventricular response (rate > 100bpm)
- Atrial flutter
- Bigeminy, trigeminy or multifocal premature ventricular complexes
- Ventricular flutter
- Ventricular fibrillation
- Torsades de Pointes
- R on T phenomenon
- Wide QRS tachycardia (diagnosis unknown)
- Electrical alternans
- Pacemaker
- Idioventricular rhythm – heart rate < 100bpm
- Mobitz type II second degree or third degree atrioventricular (AV) block
- AV dissociation
- Bifascicular Block

- Trifascicular Block
- Left bundle branch block
- Subjects without complete right bundle branch block: QTc(F) ≥ 450msec or an ECG that is unsuitable for QT measurements (e.g. poorly defined termination of the T wave)

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.

14.4 Tiotropium Prescribing Highlights and Instructions for Use

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

https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Spiriva%20Respimat/spirivarespimat.pdf#page=15

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

SPIRIVA® RESPIMAT® (tiotropium bromide) inhalation spray, for oral inhalation
Initial U.S. Approval: 2004

----------INDICATIONS AND USAGE----------
SPIRIVA RESPIMAT is an anticholinergic indicated for:
- The long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations (1.1)
- The long-term, once-daily, maintenance treatment of asthma in patients 6 years of age and older (1.2)

Limitation of Use:
- Not indicated for relief of acute bronchospasm (1.1, 1.2, 5.1)

----------DOSAGE AND ADMINISTRATION----------
For oral inhalation only
To receive the full dose of medication, SPIRIVA RESPIMAT must be administered as two inhalations once-daily.
- Treatment of COPD: 2 inhalations of SPIRIVA RESPIMAT 2.5 mcg once-daily (2)
- Treatment of asthma patients 6 years and older: 2 inhalations of SPIRIVA RESPIMAT 1.25 mcg once-daily (2)

----------DOSAGE FORMS AND STRENGTHS----------
- Inhalation spray: 1.25 mcg or 2.5 mcg tiotropium per actuation with the SPIRIVA RESPIMAT inhaler. Two actuations equal one dose (2.5 mcg or 5 mcg). (3)

----------CONTRAINDICATIONS----------
Hypersensitivity to tiotropium, ipratropium, or any component of this product (4)

----------WARNINGS AND PRECAUTIONS----------
- Not for acute use, i.e., not a rescue medication (5.1)
- Immediate hypersensitivity reactions: Discontinue SPIRIVA RESPIMAT at once and consider alternatives if immediate hypersensitivity reactions, including angioedema, urticaria, rash, bronchospasm, or anaphylaxis, occur. (5.2)
- Paradoxical bronchospasm: Discontinue SPIRIVA RESPIMAT and consider other treatments if paradoxical bronchospasm occurs. (5.3)
- 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. (5.4)
- Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patient to consult a physician immediately if this occurs. (5.5)

----------ADVERSE REACTIONS----------
The most common adverse reactions in:
- COPD: (>3% incidence in the placebo-controlled trials with treatment durations of between 4 and 48 weeks) were pharyngitis, cough, dry mouth, and sinusitis (6.1).
- Asthma: (>2% incidence in the placebo-controlled trials with treatment durations of between 12 and 52 weeks) were pharyngitis, headache, bronchitis, and sinusitis in adults (6.2).

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----------
Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administration of SPIRIVA RESPIMAT with other anticholinergic-containing drugs. (7.2)

----------USE IN SPECIFIC POPULATIONS----------
Patients with moderate to severe renal impairment should be monitored closely for potential anticholinergic side effects. (2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2019

Instructions for Use

SPIRIVA® RESPIMAT® (speh REE vah - RES peh mat) (tiotropium bromide)

inhalation spray, for oral inhalation

For oral inhalation only

Do not spray SPIRIVA RESPIMAT into your eyes.

Read this Instructions for Use before you start using SPIRIVA 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 1 time each day, at the same time each day. Each time you use it take 2 puffs.

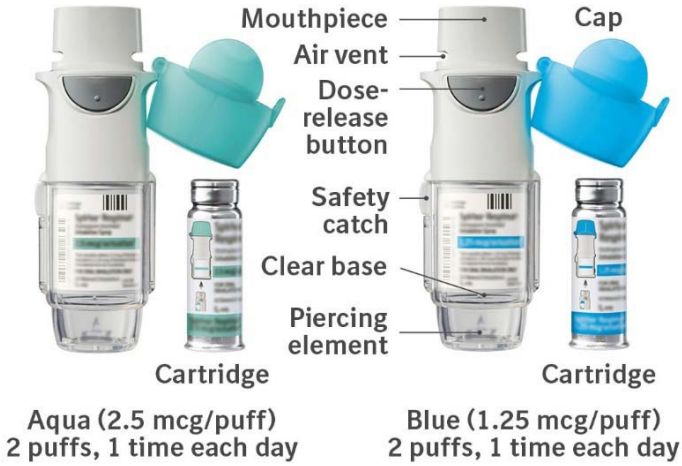
Use SPIRIVA RESPIMAT exactly as prescribed by your doctor. Do not change your dose or how often you use SPIRIVA RESPIMAT without talking with your doctor. Children should use SPIRIVA RESPIMAT with the help of an adult, as instructed by their doctor.

Tell your doctor about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. SPIRIVA RESPIMAT may affect the way some medicines work and some other medicines may affect the way SPIRIVA RESPIMAT works. Do not use other inhaled medicines with SPIRIVA RESPIMAT without talking to your doctor.

The SPIRIVA RESPIMAT inhaler has a slow moving mist that helps you inhale the medicine.

Do not turn the clear base before inserting the cartridge.

Your SPIRIVA RESPIMAT may have either an aqua or a blue cap, depending on the strength prescribed by your doctor. The steps shown below should be followed.



How to store your SPIRIVA RESPIMAT inhaler

- Store SPIRIVA RESPIMAT at room temperature between 68°F to 77°F (20°C to 25°C).
- **Do not** freeze your SPIRIVA RESPIMAT cartridge and inhaler.
- If SPIRIVA RESPIMAT has not been used for more than 3 days, release 1 puff towards the ground.
- If SPIRIVA 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 SPIRIVA RESPIMAT cartridge, inhaler, and all medicines out of the reach of children.**

How to care for your SPIRIVA RESPIMAT inhaler

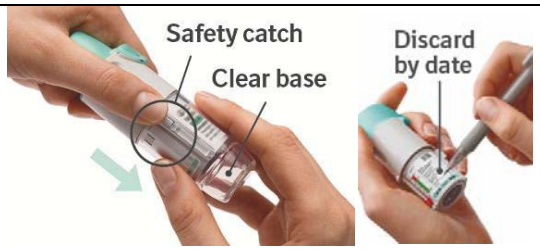
Clean the mouthpiece, including the metal part inside the mouthpiece, with a damp cloth or tissue only, at least 1 time each week. Any minor discoloration in the mouthpiece does not affect your SPIRIVA RESPIMAT inhaler.

When to get a new SPIRIVA RESPIMAT inhaler

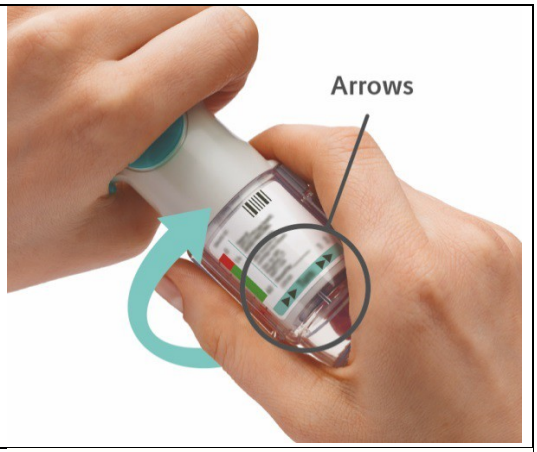
- The scale on your inhaler shows the number of puffs in the inhaler. You should use 2 puffs 1 time eachday.
- The dose indicator shows approximately how many puffs are left in the inhaler.
- When the dose indicator enters the red area of the scale you need to refill your prescription as soon as possible.
- When the dose indicator reaches the end of the red scale, your SPIRIVA 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 SPIRIVA 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 firmsurface 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 moretimes.** • **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 **Turn, Open, Press (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 SPIRIVA RESPIMAT pointing to 0 (zero)? The SPIRIVA RESPIMAT inhaler is locked after the labeled number of puffs have been used. Prepare and use your new SPIRIVA 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 SPIRIVA RESPIMAT pointing to 0 (zero)? The SPIRIVA RESPIMAT inhaler is locked after the labeled number of puffs have been used. Prepare and use your new SPIRIVA RESPIMAT inhaler.

THE DOSE INDICATOR ON THE SPIRIVA RESPIMAT REACHES 0 (ZERO) TOO SOON: DID YOU USE SPIRIVA RESPIMAT AS INDICATED (2 PUFFS 1 TIME EACH DAY)?

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 SPIRIVA RESPIMAT is working? After you have prepared SPIRIVA RESPIMAT, no test-spraying is required if used daily.

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

MY SPIRIVA 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 SPIRIVA RESPIMAT DOES NOT SPRAY:

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

Did you repeat Turn, Open, Press (TOP) less than 3 times after inserting the cartridge? Repeat Turn, Open, Press (TOP) 3 times after inserting the cartridge as shown in steps 4 to 6 under "Prepare for first use".

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

For more information about SPIRIVA RESPIMAT, including current prescribing information, or a video demonstration on how to use SPIRIVA RESPIMAT, go to www.spiriva.com, or scan the code below. You may also call 1-800-542-6257 or (TTY) 1-800-459-9906 for further information about SPIRIVA RESPIMAT.

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