



Verona Pharma

CLINICAL STUDY PROTOCOL

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

STUDY NO. RPL554-CO-202

Version: 2.0
Date: 26 April 2017
Phase: II
Investigational Medicinal Product: RPL554
EudraCT Number: 2016-004450-15

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

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Name and Title	Signature	Date
Kenneth Newman MD, MBA Chief Medical Officer		

INVESTIGATOR SIGNATURE PAGE

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

Name and Title	Signature	Date

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DETAIL OF AMENDMENTS SINCE THE PREVIOUS VERSION

Section 4.2: Exclusion Criterion no. 6 has been amended to remove the prohibition against prior exposure to RPL554.

SYNOPSIS

Title of Study:	A Phase II, randomised, double blind, placebo controlled, three way crossover study to assess the bronchodilator effect of RPL554 administered in addition to open label tiotropium in patients with COPD.
Protocol Number:	RPL554-CO-202
EudraCT Number:	2016-004450-15
Phase:	II
Sponsor:	Verona Pharma plc
Principal Investigator:	Prof S Dave Singh
Study Centre(s):	Medicines Evaluation Unit Ltd The Langley Building Southmoor Road Manchester, M23 9QZ United Kingdom (UK)
Planned Study Period:	Estimated: January to April 2017
Objectives:	<p>Primary Objective</p> <p>To investigate the bronchodilator effect on peak forced expired volume in 1 second (FEV₁) (measured in first 4 hours after dosing) and average (measured as the area under the curve [AUC]) FEV₁ over 12 hours of nebulised RPL554 dosed twice daily for 3 days (five total doses), as compared to placebo, when administered in addition to once daily tiotropium.</p> <p>Secondary Objectives</p> <ul style="list-style-type: none"> • To investigate the effect of twice daily nebulised doses of RPL554, as compared to placebo, when administered in addition to tiotropium on lung volumes • To assess the bronchodilator effect on peak FEV₁ (measured in the first 4 hours after dosing) and average (measured as the area under the curve [AUC]) FEV₁ over 12 hours of nebulised RPL554 after the first dose as compared to placebo, when administered in addition to tiotropium • To analyse plasma concentrations and assess the steady state pharmacokinetics of RPL554 when administered in addition to tiotropium • To assess the tolerability and safety of twice daily nebulised doses of RPL554 in addition to tiotropium • To assess the dose response of two different doses of RPL554 on peak, average (0 to 12 hours), and morning trough FEV₁ on Day 3 when dosed in addition to tiotropium • To determine the onset of action of RPL554 when administered with tiotropium (after the first dose) • To investigate the bronchodilator effect of nebulised RPL554, or placebo, administered in addition to tiotropium on average FEV₁ over 4 hours after each morning dose • To investigate the effects of RPL554 on specific airway conductance (sGaw) and lung volumes (residual volume [RV], functional residual capacity [FRC]) when administered in addition to tiotropium. <p>Exploratory Objectives</p> <ul style="list-style-type: none"> • To examine the effect of RPL554 on top of tiotropium on average FEV₁ over 24 hours after 3 days of dosing • To assess morning trough FEV₁ prior to the final dose of study treatment

<p>Study Design and Methodology:</p>	<p>This is a Phase II, randomised, double blind, placebo controlled, complete block three way crossover study to investigate combination treatment with nebulised RPL554 and tiotropium dry powder inhaler (DPI) in patients with moderate to severe chronic obstructive pulmonary disease (COPD). It is planned to randomise up to 30 patients to get 24 evaluable patients at one study centre.</p> <p>Patients will be screened for eligibility (Visit 1), including a reversibility test with salbutamol between 7 and 21 days before the first dose of study treatment. Eligible patients will then attend three separate 3 day treatment periods (Treatment Periods 1 to 3) each separated by a 7 to 21 day washout period (taken from last dose of study treatment).</p>
<p>Study Procedures:</p>	<p>During each treatment period, patients will be present at the study centre from the morning of Day 1 until the morning of Day 4, although they will be able to leave the facility at the discretion of the study centre personnel. Overnight residency is required on Day 3 of each treatment period. Patients will be randomised pre-dose on Day 1 of Treatment Period 1.</p> <p>During each treatment period, patients will be dosed with tiotropium once daily each morning (Day 1 to Day 3) and either RPL554 or placebo twice daily (in the morning and evening) on Day 1 and Day 2 and once in the morning only on Day 3 (total of 5 doses of RPL554 or placebo in each treatment period; there is no evening dose of RPL554 or placebo on Day 3 of each treatment period).</p> <p>The pre-dose FEV₁ at Day 1 of Treatment Period 2 and Day 1 of Treatment Period 3 must be within $\pm 20\%$ of the pre-dose FEV₁ at Day 1 of Treatment Period 1, in order to ensure consistent baseline FEV₁ for each study treatment.</p> <p>The following provides a brief overview of the major procedures to be performed during each treatment period.</p> <p>The following will be performed at Day 1 of each treatment period:</p> <ul style="list-style-type: none"> • Measurements of lung function (FEV₁ and forced vital capacity [FVC]) by spirometry pre-dose and up to 12 hours post-dose • 12-lead electrocardiogram (ECG) pre-dose and up to 4 hours post dose and vital sign (supine) measurements pre-dose and up to 12 hours post-dose • Measurement of lung volumes by whole body plethysmography pre-dose <p>The following will be performed on Day 2 of each treatment period:</p> <ul style="list-style-type: none"> • Measurement of lung function (FEV₁ and FVC) by spirometry pre-dose and for up to 4 hours post-dose • 12-lead ECG pre-dose and up to 2 hours post dose and vital sign (supine) measurements pre-dose and up to 12 hours post-dose • Measurement of lung volumes by whole body plethysmography pre-dose and at 1.25 hours post-dose • Holter monitoring pre-dose and up to at least 24 hours post-dose. <p>The following will be performed at Day 3 of each treatment period:</p> <ul style="list-style-type: none"> • Measurements of lung function (FEV₁ and FVC) by spirometry pre-dose and up to 24 hours post-dose • 12-lead ECG and vital signs (supine) measurements pre-dose and up to 24 hours post-dose • Pharmacokinetic blood sampling pre-dose and up to 24 hours post-dose • Laboratory safety tests (haematology and biochemistry) at 24 hours post-dose <p>The 24-hour assessments and Holter removal will be performed prior to discharge from the study centre on Day 4.</p> <p>Adverse events will be recorded throughout the study.</p>
<p>Number of Patients Planned:</p>	<p>24 evaluable patients (randomise up to 30 patients)</p>

<p>Main Criteria for Eligibility:</p>	<p><i>Inclusion Criteria</i></p> <p>Male and female patients with moderate to severe COPD, with a post-bronchodilator FEV₁ of 40 to 80% of predicted. They must have a baseline increase in FEV₁ of ≥150 mL after use of four puffs of salbutamol. They must have at least a 10 pack-year smoking history, and may be an ex-smoker or current smoker.</p> <p><i>Exclusion Criteria</i></p> <p>Patients must be clinically stable without recent COPD exacerbations or hospitalisations. They must not have uncontrolled disease or chronic heart failure.</p>
<p>Study Treatments:</p>	<p>All study treatments will be administered using the inhaled route.</p> <p>Patients will receive the following three dose treatment combinations (DPI treatment plus nebulised treatment) in a randomised sequence during Treatment Periods 1 to 3:</p> <p>Tiotropium 18 µg once daily + RPL554 6 mg twice daily Tiotropium 18 µg once daily + Placebo twice daily Tiotropium 18 µg once daily + RPL554 1.5 mg twice daily</p> <p>Each morning during each 3 day period, the DPI treatment (tiotropium; Spiriva® HandiHaler®) will be administered first followed immediately (starting within 2 minutes) by the nebulised treatment (RPL554 or placebo). The nebulised treatment (RPL554 or placebo) only will be repeated in the evening on Day 1 and Day 2, 12 hours after the morning dose; there is no evening dose of study treatment on Day 3 of each treatment period.</p> <p>The DPI treatment will be administered open label and the nebulised treatment will be administered double blind.</p> <p>The nebulised treatment (RPL554 or placebo) will be administered using a standard Jet nebuliser (PARI LC SPRINT® plus a PARI TurboBOY® SX compressor unit).</p> <p>The RPL554 formulation is a sterile suspension supplied as sterile stock suspensions of micronised RPL554 in pH 7 phosphate buffered saline, containing surfactants to aid suspension. The placebo is the same as the RPL554 suspension except that the active RPL554 ingredient is omitted, i.e. it consists of pH 7 phosphate buffered saline and surfactants only. It is thus a clear solution rather than a pale yellow suspension; there is no known inert yellow solid that would be acceptable for inhalation, and therefore a visually matching placebo could not be developed.</p>
<p>Duration of Treatment:</p>	<p>The approximate planned duration for each patient will be up to 82 days: 7 to 21 day screening period, up to 9 days treatment (three treatment periods of 3 days each separated by a 7 to 21 day washout period, taken from last dose of study treatment) and an end of study visit 4 to 10 days after the last treatment visit (Day 4 of Treatment Period 3).</p>
<p>Statistical Methods:</p>	<p>Treatments will be compared using analysis of covariance adjusting for treatment, period, patient and baseline. Multiplicative models will be used for FEV₁ and outcome from whole body plethysmography and additive models for blood pressure, pulse rate and ECG heart rate. RPL554 treatments will first be compared to placebo using a closed test procedure starting with the highest dose of RPL554.</p>
<p>Sample Size:</p>	<p>This is a complete block three-way crossover study. Assuming a residual coefficient of variation of 6% for peak FEV₁, 24 patients will give an 80% power to detect a pairwise difference in maximum FEV₁ of 5.1%.</p>

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ANCOVA	Analysis of covariance
ATS	American Thoracic Society
AUC	Area under the curve
BMI	Body mass index
C _{max}	Maximum concentration
COPD	Chronic obstructive pulmonary disease
CI	Confidence interval
CV	Coefficient of variation
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
ERS	European Respiratory Society
G	Gauge
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
FVC	Forced vital capacity
FEV ₁	Forced expired volume in 1 second
FRC	Functional residual capacity
ICH	International Conference on Harmonisation
IUPAC	International Union of Pure and Applied Chemistry
LABA	Long acting beta2-agonists
LAMA	Long acting muscarinic antagonists
LPS	Lipopolysaccharide
MedDRA	Medical Dictionary for Regulatory Activities
PC ₂₀ MCh	Provocative concentration of methacholine chloride causing a fall in FEV ₁ of 20% from placebo
PDE	Phosphodiesterase
pMDI	Pressurised metered dose inhaler
QTcF	QT interval corrected for heart rate using Fridericia's formula
R _{aw}	Airway resistance
RV	Residual volume
SAE	Serious adverse event
SAS	Statistical analysis software

sG _{aw}	Specific airway conductance
SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected, unexpected serious adverse reaction
TLC	Total lung capacity
t _{max}	Time to maximum concentration

1 INTRODUCTION

1.1 Disease and Study Treatment Review

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

PDE4 inhibitors (administered orally) have exhibited anti-inflammatory actions; however, they have been associated with unfavourable gastrointestinal side effects such as nausea, emesis, diarrhoea, abdominal pain, loss of appetite and weight loss (Harbinson et al, 1997; van Schalkwyk et al, 2005; Compton et al, 2001; Rabe et al, 2005; Rennard et al, 2006; Calverley et al, 2007; Gamble et al, 2003; Grootendorst et al, 2007). Dual PDE3/PDE4 inhibitors (administered by inhalation) have exhibited both bronchodilator and anti-inflammatory actions, with a more favourable side effect profile (Ukena et al, 1995). It is plausible that increased efficacy with reduced side effects may be achievable with administration of a dual PDE3/4 inhibitor by the inhaled route compared to orally administered PDE3 or PDE4 inhibitors. It has also been demonstrated in tracheal ring preparations that RPL554 causes a synergistic bronchodilator effect when added to antimuscarinic agents, as well as additive properties with beta₂-agonists (Calzetta et al, 2013; Calzetta et al, 2015).

The safety, bronchodilator, bronchoprotective and anti-inflammatory activities of RPL554 have been evaluated in five completed studies in healthy subjects, patients with mild-moderate persistent asthma and those with allergic rhinitis and COPD, using a nebulised solution of RPL554 in citrate/phosphate buffered saline at pH 3.2 (Franciosi et al, 2013; summarised in Investigator Brochure). Systemic exposure following inhalation using this solution formulation was low and somewhat variable, with maximum concentration (C_{max}) values ranging from about 0.9 ng/mL following administration at 0.018 mg/kg to about 4 ng/mL at 0.072 mg/kg. Area under the curve (AUC)_{0-t} values ranged from about 1.5 ng.h/mL to 11 ng.h/mL over the same dose range. Mean half-life values ranged from approximately 3 to 7 hours.

RPL554 delivered by inhalation as a nebulised solution was well tolerated. Adverse events were generally mild and generally of equal frequency between placebo and active treatment groups. RPL554 produced a rapid bronchodilation in both COPD and asthmatic patients, and increased the provocative concentration of methacholine chloride (PC₂₀MCh) by 1.5 doubling doses compared with placebo (95% confidence interval [CI]: 0.63-2.28; p=0.004). In healthy subjects, RPL554 also produced a significant inhibition of the lipopolysaccharide (LPS)-induced recruitment of the total number of inflammatory cells to the airways (p=0.002), as well as an inhibition of the absolute numbers of neutrophils (p=0.002), eosinophils (p=0.001), lymphocytes (p=0.001) and macrophages (p=0.04) in sputum.

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

1. Study RPL554-007-2014 was a Phase I randomised, double blind, placebo controlled study in which single ascending doses in the range 1.5 mg to 24 mg were administered to 35 healthy subjects, multiple ascending doses in the range 6 mg to 24 mg twice daily for up to 5.5 days were administered to 21 healthy subjects and multiple ascending doses in the range 1.5 mg to 12 mg twice daily for 5.5 days were administered to 23 COPD patients (RPL554-007-2014 Clinical Study Report, 2016). RPL554 was well tolerated and no maximum tolerated dose could be determined. There was a large bronchodilator response in both healthy subjects and patients with COPD. Pharmacokinetics demonstrated a terminal serum half-life of about 10 to 12 hours.
2. Study RPL554-008-2014 was a Phase II double blind, placebo controlled seven way complete block crossover study. This study enrolled 29 patients with mild-moderate chronic asthma and patients received four single doses of RPL554 (0.4 mg, 1.5 mg, 6 mg and 24 mg), two doses of nebulised salbutamol (2.5 mg and 7.5 mg) and placebo in a randomised sequence. RPL554 produced a dose-dependent bronchodilation with a magnitude that was comparable to a maximal dose of salbutamol, but with fewer of the well described salbutamol side effects (e.g. hypokalaemia, tachycardia, tremor and palpitations) (Bjermer et al, 2016).
3. Study RPL554-009-2015 was a Phase II, double blind, double dummy, placebo controlled, six way complete block crossover study in moderate to severe COPD patients. This study enrolled 36 patients who received salbutamol (200 mcg), ipratropium (40 mcg) or placebo using a pressurised metered dose inhaler (pMDI) followed immediately by nebulised RPL554 (6 mg) or placebo in a randomised sequence. RPL554 alone was as effective as standard of care bronchodilators (two puffs of either a salbutamol or ipratropium pMDI), and importantly produced significant additive bronchodilation (peak and average over 8 hours) when dosed with either salbutamol or ipratropium ($p < 0.001$). Indeed, there was an approximately 60% additional increase in peak forced expired volume in 1 second (FEV_1) in COPD patients administered RPL554 6 mg in addition to two puffs of either a salbutamol or ipratropium pMDI (RPL554-009-2015 Clinical Study Report, in preparation).

RPL554 was well tolerated in all three studies. There were no serious adverse events (SAEs) or adverse events of concern.

The pharmacokinetics of RPL554, following single nebulised inhaled doses of this suspension formulation, were characterised by approximately dose proportional systemic exposure in all three studies. Values of C_{max} were generally attained around 1 to 1.5 hours after dosing, suggesting a steady and somewhat prolonged absorption of the RPL554 dose from the lungs into the systemic circulation; plasma concentrations declined slowly with a mean terminal half-life in the range 8 to 13 hours. Peak plasma concentrations obtained with the suspension formulation were one third to one quarter of those seen with the solution formulation. In study RPL554-007-2014, the twice-daily dosing regimen adopted for the multiple ascending dose phase led to some accumulation and steady state exposure appeared to be achieved by Day 3 of twice daily dosing in both healthy subjects and COPD patients. Systemic exposure to RPL554 was generally lower in COPD and asthma patients than in healthy subjects, which is consistent with the expected reduced lung deposition in patients with obstructive lung disease. Overall, the studies performed with inhaled nebulised

suspension doses of RPL554 have shown reproducible pharmacokinetic behaviour between studies and across patient cohorts.

All clinical studies with the solution and suspension formulations are described in the Investigator's Brochure.

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

1.2 Summary of Risks and Benefits

Data from non-clinical studies suggest a potential for hypotension and tachycardia. However, RPL554 has been administered to over 240 subjects in clinical studies to date and has been well tolerated in moderate-severe COPD patients, healthy subjects, asthmatics and allergic rhinitics. No SAEs have been reported with RPL554 to date. The most common adverse events that have been reported at least twice in subjects who have received single or multiple doses of the nebulised suspension of RPL554 were generally mild and in descending order of frequency are headache, cough, dizziness, and palpitations. Adverse events for single and multiple dose studies are summarised in Investigator's Brochure Section 6.3.

The suspension formulation of RPL554 is pH balanced, and has favourable non-clinical toxicology and pharmacokinetic data. There were no effects on embryo-foetal survival and development in the rat. In the rabbit there was an effect on implantation at the highest dose tested which could be related to a pharmacological effect of RPL554, however there was no effect on embryo-foetal survival and development.

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

As RPL554 is currently planned to be administered for only 3 days (five doses) in this study, any benefit to the patients will be restricted to the immediate short-term.

2 OBJECTIVES

2.1 Primary Objective

To investigate the bronchodilator effect on peak FEV₁ (measured in first 4 hours after dosing) and average (measured as the AUC) FEV₁ over 12 hours of nebulised RPL554 dosed twice daily for 3 days (five total doses), as compared to placebo, when administered in addition to once daily tiotropium.

2.2 Secondary Objectives

- To investigate the effect of twice daily nebulised doses of RPL554, as compared to placebo, when administered in addition to tiotropium on lung volumes
- To assess the bronchodilator effect on peak FEV₁ (measured in first 4 hours after dosing) and average (measured as the AUC) FEV₁ over 12 hours of nebulised RPL554 after the first dose as compared to placebo, when administered in addition to tiotropium
- To analyse plasma concentrations and assess the steady state pharmacokinetics of RPL554 when administered in addition to tiotropium
- To assess the tolerability and safety of twice daily nebulised doses of RPL554 in addition to tiotropium
- To assess the dose response of two different doses of RPL554 on peak, average (0 to 12 hours), and morning trough FEV₁ on Day 3 when dosed in addition to tiotropium
- To determine the onset of action of RPL554 when administered with tiotropium (after the first dose)
- To investigate the bronchodilator effect of nebulised RPL554, or placebo, administered in addition to tiotropium on average FEV₁ over 4 hours after each morning dose
- To investigate the effects of RPL554 on specific airway conductance (sG_{aw}) and lung volumes (residual volume [RV], functional residual capacity [FRC]) when administered in addition to tiotropium

2.3 Exploratory Objectives

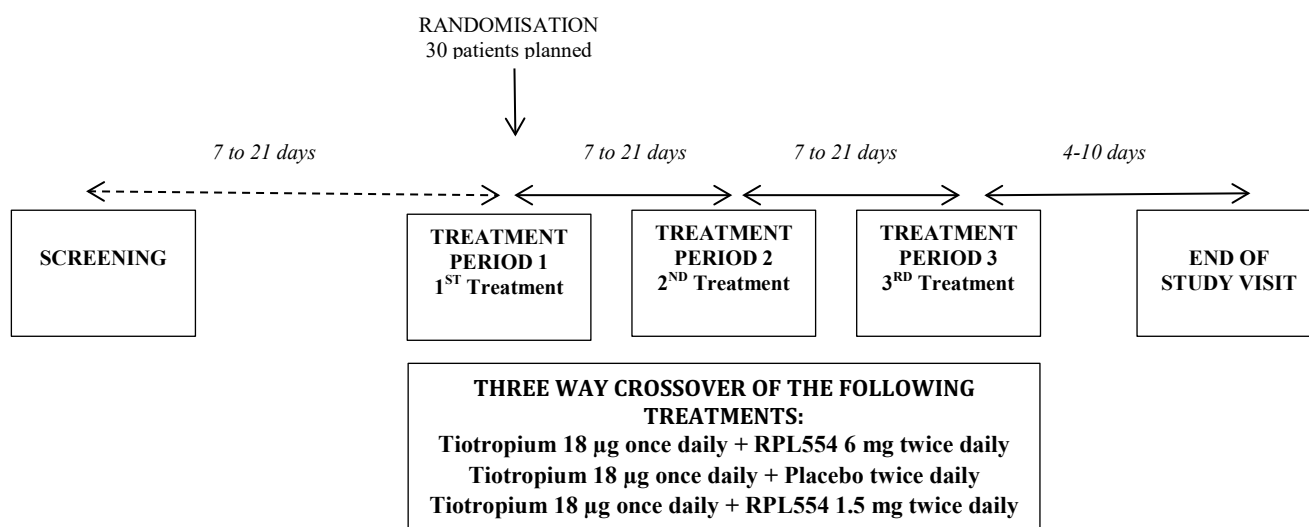
- To examine the effect of RPL554 on top of tiotropium on average FEV₁ over 24 hours after 3 days of dosing
- To assess morning trough FEV₁ prior to the final dose of study treatment

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan Description

This is a Phase IIb, randomised, double blind, placebo controlled, complete block three way crossover study to investigate treatment with nebulised RPL554 and tiotropium together in patients with moderate to severe COPD. It is planned to randomise up to 30 patients to have 24 evaluable patients at one study centre. The study comprises the following shown in Figure 1: screening, three treatment periods each lasting 3 days and an end of study visit. The procedures performed at each visit are summarised in Section 6 and the study assessments are described in Section 7.

Figure 1 Study Flow Chart



Patients will be screened for eligibility, including a reversibility test with salbutamol between 7 and 21 days before the first dose of study treatment.

Eligible patients will then attend for three separate treatment periods (Treatment Periods 1 to 3) which each last 3 days and are separated by a 7 to 21 day washout period (taken from last dose of study treatment). Patients will be randomised pre-dose at Day 1 of Treatment Period 1. During each treatment period, patients will be present at the study centre from the morning of Day 1 until the morning of Day 4, although they will be able to leave the facility at the discretion of the study centre personnel. Overnight residency is not required except on Day 3 of each treatment period.

In each treatment period, patients will receive an open label dose of tiotropium from a dry power inhaler (DPI) followed immediately (starting within 2 minutes) by a double blind dose of either RPL554 or placebo (depending on treatment sequence) from a nebuliser in the morning on Day 1, Day 2 and Day 3. The dose of RPL554 or placebo will be repeated in the evening on Day 1 and Day 2; there will not be an evening dose on Day 3.

The assessments performed in each treatment period will be the same. Lung function (FEV₁ and forced vital capacity [FVC]) will be measured by spirometry pre-dose and up to 12 hours post-dose on Day 1, up to 4 hours post-dose on Day 2 and up to 24 hours post-dose on Day 3 (i.e. Day 4). Whole body plethysmography will be performed pre-dose on Days 1 and 2 of each treatment period, and 1.25 hours after dosing on Day 2. Vital signs will be measured pre-dose and up to 4 hours post-dose on Day 1, up to 12 hours post-dose on Day 2 and up to 24 hours post-dose on Day 3 (i.e. Day 4). 12-lead electrocardiograms (ECGs) will be

performed pre-dose and up to 4 hours post-dose on Day 1, at 2 hours post-dose on Day 2 and up to 24 hours post-dose on Day 3 (i.e. Day 4). Adverse events will be recorded throughout the study.

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

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

A total of up to 30 COPD patients (to get 24 evaluable patients), either male or female, aged 40 to 75 years (inclusive) will be randomised. The purpose of the study is to investigate if RPL554 has an additive bronchodilator effect when administered in combination with a commonly used anticholinergic medication, tiotropium, in this patient population.

All patients will receive all three nebulised treatments (1.5 mg RPL554, 6 mg RPL554 and placebo) in this study in a randomised, crossover design; therefore, each patient will act as his or her own control in the study. This design makes it possible to obtain unbiased inferences about differences between treatments, based on intra-patient differences. Treatments will be administered double blind with the Investigator and patient unaware of the treatment identity to further minimise any potential bias in the overall assessment of treatment effect and safety.

The washout period between the three treatments has been selected based upon the available single dose pharmacokinetics of the suspension formulation of RPL554 in healthy male subjects (single ascending dose part of Study RPL554-007-2014). The mean (range) half-lives were 8.3 (6.0 to 10.5) hours at the 1.5 mg dose, 8.5 (7.6 to 9.21) hours at the 3.0 mg dose, 10.5 (9.1 to 11.7) hours at the 6 mg dose, 9.4 (7.8 to 11.8) hours at the 12 mg dose and 10.2 (8.1 to 12.5) hours at the 24 mg dose. Five half-lives is considered as the time for elimination of study treatment from the body. In this study, a washout period of 7 to 21 days from the last dose of study medications has been deemed adequate to ensure there was no overlap between the pharmacokinetic profiles of treatments with RPL554 in consecutive treatment periods. Whilst tiotropium has a prolonged terminal half-life of 5 to 6 days, the clinical bronchodilator effects are gone before this timepoint. As such, and in the absence of measuring pharmacokinetic levels of tiotropium, this was felt to be an adequate washout between treatment periods.

Study treatment administration, pharmacodynamics, safety and tolerability assessments will be performed whilst patients are resident at the study centre. This is to ensure standardised conditions for dosing and other study procedures. The pre-dose FEV₁ on Day 1 of both Treatment Period 2 and Treatment Period 3 must be within $\pm 20\%$ of the pre-dose FEV₁ on Day 1 of Treatment Period 1 in order to ensure consistent baseline FEV₁ for each study treatment. If the FEV₁ is greater than 20% different then the start of the treatment period must be rescheduled.

3.3 Planned Duration of the Study

The approximate planned duration for each patient could be up to 82 days: 7 to 21 days screening, up to 9 days treatment (three treatment periods of 3 days each separated by 7 to 21 days, taken from last dose of study treatment) and an end of study visit 4 to 10 days after the last treatment visit (Day 4 of Treatment Period 3).

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

3.4 Definition of the End of the Study

The end of the study is defined as the date of the last end of study visit of the last patient in the study.

4 SELECTION OF STUDY POPULATION

The population to be recruited into this study is stable patients with moderate to severe COPD and without significant heart disease. It is expected that current smokers will not comprise more than half the study population.

4.1 Inclusion Criteria

1. Sign an informed consent document indicating they understand the purpose of and procedures required for the study and are willing to participate in the study.
2. Male or female aged between 40 and 75 years inclusive, at the time of informed consent.
3. If male: must agree to meet the following from the first dose up to 2 months after the last dose of study treatment:
 - 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 highly effective form of contraception must also be used (as defined in Section 8.4)
4. If female: either be:
 - a) Of non-childbearing potential defined as being:
 - *Either:* post-menopausal (being spontaneously amenorrhoeic for at least 1 year with an appropriate clinical profile [e.g. age appropriate, history of vasomotor symptoms])
 - *Or:* permanently sterilised e.g. tubal occlusion, hysterectomy, bilateral oophorectomy, bilateral salpingectomy
 - b) Of childbearing potential and agreeing to use a highly effective method of contraception (as defined in Section 8.4) until completion of the end of study visit.
5. Have a 12-lead ECG recording at screening and randomisation (pre-dose in Treatment Period 1) showing the following:
 - Heart rate between 45 and 90 beats per minute (bpm)
 - QT interval corrected for heart rate using Fridericia's formula (QTcF) ≤ 450 msec for males and ≤ 470 ms for females
 - QRS interval ≤ 120 msec
 - No clinically significant abnormalities (as judged by the Investigator) including morphology (e.g. left bundle branch block, atrio-ventricular nodal dysfunction, ST segment abnormalities)
6. Have a screening Holter report with a minimum of 18 hours recording that is able to be evaluated for rhythm analysis which shows no abnormality which indicates a

significant impairment of patient safety or which may significantly impairs interpretation in the opinion of the Investigator including:

- Significant arrhythmias including atrial flutter, atrial fibrillation, ventricular tachycardia
 - Any symptomatic arrhythmia (except isolated extra systoles)
 - Any sustained second or third degree heart block
7. Capable of complying with all study restrictions and procedures including ability to use the study nebuliser and HandiHaler® DPI correctly.
 8. Body mass index (BMI) between 18 and 33 kg/m² (inclusive) with a minimum weight of 45 kg.
 9. 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.
 10. Post-bronchodilator (four puffs of salbutamol) spirometry at screening:
 - Post-bronchodilator FEV₁/FVC ratio of ≤0.70
 - Post-bronchodilator FEV₁ ≥40 % and ≤80% of predicted normal
 - Demonstrates ≥150 mL increase from pre-bronchodilator FEV₁
 11. Clinically stable COPD in the 4 weeks prior to screening and randomisation (pre-dose in Treatment Period 1).
 12. A chest X-ray (post-anterior) at screening, or in the 12 months prior to screening showing no abnormalities, which are both clinically significant and unrelated to COPD.
 13. Meet the concomitant medication restrictions and be expected to do so for the rest of the study.
 14. Smoking history of ≥10 pack years.
 15. Capable of withdrawing from long acting bronchodilators for the duration of the study, and short acting bronchodilators for 8 hours prior to spirometry.

4.2 Exclusion Criteria

1. A history of life-threatening COPD exacerbation including Intensive Care Unit admission and/or requiring intubation.
2. COPD exacerbation requiring oral steroids, or lower respiratory tract infection requiring antibiotics, in the 3 months prior to screening or randomisation (pre-dose in Treatment Period 1).
3. A history of one or more hospitalisations for COPD in the 12 months prior to screening or randomisation (pre-dose in Treatment Period 1).
4. Lactation (female patients only).
5. Positive urine or serum pregnancy test at screening, or a positive urine pregnancy test prior to randomisation (female patients of childbearing potential only).
6. Known hypersensitivity to RPL554 or its components.
7. Intolerance or hypersensitivity to tiotropium.
8. Evidence of cor pulmonale.
9. Other respiratory disorders: Patients with a current diagnosis of asthma, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, interstitial lung

- diseases, sleep apnoea, known alpha-1 antitrypsin deficiency or other active pulmonary diseases.
10. Previous lung resection or lung reduction surgery.
 11. Use of oral COPD medications (e.g. oral steroids, theophylline and romifulast) in the 3 months prior to screening or randomisation (pre-dose in Treatment Period 1).
 12. History of, or reason to believe, a patient has drug or alcohol abuse within the past 3 years.
 13. Inability to perform technically acceptable spirometry or whole body plethysmography (at screening or randomisation [pre-dose in Treatment Period 1])
 14. Received an experimental drug within 30 days or five half-lives, whichever is longer.
 15. Patients with a history of chronic uncontrolled disease including, but not limited to, endocrine, active hyperthyroidism, neurological, hepatic, gastrointestinal, renal, haematological, urological, immunological, or ophthalmic diseases that the Investigator believes are clinically significant.
 16. Documented cardiovascular disease: arrhythmias, angina, recent or suspected myocardial infarction, congestive heart failure, a history of unstable, or uncontrolled hypertension, or has been diagnosed with hypertension in the 3 months prior to screening or randomisation.
 17. Concurrent use of non-cardioselective oral beta-blockers.
 18. Has had major surgery, (requiring general anaesthesia) in the 6 weeks prior to screening or randomisation (pre-dose in Treatment Period 1), or will not have fully recovered from surgery, or planned surgery through the end of the study.
 19. A disclosed history or one known to the Investigator, of significant non-compliance in previous investigational studies or with prescribed medications.
 20. Requires oxygen therapy, even on an occasional basis.
 21. Clinically significant prostatic hyperplasia (judged by the Investigator) or bladder-neck obstruction or with narrow-angle glaucoma.
 22. Any other reason that the Investigator considers makes the patient unsuitable to participate.

4.3 Removal of Patients from Therapy or Assessment

Investigators have the authority to ask for the withdrawal of 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.

If a patient withdraws following randomisation, every attempt should be made to contact the patient to determine the reason for withdrawal and to complete the recording of any available efficacy data and all adverse event data. If a patient agreed to enter the study and signed a consent form but withdrew from the study, or was withdrawn from the study, without receiving any study treatment, no further follow-up is necessary.

End of study visits will occur at 4 to 10 days after completing Day 4 of Treatment Period 3. All withdrawn patients will follow this routine unless it is considered by the Investigator that they require greater medical supervision and/or investigations and in which case an unscheduled visit prior to and in addition to the scheduled follow up visit may be performed. Patients who do not complete all treatment periods should have an end of study visit.

If a patient decides to withdraw voluntarily, or is withdrawn by the Investigator responsible at any time, the reasons for withdrawal and results of all relevant tests will be recorded in the electronic case report form (eCRF). Patients who withdraw may be replaced.

4.3.1 Study Treatment Discontinuation

Study treatment must be discontinued for the following reasons:

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

4.3.2 Patient Withdrawal

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

It should be made clear that the patient is free to withdraw from the study at any time.

4.3.3 Study Discontinuation

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

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

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

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

4.3.4 Replacement Policy

It is planned to randomise 30 patients. Replacement patients may be required due to any patient withdrawal. This should be discussed with the Sponsor on a case by case basis, but it

is expected that at least 24 patients will complete at least two treatment periods. Replacement patients will be allocated the next randomisation number in the treatment sequence.

5 STUDY TREATMENTS

5.1 Study Treatments Administered

Patients will receive the three dose treatment combinations (DPI plus nebulised treatment) shown in Table 1 in a randomised sequence during Treatment Periods 1 to 3. All study treatments will be administered using the inhaled route. In each case, the DPI treatment will be administered first, followed immediately (within 2 minutes) by the nebulised RPL554 or placebo using a standard Jet nebuliser (PARI LC SPRINT[®] attached to a PARI TurboBOY[®] SX compressor unit). The DPI treatment will be open label and the nebulised treatment will be double blind.

Table 1 Treatment Combinations in RPL554-CO-202

TREATMENT COMBINATION	DPI TREATMENT	NEBULISED TREATMENT
1	Tiotropium 18 mcg qd	RPL554 6 mg bid
2	Tiotropium 18 mcg qd	Placebo bid
3	Tiotropium 18 mcg qd	RPL554 1.5 mg bid

Abbreviation: bid=twice daily; DPI=dry powder inhaler; qd=once daily

5.2 Identity of Study Treatments

5.2.1 RPL554 and Placebo

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

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

Table 2 Composition of Nebulised RPL554 and Placebo Formulations

Constituent	Concentration (mg/mL)
RPL554 (micronised)	0.5 or 6.0 mg/mL or 0 mg/mL (=placebo)
Polysorbate 20 (Tween 20)	0.5
Sorbitan Monolaurate (Span 20)	0.05
Monosodium Phosphate Dihydrate	7.44
Di-Sodium Hydrogen Phosphate Anhydrous	6.80
Sodium Chloride	4.80
Water	N/A

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

The RPL554 formulation is a sterile suspension for nebulisation, supplied as sterile stock suspensions of micronised RPL554 in pH 7 phosphate buffered saline with surfactants to aid suspension. Two concentrations of RPL554 (0.5 mg/mL and 6.0 mg/mL) and a placebo will

be provided as a nominal 5 mL fill in 10 mL clear glass vials sealed with an ethylene tetrafluoroethylene coated rubber stopper and flip tear-up cap.

The placebo is the same as the RPL554 suspension except that the active RPL554 ingredient is omitted, i.e. it consists of pH 7 phosphate buffered saline and surfactants only. It is thus a clear solution rather than a pale yellow suspension; there is no known inert yellow solid that would be acceptable for inhalation, and therefore a visually matching placebo could not be developed. The placebo will also be used as a diluent, enabling the preparation of the 6 mg dose concentration required for the study.

For nebulisation, the 1.5 mg dose of RPL554 will be dispensed as 3 mL of the 0.5 mg/mL concentration. The 6.0 mg dose of RPL554 will be dispensed as 1 mL of the 6.0 mg/mL solution diluted with 2 mL of placebo. The placebo will be dispensed as 3 mL.

5.2.2 Tiotropium DPI

Tiotropium DPI (Spiriva[®] HandiHaler[®]; Boehringer Ingelheim International GmbH; Anatomic Therapeutic Chemical Code R03BB04) is a marketed anticholinergic for the treatment of COPD. Capsules containing 18 mcg tiotropium for use with a HandiHaler[®] (see Section 15.1) will be provided by the study centre.

5.3 Preparation and Labelling

5.3.1 Nebulised RPL554 and Placebo

Stock clear glass vials of RPL554 and placebo will be labelled in compliance with GMP, released by a qualified person and then shipped to the study centre.

RPL554 and placebo will be prepared as a 3 mL volume for nebulisation by an unblinded individual who will not disclose the identity study treatment to the blinded Investigator and study centre staff. Standard aseptic technique will be used. Standard glass or medical grade plastic syringes and 25 gauge (G) syringe needles may be used. Narrower gauge needles must be avoided. Details of the dilution technique for the 6 mg dose will be provided in the pharmacy brochure.

5.3.2 Tiotropium DPI

Each tiotropium DPI HandiHaler[®] will be labelled by the site with the randomisation number and in accordance with local regulations.

5.4 Selection of Doses, Dosing Schedule and Route of Administration

5.4.1 Selection of Doses in the Study

The dose of tiotropium, 18 mcg once daily, is the approved dose for this medication, and is the standard of care.

The doses of RPL554 have been selected based on the results from Studies RPL554-007-2014, RPL554-008-2014, and RPL554-009-2015 investigating single and multiple ascending dosing in healthy subjects, single doses in asthmatics and single/multiple ascending dosing study in COPD patients. These doses were demonstrated to be both effective as a bronchodilator and well tolerated.

5.4.2 Selection and Timing of Dose for each Patient

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

For the morning dose, the tiotropium DPI will be given first, followed immediately (starting within 2 minutes) by nebulised RPL554 or placebo. The evening dose on Day 1 and Day 2 is 12 hours (± 30 minutes) later is nebulised RPL554 or placebo.

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

- Patients should refrain, where possible, from xanthine (chocolate, caffeine containing drinks and food), for at least 24 hours before and during all visits. Decaffeinated beverages are permitted
- Patients should refrain from alcohol for 24 hours before and during all visits (including visits for safety laboratory tests) and until all procedures for that study visit are completed
- Patients must fast (water permitted) from 2 hours pre-dose until 2 hours post-dose
- Patients should refrain from smoking within 1 hour of dosing, and at least 1 hour before any measurement of lung function
- Patients should refrain from strenuous exercise for 72 hours prior to all study visits and should undertake no unaccustomed strenuous exercise from screening till the end of study visit

5.4.2.1 Nebulised RPL554 and Placebo

RPL554 and placebo will be administered by inhalation of an aerosol generated by a reusable PARI LC Sprint® jet nebuliser attached to a PARI TurboBOY® SX compressor. Wherever possible, the same compressor unit should be used for each dose within a patient.

The dosing cup on each nebuliser will be obscured with tape to visually blind the study treatment.

The end time of nebulisation (sputtering) will be considered Time 0 for the purposes of scheduling all post-dose study procedures. Nebulisation time should not exceed 10 minutes. Patients must wear a protective gown on Day 3 during the dosing procedure to prevent contamination of the cannula for pharmacokinetic samples.

The following must be recorded in the eCRF:

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

5.4.2.2 Tiotropium DPI

Prior to use of the DPI, the capsule of tiotropium will be placed into the HandiHaler®. Patients will be instructed to inhale rapidly through their mouth (see instructions in Appendix 1). They will be instructed to hold their breath for 10 seconds, or as long as comfortable. A second inhalation is required to ensure the capsule is completely empty. The time of dosing will be recorded in the eCRF.

Further information is provided in Section 15.1.

5.5 Storage

During transport RPL554 and placebo should be stored at room temperature and up to 25°C. The expiry date will be indicated on the box label.

At the study centre, RPL554 and placebo should be stored at room temperature and up to 25°C.

Tiotropium HandiHaler[®] should be stored as specified in Section 15.1.

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

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

5.6 Accountability

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

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

Written records must also be maintained to confirm the purpose and reason for any study treatment disposal, e.g. the amount contaminated, broken, or lost, and the name/signature of the personnel responsible for destruction. No study material (including used vials) may be destroyed until final study treatment accountability has been performed and written approval has been received from the Sponsor.

At the end of the study, the unused study treatment will be destroyed locally after accountability has been verified.

5.7 Method of Assigning Patients to Treatment Groups

All patients consented will be assigned a screening number using the study centre's standard convention.

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

Randomisation numbers will follow the convention XX-YYY where XX is the centre number and YYY is the sequential randomisation number.

A dummy randomisation schedule will be approved by the Sponsor before the final randomisation schedule is produced.

5.8 Blinding

Tiotropium will be provided in trade dress and will not be blinded.

RPL554 and placebo will be administered double blind. It has not been possible to completely match the placebo to RPL554, as the visual appearance is slightly different. The study personnel preparing the RPL554 and placebo, placing them into the nebuliser, and supervising dosing will therefore not be blinded to treatment identity. The dosing cup on each nebuliser will be obscured with tape to visually blind the study treatment. The Sponsor, Investigator (defined as Principal Investigator and all study physicians), all patients and all other research personnel (except bioanalytical personnel performing the pharmacokinetic assays) will therefore be blinded to the treatment allocation.

The blind should be broken only if specific emergency treatment would be dictated by knowing the treatment status of the patient. If the blind needs to be broken, the Investigator should discuss it with the Sponsor's Medical monitor in advance.

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 Therapies

All prior therapies for COPD taken in the 3 months prior the first study treatment administration and all concomitant COPD therapies for 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.

Oral therapies for COPD (e.g. oral steroids, theophylline, and roflumilast) are not allowed in the 3 months prior to screening and throughout the study. Inhaled steroids may continue during the study at a maintenance dose.

All long acting (once or twice daily) bronchodilators will be stopped at the screening visit and are not allowed during the study. Patients should not use a long acting bronchodilator (long acting muscarinic antagonists [LAMA], long acting beta2-agonists [LABA], or combination LABA/inhaled steroid) on the day of screening.

Patients taking LAMAs and LABAs should be placed on short acting bronchodilators (e.g. salbutamol, ipratropium or Combivent[®]) as per the discretion of the Investigator. These can be dosed on a regular scheduled basis and/or as needed use. Patients taking LABA/inhaled steroid combination products should be prescribed the inhaled steroid at the same or equivalent dose contained in the combination product to allow continuation of steroid use regularly throughout the study whilst stopping the LABA component. Patients currently taking terbutaline will be switched to other short acting bronchodilators (e.g. salbutamol).

If this is inadequate to control their symptoms, they should contact the Investigator. No scheduled use of salbutamol or ipratropium is allowed during the 3-day treatment periods; but may be used as a rescue medication (see Section 5.10). Salbutamol and ipratropium (or Combivent[®]) must be withheld for at least 8 hours prior to spirometry and this confirmed in the eCRF at the start of each treatment period. If this withhold is not met, the patient should be rescheduled for a repeat visit within permitted windows. Short acting bronchodilators

should be withheld during each treatment period for the time periods stated below unless absolutely necessary:

- 8 hours prior to pre-dose spirometry for Day 1, Day 2 and Day 3.
- Post-dose:
 - Day 1 until after +12 hours spirometry
 - Day 2 until after + 4 hours spirometry
 - Day 3 until after + 24 hours spirometry

Patients may continue other prescribed non-respiratory therapies during the study; however, pulmonary rehabilitation programs should not be started or completed during this period. Oxygen therapy and beta blockers are exclusion criteria for this study.

5.9.2 Prior and Concomitant Medications

Other prior prescription or non-prescription medications (medication, dose, route, treatment duration and indication) taken 3 months before the first study treatment administration must be recorded in order to confirm compliance with the inclusion and exclusion criteria.

All concomitant medications must also be documented on the eCRF. The impact of any concomitant medications will be evaluated during the pre-database lock review and the decision taken whether to exclude the patient from any analysis populations.

5.10 Rescue Medications

Standard procedures for emergency care should be followed for any individual adverse event, whenever clinically needed (decision to be taken by the Investigator). Short acting bronchodilators (e.g. salbutamol, ipratropium or Combivent) may be used as rescue medication. Rescue medication (salbutamol and ipratropium) will be sourced by the study centre and both will be dispensed at the screening visit. Salbutamol should be considered the primary rescue medication and ipratropium secondary.

Rescue medication use during each treatment period must be separately documented on the eCRF (medication, dose, route, date and time of each administration). Protocol procedures must still continue even if rescue medication has been taken. Salbutamol is to be used for primary rescue use.

5.11 Treatment Compliance

Study treatment administration will take place at the study centre and will be administered by the Investigator or designated and trained study centre personnel. The precise date and time of administrations shall be documented in the eCRF. 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.

6 STUDY PROCEDURES AT EACH VISIT

The study will consist of the following:

- Screening will take place in the period between 7 and 21 days prior to the first study treatment administration
- Three treatment periods (Treatment Period 1 to Treatment Period 3), each 3 days in duration and separated by 7 to 21 days (from last dose of study treatment on Day 3 of each treatment period)
- An end of study visit between 4 and 10 days after Day 4 of Treatment Period 3

Screening may be performed as a single visit or more than one visit. Eligible patients may be re-screened at the discretion of the Investigator, and following discussion with the Sponsor, if the reason for screen failure was considered temporary in nature. All screening data must be obtained within 21 days prior to administration of study treatment.

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

The overall schedule of assessments at each visit is shown in Table 3 and the schedule of assessments on each day of each treatment period is shown in Table 4. Assessments are listed by visit in Section 6.1 to Section 6.5 and are described in Section 7.

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

Permitted time windows on assessments will be specified in the study reference manual.

Table 3 Overall Schedule of Assessments at each Visit in RPL554-CO-202

Procedures	Screen	Treatment Periods 1 to 3 (7 to 21 days between Treatment Periods)				End of Study
	Day -21 to -7	Day 1	Day 2	Day 3	Day 4	4 – 10 days after Day 4
Informed consent	X					
Demographics including height and weight	X					
Medical/surgical and disease history	X					
Eligibility criteria	X	X[a]				
Physical examination	X (Full)	X (Brief)			X (Brief)	X (Full)
Vital signs	X	X	X	X	X	X
Safety laboratory tests: haematology and biochemistry	X				X	X
Safety laboratory tests: urinalysis	X					X
Viral serology	X					
Alcohol breath test	X					
Serum pregnancy test (females of childbearing potential)	X					
Urine pregnancy test (females of childbearing potential)	X[b]	X				X
Chest X-ray (or in last 12 months)	X					
12-lead ECG	X	X	X	X	X	X
24-hour Holter monitoring	X		X			
Spirometry: Reversibility test	X					
Spirometry: Study measurements		X	X	X	X	X
Whole body plethysmography training	X					
Whole body plethysmography		X	X			
Inhalation training (nebuliser and DPI)	X	X				
Randomisation		X[a]				
Tiotropium and RPL554 or placebo dosing		X	X	X		
Pharmacokinetic sampling				X	X	
Prior/concomitant medications and therapies	Throughout the study					
Adverse events	Throughout the study					
Abbreviations: DPI=dry powder inhaler; ECG=electrocardiogram						
[a] Treatment Period 1 only						
[b] Prior to chest X-ray						

Table 4 Pre-dose and Post-dose Assessments on each day of Treatment Periods 1 to 3 in RPL554-CO-202

Procedures	Day 1											
	Pre-	0	5 m	15m	30m	1h	1.5h	2h	4h	6h	8h	12h[a]
Tiotropium dosing by DPI		X										
RPL554 or placebo dosing by nebulisation		X										X
Brief physical examination	X											
Vital signs	X				X	X		X	X	X	X	X
12-lead ECG	X							X	X			
Spirometry	X		X	X	X	X	X	X	X	X	X	X
Inhalation training	X											
Whole body plethysmography	X											
Randomisation [b]	X											
Urine pregnancy test	X											
Adverse events	Throughout											
Abbreviations: DPI=dry powder inhaler; ECG=electrocardiogram; h=hour; m=minutes												
[a] Post-dose samples will be taken in relation to the morning dose of tiotropium DPI and RPL554 or placebo. The 12 hour procedures will therefore be performed pre-dose before the evening dose of RPL554 or placebo												
[b] Treatment Period 1 Day 1 only												

Procedures	Day 2									
	Pre-	0	15m	30m	1h	1.25h	2h	3h	4h	12h[a]
Tiotropium dosing by DPI		X								
RPL554 or placebo dosing by nebulisation		X								X
Vital signs	X			X	X		X	X	X	X
12-lead ECG	X						X			
Spirometry	X		X	X	X		X	X	X	
Whole body plethysmography	X					X				
Place 24 hour Holter	X									
Adverse events	Throughout									
Abbreviations: DPI=dry powder inhaler; ECG=electrocardiogram; h=hour; m=minutes										
[a] Post-dose samples will be taken in relation to the morning dose of tiotropium DPI and RPL554 or placebo. The 12 hour procedures will therefore be performed pre-dose before the evening dose of RPL554 or placebo.										

Procedures	Day 3														Day 4
	Pre-	0	5 m	15m	30m	45m	1h	1.5h	2h	4h	6h	8h	12h	15 h	24 h[a]
Tiotropium dosing by DPI		X													
RPL554 or placebo dosing by nebulisation		X													
Brief physical examination															X[b]
Vital signs	X				X		X		X	X	X	X			X
12-lead ECG	X								X	X					X
Remove Holter monitor	X														
Spirometry	X		X	X	X		X	X	X	X	X	X	X	X	X
Pharmacokinetic samples	X		X		X	X	X	X	X	X		X	X	X	X
Haematology and biochemistry															X
Adverse events	Throughout														
Abbreviations: DPI=dry powder inhaler; ECG=electrocardiogram; h=hour; m=minutes															
[a] Procedures performed prior to discharge from the study centre on the morning of Day 4, 24 hours after dosing on Day 3															
[b] Can be performed any time prior to discharge															

6.1 Screening

Written informed consent will be obtained by the Investigator as specified in Section 11.3 prior to any study related procedures being performed. Obtaining the informed consent can be performed on a separate visit prior to the screening period. Screening procedures may be performed over more than one day.

Patients will be screened to determine eligibility against the inclusion and exclusion criteria between 7 and 21 days before the first dose of study treatment. There are no fasting requirements for the screening visit. Patients must withhold long acting bronchodilators, ipratropium and salbutamol (or Combivent[®]) prior to screening as defined in Section 5.9.1.

The following assessments will be performed:

- Recording of demographic information, including height and weight
- Recording of medical/surgical and disease history
- Recording of prior medications and therapies
- Vital signs
- Full physical examination
- Alcohol breath test
- 12-lead ECG
- Chest X-ray (unless historical X-ray performed in last 12 months is available)
- Whole body plethysmography training and assessment of capacity to perform procedure (may be performed more than once as required)
- Pre-salbutamol spirometry
- Reversibility test (4 puffs salbutamol)
- Post-salbutamol spirometry (starting 20 to 30 minutes after administration)
- Place 24 hour Holter monitor; patients will be instructed to return the next day for removal of the Holter monitoring
- Blood and urine samples for laboratory safety tests (haematology, biochemistry, urinalysis), pregnancy tests (female patients of childbearing potential only), and viral serology. The urine pregnancy test result should be obtained prior to chest X-ray for females of childbearing potential.
- Instruct patients to stop all long acting bronchodilators for the duration of the study
- Inhalation training for use of nebuliser and DPI. This will be verbal instruction and demonstration of the device
- Questioning for adverse events

If the patient meets the inclusion and none of the exclusion criteria they will be instructed to return in 7 to 21 days for Treatment Period 1, Day 1.

6.2 Treatment Period 1; Day 1

This visit is approximately 72 hours in duration. Patients must withhold long acting bronchodilators, ipratropium and salbutamol (or Combivent[®]) prior to the start of the treatment period as defined in Section 5.9.1. Patients will be fasting from 2 hours pre-dose until 2 hours post-dose (except for water) and other restrictions defined in Section 5.4.2 should be adhered to.

At the start of Treatment Period 1, patients will be evaluated to ascertain if the inclusion and exclusion criteria are still met. If so, patients will receive a randomisation number. The following assessments will be performed:

6.2.1 Pre-Dose Assessments

- Confirm that respiratory medications were withheld as required. If not reschedule the visit for within the permitted windows
- Questioning for adverse events
- Urine pregnancy test (females of childbearing potential only)
- 12-lead ECG
- Vital signs
- Brief physical examination
- Spirometry
- Whole body plethysmography
- Inhalation training for use of nebuliser and DPI. This will be verbal instruction and demonstration of the device

6.2.2 Study Treatment Administration

Patients will be dosed with open label tiotropium DPI 18 mcg (two inhalations from one capsule) followed immediately (within 2 minutes) with either blinded RPL554 or placebo using a nebuliser according to randomisation scheme. At 12 hours (± 30 minutes) after the morning dose, the second dose of RPL554 or placebo will be administered by nebulisation.

6.2.3 Post-Dose Assessments (after morning doses only)

- Spirometry at 5, 15 and 30 minutes and 1, 1.5, 2, 4, 6, 8 and 12 hours
- Vital signs at 30 minutes and 1, 2, 4, 6, 8 and 12 hours
- 12-lead ECGs at 2 and 4 hours
- Questioning for adverse events

Patients will stay at the study centre overnight, unless they need to return home overnight and this is agreeable to the Investigator.

6.3 Treatment Period 1; Day 2

Patients will be fasting from 2 hours pre-dose until 2 hours post-dose (except for water) and other restrictions defined in Section 5.4.2 should be adhered to. The following assessments will be performed:

6.3.1 Pre-Dose Assessments

- Questioning for adverse events
- Place 24 hour Holter monitor (at least 30 minutes pre-dose)
- 12-lead ECG
- Vital signs
- Spirometry
- Whole body plethysmography

6.3.2 Study Treatment Administration

Patients will be dosed with open label tiotropium DPI 18 mcg (two inhalations from one capsule) followed immediately (within 2 minutes) with either blinded RPL554 or placebo using a nebuliser according to randomisation scheme. At 12 hours (± 30 minutes) after the morning dose, the second dose of RPL554 or placebo will be administered by nebulisation.

6.3.3 Post-Dose Assessments (after morning doses only)

- 12-lead ECGs at 2 hours
- Vital signs at 30 minutes and 1, 2, 3, 4 and 12 hours
- Spirometry at 15 and 30 minutes and 1, 2, 3 and 4 hours
- Whole body plethysmography at 1.25 hours
- Questioning for adverse events
- Continue 24 hour Holter monitoring to at least 24 hours post-dose and prior to Day 3 dose

Patients will stay at the study centre overnight, unless they need to return home overnight and this is agreeable to the Investigator.

6.4 Treatment Period 1; Days 3 to 4

Patients must remain in the unit for at least 24 hours after morning dosing on Day 3. Patients will be fasting from 2 hours pre-dose until 2 hours post-dose (except for water) and other restrictions defined in Section 5.4.2 should be adhered to. The following assessments will be performed:

6.4.1 Pre-Dose Assessments

- Questioning for adverse events
- 12-lead ECG
- Vital signs
- Spirometry
- 24 hour Holter monitor removed
- Blood sample for pharmacokinetics

6.4.2 Study Treatment Administration

Patients will be dosed with open label tiotropium DPI 18 mcg (two inhalations from one capsule) followed immediately (within 2 minutes) with either blinded RPL554 or placebo using a nebuliser according to randomisation scheme. There is no evening dose of study treatment on Day 3 of each period.

6.4.3 Post-Dose Assessments

Note: 24 hour assessments will be performed in the morning on Day 4 prior to discharge from the study centre.

- 12-lead ECGs at 2, 4 and 24 hours
- Vital signs at 30 minutes and 1, 2, 4, 6, 8 and 24 hours
- Spirometry at 5, 15 and 30 minutes and 1, 1.5, 2, 4, 6, 8, 12, 15 and 24 hours
- Questioning for adverse events

- Blood samples for pharmacokinetics at 5, 30 and 45 minutes and 1, 1.5, 2, 4, 8, 12, 15 and 24 hours
- Blood sample for laboratory safety tests (haematology and biochemistry) at 24 hours
- Brief physical examination, can be performed any time prior to discharge (Day 4)

The procedures listed above for Treatment Period 1 will be repeated for Treatment Period 2 and Treatment Period 3. Patients will be instructed to return in 7 to 21 days (taken from last dose of study medication on Day 3) for the next visit, or if Treatment Period 3, to return in 4 to 10 days (from Day 4) for the end of study visit.

6.5 End of Study Visit

The following will be performed:

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

7 STUDY METHODOLOGY

7.1 Demographics, Baseline Characteristics and Eligibility Assessments

Safety assessments (laboratory safety assessments, vital signs, 12-lead ECG and physical examination) will be performed at screening as part of the eligibility assessment as described in Section 7.4.2 to Section 7.4.5.

7.1.1 Demographic Variables

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

7.1.2 Medical/Surgical and Disease History

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

7.1.3 Reversibility Test

Reversibility in response to salbutamol will be assessed at screening as an eligibility measure. Spirometry (FEV₁ and FVC) assessment before and after four puffs (400 mcg) of salbutamol administered using a pMDI will be performed.

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

The following must be confirmed for inclusion:

- Post-bronchodilator FEV₁/FVC ratio of ≤ 0.70
- Post-bronchodilator FEV₁ $\geq 40\%$ and $\leq 80\%$ of predicted normal*
- Demonstrates ≥ 150 mL increase from pre-bronchodilator FEV₁

*NHANES III (Hankinson et al, 1999) will be used as a reference for normal predicted values.

7.1.4 Screening Laboratory Eligibility Assessments

At screening, blood samples will be taken and tested at the Local Laboratory for human immunodeficiency virus, hepatitis B and hepatitis C serology. All female patients of childbearing potential will have a serum pregnancy test.

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

An alcohol breath test will be performed by the study centre at screening. Urine pregnancy tests for female patients of childbearing potential will also be performed by the study centre at screening (confirmed to be negative prior to the chest X-ray), on Day 1 of each treatment period and at the end of study visit.

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

7.1.5 Prior and Concomitant Medications and Therapies

Prior COPD therapies and medications will be recorded at screening and concomitant use during the study recorded as described in Section 5.9.1.

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

7.1.6 Eligibility Check

Patients will be confirmed as eligible according to the inclusion and exclusion criteria from assessments made at screening with a final check of all results pre-dose in Treatment Period 1.

7.2 Pharmacodynamic Assessments

7.2.1 Pulmonary Function Tests

Spirometry (FEV₁ and FVC) will be performed at screening, the end of study visit and the following time points in each treatment period:

- Day 1: pre-dose; 5, 15 and 30 minutes and 1, 1.5, 2, 4, 6, 8 and 12 hours
- Day 2: pre-dose; 15 and 30 minutes and 1, 2, 3 and 4 hours
- Day 3: pre-dose; 5, 15 and 30 minutes and 1, 1.5, 2, 4, 6, 8, 12, 15 and 24 hours

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

Spirometry assessments will be made in accordance with ATS/ERS guidelines (Miller et al, 2005). At all timepoints, three technically acceptable measurements should be made and recorded. Spirometry assessments may be performed up to eight times to obtain three acceptable readings according to ATS guidelines (Miller, 2005). The highest FEV₁ and FVC readings from each assessment will be used for analysis even if the FEV₁ and FVC values come from two different forced exhalations.

7.2.2 Whole Body Plethysmography

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

Whole body plethysmography will be performed pre-dose on Day 1 and pre-dose and 1.25 hours post-dose on Day 2 of each treatment period. Assessments will be made in accordance with ATS/ERS guidelines (Wanger et al, 2005).

Patients will be placed on a body box for plethysmographic determination of lung volumes, to include RV, FRC and total lung capacity (TLC). Additionally, measurements will be made of sG_{aw} and airway resistance (R_{aw}).

7.3 Pharmacokinetic Assessments

Pharmacokinetic analysis will be performed on samples taken from patients on Day 3 of each treatment period. Blood samples (4 mL at each time point) will be collected at the following timepoints: pre-dose, 5, 30 and 45 minutes and 1, 1.5, 2, 4, 8, 12, 15 and 24 hours post-dose (the 24 hour sample will be taken in the morning on Day 4 prior to discharge from the study centre). Samples will be collected by venepuncture or via indwelling cannula in the forearm into lithium heparin tubes and will be immediately chilled (ice bath). The blood will be centrifuged within 30 minutes of collection. The plasma will be separated in a refrigerated centrifuge (about 4°C) at 1100g for 15 minutes and transferred into polypropylene tubes.

After each blood collection, the plasma will be dispensed into two aliquots. After appropriate labelling, the plasma samples will be stored at, or below -20°C. The plasma samples will then be transported in dry ice to an external laboratory where they will be stored at or below -20°C until they are submitted for analysis with a validated method. Analysis will be performed by a Central Laboratory.

7.4 Safety Assessments

7.4.1 Adverse Events

Recording and reporting adverse events is described in detail in Section 8.

7.4.2 Laboratory Safety Tests

In addition to the laboratory tests detailed in Section 7.4.2.1 to Section 7.4.2.3, unscheduled and/or repeat testing may be performed at the discretion of the Investigator. Any additional laboratory results will also be merged into the final database. Laboratory results will be provided to the Investigator for each patient and each visit. The Investigator should assign whether each abnormal result is not clinically significant or a clinically significant by manually annotating a print out of the results.

Samples will be taken and handled according to the laboratory manual and analysed at an approved Local Laboratory.

7.4.2.1 Haematology

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

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

7.4.2.2 Biochemistry

The following will be measured at screening, on Day 4 of each treatment period and at the end of study visit: creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine transaminase, gamma-GT, lactate dehydrogenase, creatine kinase, thyroid stimulating hormone, triiodothyronine and thyroxine, glucose, potassium, sodium and calcium.

At each timepoint, a sample of venous blood will be collected in a vacutainer collection tube.

7.4.2.3 Urinalysis

A midstream urine sample will be collected in a sterile container at screening and at the end of study visit. The following will be tested: leukocytes, blood, ketones, bilirubin, urobilinogen, protein and glucose.

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

7.4.3 Vital Signs

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

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

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

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

7.4.4 Physical Examination

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

A brief physical examination, including assessments of the skin, respiratory system, cardiovascular system, and abdomen (liver and spleen). will be performed pre-dose on Day 1 and prior to discharge from the study centre on Day 4.

7.4.5 12-Lead ECG

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

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

Post-dose measurements will be taken in relation to the morning dose of tiotropium DPI and RPL554 or placebo. The 24 hour measurement on Day 3 will be taken in the morning on Day 4 prior to discharge from the study centre.

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

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

7.4.6 Holter Monitoring

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

A Holter monitor will also be placed at least 30 minutes pre-dose on Day 2 of each treatment period and removed after at least 24 hours post-dose and pre-dose on Day 3.

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

7.5 Appropriateness of Measurements

The assessments planned in this study are recognised as reliable, accurate and relevant.

Plasma concentrations of RPL554 will be evaluated using a validated assay and quality control samples will be analysed throughout the study. The concentrations will be used to determine within run, between run and overall precision and accuracy of the method. The procedures, including the limits of quantitation and results will be described in detail in a separate bioanalytical protocol and report. The timing of pharmacokinetic samples is deemed appropriate to establish the exposure of patients.

Spirometry is a standard lung function test used to screen for, and monitor, respiratory disease. Spirometry will be performed in accordance with ATS/ERS task force standardisation guidelines (Miller et al, 2005). Spirometers must be maintained and calibrated according to manufacturers' guidelines. Whole body plethysmography is a further non-invasive method to obtain information on airway obstruction (airway resistance) and lung volumes that is not available through spirometry. This method of assessing the functional state of the airways is of value for characterising the multiple, heterogeneous alterations occurring in patients with COPD. Whole body plethysmography will be performed in accordance with ATS/ERS task force standardisation guidelines (Wanger et al, 2005). Both spirometry and whole body plethysmography will be performed using the study centre's standard equipment and standard operating procedures (SOPs).

Physical examinations, vital signs, 12-lead ECGs, adverse event recording and laboratory safety tests are standard assessments of safety and tolerability. The range of assessments to be performed is deemed appropriate to detect any safety signals.

Holter monitoring is a standard method of continuously recording heart activity over periods of at least 24 hours. Interpretation will be performed by a specialised central vendor.

8 HANDLING OF ADVERSE EVENTS AND PREGNANCIES

8.1 Adverse Event Definitions

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 treatment. An adverse event may be any of the following:

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

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

Adverse reaction is defined as all untoward and unintended responses to study treatment related to any dose administered.

Serious adverse event (SAE) is any adverse experience that:

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

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

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

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

8.2 Recording and Assessing Adverse Events

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

8.2.1 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

8.2.2 Chronicity

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

8.2.3 Causality

Not related	This category applies to those adverse events which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.)
Unlikely	<p>In general, this category can be considered applicable to those adverse events which, after careful medical consideration at the time they are evaluated, are deemed unlikely to be related to the study treatment but cannot be ruled out with certainty. An adverse event may be considered unlikely to be related if or when (must have two of the following):</p> <ol style="list-style-type: none">1. It does not follow a reasonable temporal sequence from administration of the study treatment.2. It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patients.3. It does not follow a known pattern of response to the study treatment.4. It does not reappear or worsen when the drug is re-administered.
Possibly	<p>This category applies to those adverse events for which, after careful medical consideration at the time they are evaluated, a plausible temporal relationship with the study treatment administration and a biological plausibility are present. An adverse event may be considered possibly related if or when (must have two of the following):</p> <ol style="list-style-type: none">1. It follows a reasonable temporal sequence from administration of the study treatment.2. It could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patients.

- Definitely
3. It follows a known pattern of response to the study treatment.
- This category applies to those adverse events which the Investigator feels are incontrovertibly related to study treatment. An adverse event may be assigned an attribution of definitely related if or when (must have all of the following):
1. It follows a reasonable temporal sequence from administration of the study treatment.
 2. It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental, or toxic factors, or other modes of therapy administered to the patients.
 3. It disappears or decreases on cessation or reduction in dose and recurs with re-exposure to study treatment. (Note: this is not to be construed as requiring re-exposure of the patient; however, a category of definitely related can only be used when a recurrence is observed.)
 4. It follows a known pattern of response to the study treatment.

8.2.4 Action and Outcome

- Action taken with study treatment (none, study treatment stopped, study treatment temporarily interrupted)
- Other actions (none, concomitant medication, study discontinuation, hospitalisation, other)
- The outcome and date of outcome according to the following definitions:
 - Recovered or resolved (adverse event disappeared)
 - Recovering or resolving (patient is recovering)
 - Not recovered or not resolved (adverse event remains without signs of improvement)
 - Recovered or resolved with sequelae (adverse event has resulted in permanent disability or incapacity)
 - Fatal
 - Unknown (only applicable if patient has been lost to follow-up)
- Seriousness (yes or no)

8.3 Reporting Procedure for SAEs

The Investigator must report all SAEs to the Sponsor in writing using the Sponsor's reporting form and emailed (email address included on Page 2) to as soon as practical, but in no case should it be more than 24 hours of awareness. Any SAEs notified in the 30 day period after the last dose of study treatment must also be reported

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

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

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

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

8.4 Management of Pregnancies

Women of childbearing potential (female subjects and partners of male subjects) should use a highly effective method of contraception, defined as:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
 - Oral
 - Intravaginal
 - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
 - Oral
 - Injectable
 - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence - 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 preferred and usual lifestyle of the subject.

Should a female patient become pregnant or a male patient father a child during the study or in the 2 months after the last study treatment they must inform the Investigator immediately. The Investigator will report this information to the Sponsor within 7 days of awareness using a pregnancy reporting form. 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.

9 QUALITY ASSURANCE AND QUALITY CONTROL

The study will be conducted in accordance with the current approved protocol, SOPs and all applicable guidelines and requirements (see Section 11).

9.1 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.

9.2 Monitoring and Source Document Verification

The Sponsor will arrange for the study to be monitored in accordance with the principles of ICH GCP. The frequency of monitoring visits will be determined by the rate of patient recruitment.

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

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

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

The Investigator must permit the study monitor, the ethics committee, the Sponsor's auditors and representatives from regulatory authorities direct access to all source documents for confirmation of the accuracy and reliability of data contained within the eCRFs (source document verification).

Patient confidentiality will be protected at all times. Identifying information (including name) will be made known to certain Sponsor personnel or designees (e.g. monitor, auditor) as well as regulatory authorities (e.g. inspector) whilst they are on site, but only to the extent necessary for review of source documents.

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 adverse events/medication changes, SAEs and information on patient withdrawal

- Informed consent form
- 12-lead ECGs
- Laboratory reports
- Visit dates
- Study treatment 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.

9.3 Data Management and Coding

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

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

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

Data entered into the eCRF will be validated as defined in the data validation plan. Validation includes, but is not limited to, validity checks (e.g. range checks), consistency checks and customised checks (logical checks between variables to ensure that study data are accurately reported) for eCRF data and external data (e.g. laboratory 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 eCRFs to improve data quality.

Laboratory safety test, Holter, 12-lead ECG and pharmacokinetic data will be transferred electronically into the study database. Discrepancies will be queried to the site and/or the laboratory until the electronic data and the database are reconciled.

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

Once the full set of eCRFs have been completed and locked, the Sponsor will authorise database lock and all electronic data will be sent to the designated statistician for analysis.

Subsequent changes to the database will then only be made only by written agreement of the Sponsor.

Adverse events will be coded from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA) ([specify version] or later). Prior and concomitant medications and COPD therapies will be coded according to the World health Organisation drug code. An independent coding review will be performed by the Sponsor.

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

10 STATISTICAL METHODS

10.1 Statistical and Analytical Plans

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

10.2 Populations to be Analysed

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

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

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

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

10.3 Study Endpoints

10.3.1 Primary Endpoints

Peak FEV₁ (measured in first 4 hours after dosing) and AUC_{0-12h} FEV₁. These will be measured after dosing on Day 3.

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

10.3.2 Secondary Endpoints

- Determination of AUC_{0-4h} FEV₁ after morning dosing
- Peak FEV₁ (measured in first 4 hours after dosing) and AUC_{0-12h} FEV₁. These will be measured after dosing on Day 1.
- Determination of onset of action (>10% increase in FEV₁, from pre-first dose, censored at 120 minutes) on Day 1
- RV, FRC and sG_{aw} at 1.25 hours after dosing on Day 2
- RPL554 steady state pharmacokinetics (AUC, C_{max}, time to maximum concentration [t_{max}], half-life)
- Safety and tolerability:
 - Continuous monitoring of adverse events
 - Laboratory safety tests [haematology, biochemistry and urinalysis]
 - 12-lead ECG (including QTcF and heart rate), supine vital signs [blood pressure and pulse rate]

- Peak (measured in first 4 hours after dosing) and AUC_{0-4h} pulse rate for each treatment period.
- Holter monitor results

10.3.3 Exploratory Endpoints

- AUC_{0-24h} FEV₁ on Day 3
- Pre-dose FEV₁ on Day 3

10.4 Statistical Methods

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

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

10.4.1 Patient Disposition

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

10.4.2 Protocol Deviations

All protocol deviations collected will be divided into 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.

10.4.3 Demographics and Other Baseline Characteristics

Demographics and baseline characteristics (including pre- and post-bronchodilator FEV₁ [both in litres and in percentage of predicted normal], post-bronchodilator FEV₁/FVC, FEV₁ reversibility, duration of COPD [time since diagnosis], smoking habits including number of pack years, number of patients taking COPD medications by therapeutic class) will be listed and summarised appropriately.

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

10.4.4 Extent of Exposure and Treatment Compliance

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

10.4.5 Efficacy/Pharmacodynamics

FEV₁ and FVC will be summarised as actual and change from baseline using descriptive statistics over time.

The peak effect on FEV₁ during these time intervals will be computed as the maximum value in the 4 hours after dosing minus the pre-dose Day 1 baseline value. The average effect will be calculated as the AUC divided by the length of the time interval of interest divided by the pre-dose Day 1 baseline value.

Computed pharmacodynamic parameters for FEV₁ will be compared between the three study treatments using analysis of covariance (ANCOVA) models with fixed factors for treatment, period and patient, and using the baseline of the visit (pre-first dose in a treatment period) as a covariate. FEV₁ will be analysed using multiplicative models, which means that data (dependent and baseline) is logged prior to analysis and the result then transformed back to the linear scale giving treatment differences as ratios of geometric means.

Primarily the combination RPL554+tiotropium will be compared to tiotropium alone for each of the two doses of RPL554. Results of the comparisons will be expressed as the mean geometric ratio with 95% confidence intervals and associated, 2-sided, p-value.

Onset of action will be summarised by treatment and a Kaplan-Meier plot illustrating time to onset constructed.

Outcomes from the whole body plethysmography at 1.25 hours post-dose on Day 2 will be compared in the same way as FEV₁ using multiplicative ANOVA models. The baseline of the visit (pre-first dose in a treatment period) will be used as covariate in these models.

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

10.4.6 Pharmacokinetics

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

- AUC_{0-12h} and AUC_{0-24h} represent the area under the plasma concentration curve from time 0 to either 12 or 24 hours after dose on Day 3. The AUC_{0-12h} value is indicative of the steady state AUC_T for a twice daily dosage regimen of RPL554 for the study cohort
- C_{max} denotes the highest plasma concentration measured
- t_{max} denotes the time point corresponding to C_{max}
- t_{1/2} denotes the estimated half-life and is computed as $\ln(2)/\lambda_z$

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

10.4.7 Safety

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

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

10.4.8 Handling of Withdrawals or Missing Data

Patients withdrawn after only one treatment period will not be included in the efficacy analyses. Imputation of data for calculation of average (AUC) effects for FEV₁ will be described in the statistical analysis plan. No other imputation of missing data will be performed.

All available data from all dosed patients who have received study treatment will be listed and summarised. Any unscheduled or unplanned readings will be presented within the patient listings, but only the scheduled readings will be used in any summaries. If a visit is rescheduled due to variability in FEV₁ or other reason, the rescheduled visit will be listed and summarised as the valid visit.

10.4.9 Interim Analyses

No formal interim analysis is planned for the study.

10.5 Determination of Sample Size

This is a complete block three way crossover study. Assuming a residual CV of 6% for peak FEV₁, 24 patients will give an 80% power to detect a pairwise difference in peak FEV₁ of 5.1%. Assuming a mean baseline FEV₁ of 1.3 litres this will correspond to a difference of about 66 mL. The detectable difference for FEV₁ AUC_{0-12h} is expected to be similar as for the peak.

11 ETHICAL CONSIDERATIONS

11.1 Guidelines

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

11.2 Ethics and Regulatory Approval

The Sponsor will supply all background data necessary to enable submission to the appropriate ethics committee and regulatory authority. 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.

11.3 Informed Consent Process

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

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

11.4 Patient Confidentiality

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

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

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

11.5 Record Maintenance/Retention

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

11.6 Availability of Study Results

A summary of the study results will be made available via press release and posted at clinicaltrials.gov. Study patients inquiring about the results will be provided with instructions to access these references.

12 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.

13 PUBLICATION POLICY

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

14 REFERENCES

Abbott-Banner KH, Page CP. Dual PDE3/4 and PDE4 inhibitors: novel treatments for COPD and other inflammatory airway diseases. *Basic Clin Pharmacol Toxicol*. 2014 May;114(5):365-76. Doi: 10.1111/bcpt.12209. Epub 2014 Mar 6.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Verona Pharma plc RPL554 Investigator Brochure 10/2016.

Verona Pharma plc RPL554 Investigational Medicinal Product Dossier current version

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

Verona Pharma plc. RPL554-009-2015 Clinical Study Report (in preparation).

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

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

15 APPENDICES

15.1 Instructions for Tiotropium Use

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SPIRIVA HANDIHALER safely and effectively. See full prescribing information for SPIRIVA HANDIHALER.

SPIRIVA® HANDIHALER® (tiotropium bromide inhalation powder), for oral inhalation use
Initial U.S. Approval: 2004

INDICATIONS AND USAGE

SPIRIVA HANDIHALER 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)

DOSAGE AND ADMINISTRATION

- For oral inhalation only. DO NOT swallow SPIRIVA capsules. Only use SPIRIVA capsules with the HANDIHALER device (2)
- Two inhalations of the powder contents of a single SPIRIVA capsule (18 mcg) once daily (2)

DOSAGE FORMS AND STRENGTHS

Inhalation powder: SPIRIVA capsules contain 18 mcg tiotropium powder for use with HANDIHALER device (3)

CONTRAINDICATIONS

Hypersensitivity to tiotropium, ipratropium, or any components of SPIRIVA capsules (4)

WARNINGS AND PRECAUTIONS

- Not for acute use: Not a rescue medication (5.1)
- Immediate hypersensitivity reactions: Discontinue SPIRIVA HANDIHALER at once and consider alternatives if immediate hypersensitivity reactions, including angioedema, bronchospasm, or

anaphylaxis, occur. Use with caution in patients with severe hypersensitivity to milk proteins. (5.2)

- Paradoxical bronchospasm: Discontinue SPIRIVA HANDIHALER 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 patients to consult a physician immediately if this occurs. (5.5)

ADVERSE REACTIONS

The most common adverse reactions (>5% incidence in the 1-year placebo-controlled trials) were upper respiratory tract infection, dry mouth, sinusitis, pharyngitis, non-specific chest pain, urinary tract infection, dyspepsia, and rhinitis (6.1)

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 HANDIHALER 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: 1/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SPIRIVA HANDIHALER (tiotropium bromide inhalation powder) is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. SPIRIVA HANDIHALER is indicated to reduce exacerbations in COPD patients.

2 DOSAGE AND ADMINISTRATION

For oral inhalation only. Do not swallow SPIRIVA capsules, as the intended effects on the lungs will not be obtained. The contents of the SPIRIVA capsules should only be used with the HANDIHALER device [see *Overdosage (10)*].

The recommended dose of SPIRIVA HANDIHALER is two inhalations of the powder contents of one SPIRIVA capsule, once-daily, with the HANDIHALER device [see *Patient Counseling Information (17)*]. Do not take more than one dose in 24 hours.

For administration of SPIRIVA HANDIHALER, a SPIRIVA capsule is placed into the center chamber of the HANDIHALER device. The SPIRIVA capsule is pierced by pressing and releasing the green piercing button on the side of the HANDIHALER device. The tiotropium formulation is dispersed into the air stream when the patient inhales through the mouthpiece [see *Patient Counseling Information (17)*].

No dosage adjustment is required for geriatric, hepatically-impaired, or renally-impaired patients. However, patients with moderate to severe renal impairment given SPIRIVA HANDIHALER should be monitored closely for anticholinergic effects [see *Warnings and Precautions (5.6)*, *Use in Specific Populations (8.5, 8.6, 8.7)*, and *Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

Inhalation Powder: SPIRIVA HANDIHALER consists of SPIRIVA capsules containing tiotropium powder for oral inhalation and a HANDIHALER device. SPIRIVA capsules contain 18 mcg of tiotropium in a light green, hard gelatin capsule with TI 01 printed on one side and Boehringer Ingelheim company logo on the other side. The HANDIHALER device is only intended for use with the SPIRIVA capsules.

4 CONTRAINDICATIONS

SPIRIVA HANDIHALER is contraindicated in patients with a hypersensitivity to tiotropium, ipratropium, or any components of this product [see *Warnings and Precautions (5.2)*]. In clinical trials and postmarketing experience with SPIRIVA HANDIHALER, immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash have been reported [see *Warnings and Precautions (5.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Not for Acute Use

SPIRIVA HANDIHALER is intended as a once-daily maintenance treatment for COPD and should not be used for relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm.

5.2 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions, including urticaria, angioedema (including swelling of the lips, tongue, or throat), rash, bronchospasm, anaphylaxis, or itching, may occur after administration of SPIRIVA HANDIHALER. If such a reaction occurs, therapy with SPIRIVA HANDIHALER should be stopped at once and alternative treatments should be considered. Given the similar structural formula of atropine to tiotropium, patients with a history of hypersensitivity reactions to atropine or its derivatives should be closely monitored for similar hypersensitivity reactions to SPIRIVA HANDIHALER. In addition, SPIRIVA HANDIHALER should be used with caution in patients with severe hypersensitivity to milk proteins.

5.3 Paradoxical Bronchospasm

Inhaled medicines, including SPIRIVA HANDIHALER, may cause paradoxical bronchospasm. If this occurs, it should be treated immediately with an inhaled short-acting beta₂-agonist such as albuterol. Treatment with SPIRIVA HANDIHALER should be stopped and other treatments considered.

5.4 Worsening of Narrow-Angle Glaucoma

SPIRIVA HANDIHALER should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

5.5 Worsening of Urinary Retention

SPIRIVA HANDIHALER should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

5.6 Renal Impairment

As a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of <60 mL/min) treated with SPIRIVA HANDIHALER should be monitored closely for anticholinergic side effects [see *Clinical Pharmacology (12.3)*].

6 ADVERSE REACTIONS

The following adverse reactions are described, or described in greater detail, in other sections:

- Immediate hypersensitivity reactions [see *Warnings and Precautions (5.2)*]

- Paradoxical bronchospasm [see Warnings and Precautions (5.3)]
- Worsening of narrow-angle glaucoma [see Warnings and Precautions (5.4)]
- Worsening of urinary retention [see Warnings and Precautions (5.5)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the incidence of adverse reactions observed in the clinical trials of a drug cannot be directly compared to the incidences in the clinical trials of another drug and may not reflect the incidences observed in practice.

6-Month to 1-Year Trials

The data described below reflect exposure to SPIRIVA HANDIHALER in 2663 patients. SPIRIVA HANDIHALER was studied in two 1-year placebo-controlled trials, two 1-year active-controlled trials, and two 6-month placebo-controlled trials in patients with COPD. In these trials, 1308 patients were treated with SPIRIVA HANDIHALER at the recommended dose of 18 mcg once a day. The population had an age ranging from 39 to 87 years with 65% to 85% males, 95% Caucasian, and had COPD with a mean pre-bronchodilator forced expiratory volume in one second (FEV₁) percent predicted of 39% to 43%. Patients with narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials. An additional 6-month trial conducted in a Veteran's Affairs setting is not included in this safety database because only serious adverse events were collected.

The most commonly reported adverse drug reaction was dry mouth. Dry mouth was usually mild and often resolved during continued treatment. Other reactions reported in individual patients and consistent with possible anticholinergic effects included constipation, tachycardia, blurred vision, glaucoma (new onset or worsening), dysuria, and urinary retention.

Four multicenter, 1-year, placebo-controlled and active-controlled trials evaluated SPIRIVA HANDIHALER in patients with COPD. Table 1 shows all adverse reactions that occurred with a frequency of $\geq 3\%$ in the SPIRIVA HANDIHALER group in the 1-year placebo-controlled trials where the rates in the SPIRIVA HANDIHALER group exceeded placebo by $\geq 1\%$. The frequency of corresponding reactions in the ipratropium-controlled trials is included for comparison.

Table 1 Adverse Reactions (% Patients) in One-Year COPD Clinical Trials

Body System (Event)	Placebo-Controlled Trials		Ipratropium-Controlled Trials	
	SPIRIVA (n = 550)	Placebo (n = 371)	SPIRIVA (n = 356)	Ipratropium (n = 179)
Body as a Whole				
Chest Pain (non-specific)	7	5	5	2
Edema, Dependent	5	4	3	5
Gastrointestinal System Disorders				
Dry Mouth	16	3	12	6
Dyspepsia	6	5	1	1
Abdominal Pain	5	3	6	6
Constipation	4	2	1	1
Vomiting	4	2	1	2
Musculoskeletal System				
Myalgia	4	3	4	3
Resistance Mechanism Disorders				
Infection	4	3	1	3
Moniliasis	4	2	3	2
Respiratory System (Upper)				
Upper Respiratory Tract Infection	41	37	43	35
Sinusitis	11	9	3	2
Pharyngitis	9	7	7	3
Rhinitis	6	5	3	2
Epistaxis	4	2	1	1
Skin and Appendage Disorders				
Rash	4	2	2	2
Urinary System				
Urinary Tract Infection	7	5	4	2

Arthritis, coughing, and influenza-like symptoms occurred at a rate of $\geq 3\%$ in the SPIRIVA HANDIHALER treatment group, but were $<1\%$ in excess of the placebo group.

Other reactions that occurred in the SPIRIVA HANDIHALER group at a frequency of 1% to 3% in the placebo-controlled trials where the rates exceeded that in the placebo group include: *Body as a Whole*: allergic reaction, leg pain; *Central and Peripheral Nervous System*: dysphonia, paresthesia; *Gastrointestinal System Disorders*: gastrointestinal disorder not otherwise specified (NOS), gastroesophageal reflux, stomatitis (including ulcerative stomatitis); *Metabolic and Nutritional Disorders*: hypercholesterolemia, hyperglycemia; *Musculoskeletal System Disorders*: skeletal pain; *Cardiac Events*: angina pectoris (including aggravated angina pectoris); *Psychiatric Disorder*: depression; *Infections*: herpes zoster; *Respiratory System Disorder (Upper)*: laryngitis; *Vision Disorder*: cataract. In addition, among the adverse reactions observed in the clinical trials with an incidence of $<1\%$ were atrial fibrillation, supraventricular tachycardia, angioedema, and urinary retention.

In the 1-year trials, the incidence of dry mouth, constipation, and urinary tract infection increased with age [see Use in Specific Populations (8.5)].

Two multicenter, 6-month, controlled studies evaluated SPIRIVA HANDIHALER in patients with COPD. The adverse reactions and the incidence rates were similar to those seen in the 1-year controlled trials.

4-Year Trial

The data described below reflect exposure to SPIRIVA HANDIHALER in 5992 COPD patients in a 4-year placebo-controlled trial. In this trial, 2986 patients were treated with SPIRIVA HANDIHALER at the recommended dose of 18 mcg once a day. The population had an age range from 40 to 88 years, was 75% male, 90% Caucasian, and had COPD with a mean pre-bronchodilator FEV₁ percent predicted of 40%. Patients with narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials. When the adverse reactions were analyzed with a frequency of $\geq 3\%$ in the SPIRIVA HANDIHALER group where the rates in the SPIRIVA HANDIHALER group exceeded placebo by $\geq 1\%$, adverse reactions included (SPIRIVA HANDIHALER, placebo): pharyngitis (12.5%, 10.8%), sinusitis (6.5%, 5.3%), headache (5.7%, 4.5%), constipation (5.1%, 3.7%), dry mouth (5.1%, 2.7%), depression (4.4%, 3.3%), insomnia (4.4%, 3.0%), and arthralgia (4.2%, 3.1%).

Additional Adverse Reactions

Other adverse reactions not previously listed that were reported more frequently in COPD patients treated with SPIRIVA HANDIHALER than placebo include: dehydration, skin ulcer, stomatitis, gingivitis, oropharyngeal candidiasis, dry skin, skin infection, and joint swelling.

6.2 Postmarketing Experience

Adverse reactions have been identified during worldwide post-approval use of SPIRIVA HANDIHALER. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions are: application site irritation (glossitis, mouth ulceration, and pharyngolaryngeal pain), dizziness, dysphagia, hoarseness, intestinal obstruction including ileus paralytic, intraocular pressure increased, oral candidiasis, palpitations, pruritus, tachycardia, throat irritation, and urticaria.

7 DRUG INTERACTIONS

7.1 Sympathomimetics, Methylxanthines, Steroids

SPIRIVA HANDIHALER has been used concomitantly with short-acting and long-acting sympathomimetic (beta-agonists) bronchodilators, methylxanthines, and oral and inhaled steroids without increases in adverse reactions.

7.2 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid coadministration of SPIRIVA HANDIHALER with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects [see *Warnings and Precautions (5.4, 5.5) and Adverse Reactions (6)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. SPIRIVA HANDIHALER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

No evidence of structural alterations was observed in rats and rabbits at approximately 790 and 8 times the maximum recommended human daily inhalation dose (MRHDID), respectively (on a mcg/m² basis at maternal inhalation doses of 1471 and 7 mcg/kg/day in rats and rabbits, respectively). However, in rats, tiotropium caused fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation at inhalation tiotropium doses of approximately 40 times the MRHDID (on a mcg/m² basis at a maternal inhalation dose of 78 mcg/kg/day). In rabbits, tiotropium caused an increase in post-implantation loss at an inhalation dose of approximately 430 times the MRHDID (on a mcg/m² basis at a maternal inhalation dose of 400 mcg/kg/day). Such effects were not observed at inhalation doses of approximately 5 and 95 times the MRHDID, respectively (on a mcg/m² basis at inhalation doses of 9 and 88 mcg/kg/day in rats and rabbits, respectively).

8.2 Labor and Delivery

The safety and effectiveness of SPIRIVA HANDIHALER has not been studied during labor and delivery.

8.3 Nursing Mothers

Clinical data from nursing women exposed to tiotropium are not available. Based on lactating rodent studies, tiotropium is excreted into breast milk. It is not known whether tiotropium is excreted in human milk, but because many drugs are excreted in human milk and given these findings in rats, caution should be exercised if SPIRIVA HANDIHALER is administered to a nursing woman.

8.4 Pediatric Use

SPIRIVA HANDIHALER is not indicated for use in children. The safety and effectiveness of SPIRIVA HANDIHALER in pediatric patients have not been established.

8.5 Geriatric Use

Based on available data, no adjustment of SPIRIVA HANDIHALER dosage in geriatric patients is warranted [see *Clinical Pharmacology (12.3)*].

Of the total number of patients who received SPIRIVA HANDIHALER in the 1-year clinical trials, 426 were <65 years, 375 were 65 to 74 years, and 105 were ≥ 75 years of age. Within each age subgroup, there were no differences between the proportion of patients with adverse events in the SPIRIVA HANDIHALER and the comparator groups for most events. Dry mouth increased with age in the SPIRIVA HANDIHALER group (differences from placebo were 9.0%, 17.1%, and 16.2% in the aforementioned age subgroups). A higher frequency of constipation and urinary tract infections with increasing age was observed in the SPIRIVA HANDIHALER group in the placebo-controlled studies. The differences from placebo for constipation were 0%, 1.8%, and 7.8% for each of the age groups. The differences from placebo for urinary tract infections were -0.6%, 4.6%, and 4.5%. No overall differences in effectiveness were observed among these groups.

8.6 Renal Impairment

Patients with moderate to severe renal impairment (creatinine clearance of <60 mL/min) treated with SPIRIVA HANDIHALER should be monitored closely for anticholinergic side effects [see *Dosage and Administration* (2), *Warnings and Precautions* (5.6), and *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied.

10 OVERDOSAGE

High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 mcg tiotropium in 6 healthy volunteers. In a study of 12 healthy volunteers, bilateral conjunctivitis and dry mouth were seen following repeated once-daily inhalation of 141 mcg of tiotropium.

Treatment of overdosage consists of discontinuation of SPIRIVA HANDIHALER together with institution of appropriate symptomatic and/or supportive therapy.

Accidental Ingestion

Acute intoxication by inadvertent oral ingestion of SPIRIVA capsules is unlikely since it is not well-absorbed systemically.

A case of overdose has been reported from postmarketing experience. A female patient was reported to have inhaled 30 capsules over a 2.5 day period, and developed altered mental status, tremors, abdominal pain, and severe constipation. The patient was hospitalized, SPIRIVA HANDIHALER was discontinued, and the constipation was treated with an enema. The patient recovered and was discharged on the same day.

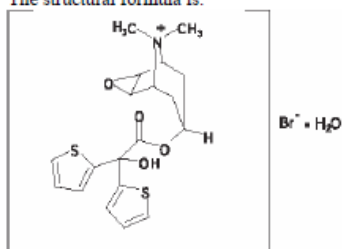
11 DESCRIPTION

SPIRIVA HANDIHALER consists of SPIRIVA capsules and a HANDIHALER device. Each light green, hard gelatin SPIRIVA capsule contains a dry powder consisting of 18 mcg tiotropium (equivalent to 22.5 mcg tiotropium bromide monohydrate) blended with lactose monohydrate (which may contain milk proteins).

The contents of SPIRIVA capsules are intended for oral inhalation only, and are intended for administration only with the HANDIHALER device.

The active component of SPIRIVA HANDIHALER is tiotropium. The drug substance, tiotropium bromide monohydrate, is an anticholinergic with specificity for muscarinic receptors. It is chemically described as (1 α , 2 β , 4 β , 5 α , 7 β)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}]nonane bromide monohydrate. It is a synthetic, non-chiral, quaternary ammonium compound. Tiotropium bromide is a white or yellowish white powder. It is sparingly soluble in water and soluble in methanol.

The structural formula is:



Tiotropium bromide (monohydrate) has a molecular mass of 490.4 and a molecular formula of $\text{C}_{19}\text{H}_{22}\text{NO}_4\text{S}_2\text{Br} \cdot \text{H}_2\text{O}$.

The HANDIHALER device is an inhalation device used to inhale the dry powder contained in the SPIRIVA capsule. The dry powder is delivered from the HANDIHALER device at flow rates as low as 20 L/min. Under standardized *in vitro* testing, the HANDIHALER device delivers a mean of 10.4 mcg tiotropium when tested at a flow rate of 39 L/min for 3.1 seconds (2 L total). In a study of 26 adult patients with COPD and severely compromised lung function [mean FEV₁ 1.02 L (range 0.45 to 2.24 L); 37.6% of predicted (range 16% to 65%)], the median peak inspiratory flow (PIF) through the HANDIHALER device was 30.0 L/min (range 20.4 to 45.6 L/min). The amount of drug delivered to the lungs will vary depending on patient factors such as inspiratory flow and peak inspiratory flow through the HANDIHALER device, which may vary from patient to patient, and may vary with the exposure time of the SPIRIVA capsule outside the blister pack.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tiotropium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors, M₁ to M₅. In the airways, it exhibits pharmacological effects through inhibition of M₃-receptors at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical *in vitro* as well as *in vivo* studies, prevention of methacholine-induced bronchoconstriction effects was dose-dependent and lasted longer than 24 hours. The bronchodilation following inhalation of tiotropium is predominantly a site-specific effect.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a multicenter, randomized, double-blind trial using tiotropium dry powder for inhalation that enrolled 198 patients with COPD, the number of subjects with changes from baseline-corrected QT interval of 30 to 60 msec was higher in the SPIRIVA HANDIHALER group as compared with placebo. This difference was apparent using both the Bazett (QTcB) [20 (20%) patients vs. 12 (12%) patients] and Fredericia (QTcF) [16 (16%) patients vs. 1 (1%) patient] corrections of QT for heart rate. No patients in either group had either QTcB or QTcF of >500 msec. Other clinical studies with SPIRIVA HANDIHALER did not detect an effect of the drug on QTc intervals.

The effect of tiotropium dry powder for inhalation on QT interval was also evaluated in a randomized, placebo- and positive-controlled crossover study in 53 healthy volunteers. Subjects received tiotropium dry powder for inhalation 18 mcg, 54 mcg (3 times the recommended dose), or placebo for 12 days. ECG assessments were performed at baseline and throughout the dosing interval following the first and last dose of study medication. Relative to placebo, the maximum mean change from baseline in study-specific QTc interval was 3.2 msec and 0.8 msec for tiotropium dry powder for inhalation 18 mcg and 54 mcg, respectively. No subject showed a new onset of QTc >500 msec or QTc changes from baseline of ≥ 60 msec.

12.3 Pharmacokinetics

Tiotropium is administered by dry powder inhalation. Some of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy. A dedicated pharmacokinetic study in patients with COPD evaluating once-daily tiotropium delivered from the RESPIMAT inhaler (5 mcg) and as inhalation powder (18 mcg) from the HANDIHALER device resulted in a similar systemic exposure between the two products.

Absorption

Following dry powder inhalation by young healthy volunteers, the absolute bioavailability of 19.5% suggests that the fraction reaching the lung is highly bioavailable. Oral solutions of tiotropium have an absolute bioavailability of 2-3%. Food is not expected to influence the absorption of tiotropium. Maximum tiotropium plasma concentrations were observed 7 minutes after inhalation.

Distribution

Tiotropium is 72% bound to plasma protein and had a volume of distribution of 32 L/kg after intravenous administration to young healthy volunteers. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium does not readily penetrate the blood-brain barrier.

Elimination

The terminal half-life of tiotropium in COPD patients following once daily inhalation of 5 mcg tiotropium was approximately 25 hours. Total clearance was 880 mL/min after intravenous administration in young healthy volunteers. After chronic once-daily dry powder inhalation by COPD patients, pharmacokinetic steady state was reached by day 7 with no accumulation thereafter.

Metabolism

The extent of metabolism is small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium, an ester, is nonenzymatically cleaved to the alcohol N-methylscopine and dithienylglycolic acid, neither of which binds to muscarinic receptors.

In vitro experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered dose (74% of an intravenous dose is excreted unchanged in the urine, leaving 25% for metabolism) is metabolized by cytochrome P450-dependent oxidation and subsequent glutathione conjugation to a variety of Phase II metabolites. This enzymatic pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene. Thus, CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose. *In vitro* studies using human liver microsomes showed that tiotropium in supra-therapeutic concentrations did not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

Excretion Intravenously administered tiotropium bromide is mainly excreted unchanged in urine (74%). After dry powder inhalation to COPD patients at steady state, urinary excretion was 7% (1.3 μ g) of the unchanged dose over 24 hours. The renal clearance of tiotropium exceeds the creatinine clearance, indicating secretion into the urine.

Specific Populations

Geriatric Patients

As expected for all predominantly renally excreted drugs, advancing age was associated with a decrease of tiotropium renal clearance (365 mL/min in COPD patients <65 years to 271 mL/min in COPD patients ≥ 65 years). This did not result in a corresponding increase in AUC_{0-6,11} and C_{max,11} values following administration via HANDIHALER device.

Renal Impairment

Following 4-week SPIRIVA HANDIHALER or SPIRIVA RESPIMAT once daily dosing in patients with COPD, mild renal impairment (creatinine clearance 60-90 mL/min) resulted in 6-23% higher AUC_{0-6,11} and 6-17% higher C_{max,11} values; moderate renal impairment (creatinine clearance 30-60 mL/min) resulted in 54-57% higher AUC_{0-6,11} and 15-31% higher C_{max,11} values compared to COPD patients with normal renal function (creatinine clearance >90 mL/min). There is insufficient data for tiotropium exposure in patients with severe renal impairment (creatinine clearance <30 mL/min) following inhalation of SPIRIVA HANDIHALER or SPIRIVA RESPIMAT. However AUC₀₋₄ and C_{max} were 94% and 52% higher, respectively, in patients with severe renal impairment following intravenous infusion of tiotropium bromide.

Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied.

Drug Interactions

An interaction study with tiotropium (14.4 mcg intravenous infusion over 15 minutes) and cimetidine 400 mg three times daily or ranitidine 300 mg once daily was conducted. Concomitant administration of cimetidine with tiotropium resulted in a 20% increase in the AUC_{0-4h} , a 28% decrease in the renal clearance of tiotropium and no significant change in the C_{max} and amount excreted in urine over 96 hours. Co-administration of tiotropium with ranitidine did not affect the pharmacokinetics of tiotropium.

Common concomitant medications (long-acting beta₂-adrenergic agonists (LABA), inhaled corticosteroids (ICS)) used by patients with COPD were not found to alter the exposure to tiotropium.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was observed in a 104-week inhalation study in rats at tiotropium doses up to 59 mcg/kg/day, in an 83-week inhalation study in female mice at doses up to 145 mcg/kg/day, and in a 101-week inhalation study in male mice at doses up to 2 mcg/kg/day. These doses correspond to approximately 30, 40, and 0.5 times the recommended human daily inhalation dose (MRHDID) on a mcg/m² basis, respectively.

Tiotropium bromide demonstrated no evidence of mutagenicity or clastogenicity in the following assays: the bacterial gene mutation assay, the V79 Chinese hamster cell mutagenesis assay, the chromosomal aberration assays in human lymphocytes *in vitro* and mouse micronucleus formation *in vivo*, and the unscheduled DNA synthesis in primary rat hepatocytes *in vitro* assay.

In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation tiotropium doses of 78 mcg/kg/day or greater (approximately 40 times the MRHDID on a mcg/m² basis). No such effects were observed at 9 mcg/kg/day (approximately 5 times the MRHDID on a mcg/m² basis). The fertility index, however, was not affected at inhalation doses up to 1689 mcg/kg/day (approximately 910 times the MRHDID on a mcg/m² basis).

14 CLINICAL STUDIES

The SPIRIVA HANDIHALER (tiotropium bromide inhalation powder) clinical development program consisted of six Phase 3 studies in 2663 patients with COPD (1308 receiving SPIRIVA HANDIHALER): two 1-year, placebo-controlled studies, two 6-month, placebo-controlled studies and two 1-year, ipratropium-controlled studies. These studies enrolled patients who had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had a forced expiratory volume in one second (FEV₁) less than or equal to 60% or 65% of predicted, and a ratio of FEV₁/FVC of less than or equal to 0.7.

In these studies, SPIRIVA HANDIHALER, administered once-daily in the morning, provided improvement in lung function (FEV₁), with peak effect occurring within 3 hours following the first dose.

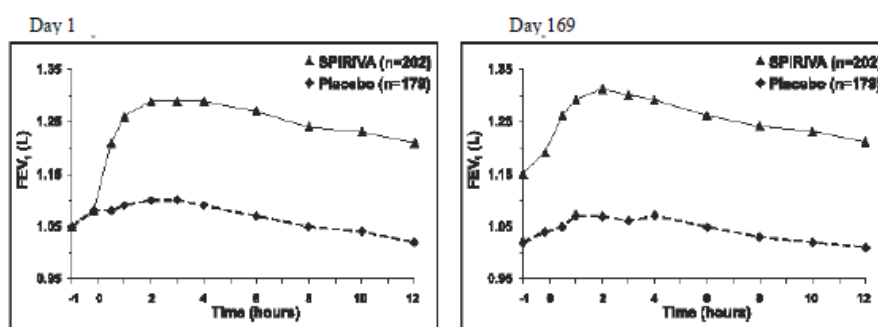
Two additional trials evaluated exacerbations: a 6-month, randomized, double-blind, placebo-controlled, multicenter clinical trial of 1829 COPD patients in a US Veterans Affairs setting and a 4-year, randomized, double-blind, placebo-controlled, multicenter, clinical trial of 5992 COPD patients. Long-term effects on lung function and other outcomes, were also evaluated in the 4-year multicenter trial.

6-Month to 1-Year Effects on Lung Function

In the 1-year, placebo-controlled trials, the mean improvement in FEV₁ at 30 minutes was 0.13 liters (13%) with a peak improvement of 0.24 liters (24%) relative to baseline after the first dose (Day 1). Further improvements in FEV₁ and forced vital capacity (FVC) were observed with pharmacodynamic steady state reached by Day 8 with once-daily treatment. The mean peak improvement in FEV₁, relative to baseline, was 0.28 to 0.31 liters (28% to 31%), after 1 week (Day 8) of once-daily treatment. Improvement of lung function was maintained for 24 hours after a single dose and consistently maintained over the 1-year treatment period with no evidence of tolerance.

In the two 6-month, placebo-controlled trials, serial spirometric evaluations were performed throughout daytime hours in Trial A (12 hours) and limited to 3 hours in Trial B. The serial FEV₁ values over 12 hours (Trial A) are displayed in Figure 1. These trials further support the improvement in pulmonary function (FEV₁) with SPIRIVA HANDIHALER, which persisted over the spirometric observational period. Effectiveness was maintained for 24 hours after administration over the 6-month treatment period.

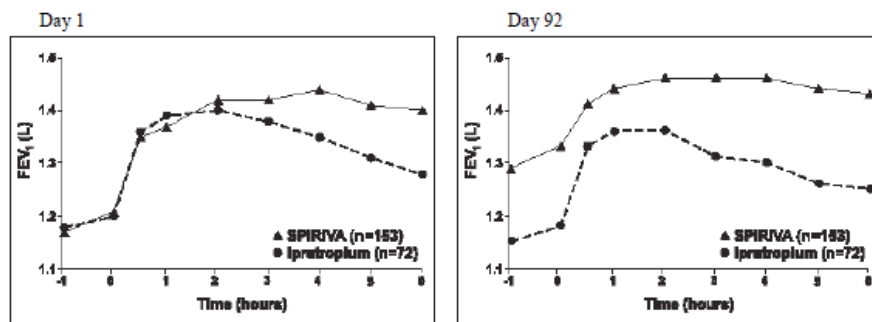
Figure 1 Mean FEV₁ Over Time (prior to and after administration of study drug) on Days 1 and 169 for Trial A (a Six-Month Placebo-Controlled Study)*



*Means adjusted for center, treatment, and baseline effect. On Day 169, a total of 183 and 149 patients in the SPIRIVA HANDIHALER and placebo groups, respectively, completed the trial. The data for the remaining patients were imputed using the last observation or least favorable observation carried forward.

Results of each of the 1-year ipratropium-controlled trials were similar to the results of the 1-year placebo-controlled trials. The results of one of these trials are shown in Figure 2.

Figure 2 Mean FEV₁ Over Time (0 to 6 hours post-dose) on Days 1 and 92, Respectively for One of the Two Ipratropium-Controlled Studies*



*Means adjusted for center, treatment, and baseline effect. On Day 92 (primary endpoint), a total of 151 and 69 patients in the SPIRIVA HANDIHALER and ipratropium groups, respectively, completed through 3 months of observation. The data for the remaining patients were imputed using the last observation or least favorable observation carried forward.

A randomized, placebo-controlled clinical study in 105 patients with COPD demonstrated that bronchodilation was maintained throughout the 24-hour dosing interval in comparison to placebo, regardless of whether SPIRIVA HANDIHALER was administered in the morning or in the evening.

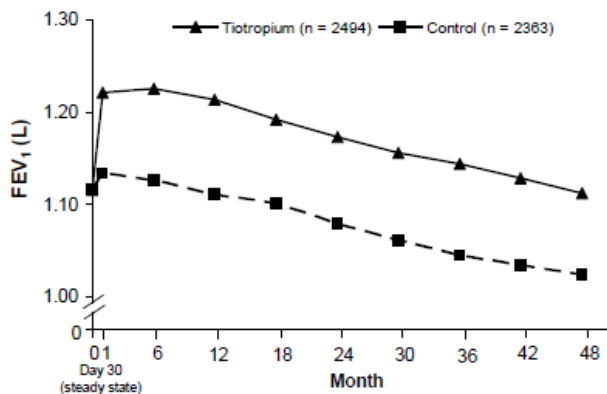
Throughout each week of the 1-year treatment period in the two placebo-controlled trials, patients taking SPIRIVA HANDIHALER had a reduced requirement for the use of rescue short-acting beta₂-agonists. Reduction in the use of rescue short-acting beta₂-agonists, as compared to placebo, was demonstrated in one of the two 6-month studies.

4-Year Effects on Lung Function

A 4-year, randomized, double-blind, placebo-controlled, multicenter clinical trial involving 5992 COPD patients was conducted to evaluate the long-term effects of SPIRIVA HANDIHALER on disease progression (rate of decline in FEV₁). Patients were permitted to use all respiratory medications (including short-acting and long-acting beta-agonists, inhaled and systemic steroids, and theophyllines) other than inhaled anticholinergics. The patients were 40 to 88 years of age, 75% male, and 90% Caucasian with a diagnosis of COPD and a mean pre-bronchodilator FEV₁ of 39% predicted (range = 9% to 76%) at study entry. There was no difference between the groups in either of the co-primary efficacy endpoints, yearly rate of decline in pre- and post-bronchodilator FEV₁, as demonstrated by similar slopes of FEV₁ decline over time (Figure 3).

SPIRIVA HANDIHALER maintained improvements in trough (pre-dose) FEV₁ (adjusted means over time: 87 to 103 mL) throughout the 4 years of the study (Figure 3).

Figure 3 Trough (pre-dose) FEV₁ Mean Values at Each Time Point



Repeated measure ANOVA was used to estimate means. Means are adjusted for baseline measurements. Baseline trough FEV₁ (observed mean) = 1.12. Patients with ≥ 3 acceptable pulmonary function tests after Day 30 and non-missing baseline value were included in the analysis.

Exacerbations

The effect of SPIRIVA HANDIHALER on COPD exacerbations was evaluated in two clinical trials: a 4-year clinical trial described above and a 6-month clinical trial of 1829 COPD patients in a Veterans Affairs setting. In the 6-month trial, COPD exacerbations were defined as a complex of respiratory symptoms (increase or new onset) of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness with a duration of at least 3 days requiring treatment with antibiotics, systemic steroids, or hospitalization. The population had an age ranging from 40 to 90 years with 99% males, 91% Caucasian, and had COPD with a mean pre-

bronchodilator FEV₁ percent predicted of 36% (range = 8% to 93%). Patients were permitted to use respiratory medications (including short-acting and long-acting beta-agonists, inhaled and systemic steroids, and theophyllines) other than inhaled anticholinergics. In the 6-month trial, the co-primary endpoints were the proportion of patients with COPD exacerbation and the proportion of patients with hospitalization due to COPD exacerbation. SPIRIVA HANDIHALER significantly reduced the proportion of COPD patients who experienced exacerbations compared to placebo (27.9% vs. 32.3%, respectively; Odds Ratio (OR) (tiotropium/placebo) = 0.81; 95% CI = 0.66, 0.99; p = 0.037). The proportion of patients with hospitalization due to COPD exacerbations in patients who used SPIRIVA HANDIHALER compared to placebo was 7.0% vs. 9.5%, respectively; OR = 0.72; 95% CI = 0.51, 1.01; p = 0.056.

Exacerbations were evaluated as a secondary outcome in the 4-year multicenter trial. In this trial, COPD exacerbations were defined as an increase or new onset of more than one of the following respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three or more days requiring treatment with antibiotics and/or systemic (oral, intramuscular, or intravenous) steroids. SPIRIVA HANDIHALER significantly reduced the risk of an exacerbation by 14% (Hazard Ratio (HR) = 0.86; 95% CI = 0.81, 0.91; p < 0.001) and reduced the risk of exacerbation-related hospitalization by 14% (HR = 0.86; 95% CI = 0.78, 0.95; p < 0.002) compared to placebo. The median time to first exacerbation was delayed from 12.5 months (95% CI = 11.5, 13.8) in the placebo group to 16.7 months (95% CI = 14.9, 17.9) in the SPIRIVA HANDIHALER group.

All-Cause Mortality

In the 4-year placebo-controlled lung-function trial described above, all-cause mortality compared to placebo was assessed. There were no significant differences in all-cause mortality rates between SPIRIVA HANDIHALER and placebo.

The all-cause mortality of SPIRIVA HANDIHALER was also compared to tiotropium inhalation spray 5 mcg (SPIRIVA RESPIMAT 5 mcg) in an additional long-term, randomized, double-blind, double-dummy active-controlled study with an observation period up to 3 years. All-cause mortality was similar between SPIRIVA HANDIHALER and SPIRIVA RESPIMAT.

16 HOW SUPPLIED/STORAGE AND HANDLING

SPIRIVA HANDIHALER consists of SPIRIVA capsules and the HANDIHALER device. SPIRIVA capsules contain 18 mcg of tiotropium and are light green, with the Boehringer Ingelheim company logo on the SPIRIVA capsule cap and TI 01 on the SPIRIVA capsule body, or vice versa.

The HANDIHALER device is gray colored with a green piercing button. It is imprinted with SPIRIVA HANDIHALER (tiotropium bromide inhalation powder), the Boehringer Ingelheim company logo. It is also imprinted to indicate that SPIRIVA capsules should not be stored in the HANDIHALER device and that the HANDIHALER device is only to be used with SPIRIVA capsules.

SPIRIVA capsules are packaged in an aluminum/aluminum blister card and joined along a perforated-cut line. SPIRIVA capsules should always be stored in the blister and only removed immediately before use. The drug should be used immediately after the packaging over an individual SPIRIVA capsule is opened.

The following packages are available:

- carton containing 5 SPIRIVA capsules (1 unit-dose blister card) and 1 HANDIHALER inhalation device (NDC 0597-0075-75) (institutional pack)
- carton containing 30 SPIRIVA capsules (3 unit-dose blister cards) and 1 HANDIHALER inhalation device (NDC 0597-0075-41)
- carton containing 90 SPIRIVA capsules (9 unit-dose blister cards) and 1 HANDIHALER inhalation device (NDC 0597-0075-47)

Keep out of reach of children. Do not get powder into eyes.

Storage

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

The SPIRIVA capsules should not be exposed to extreme temperature or moisture. Do not store SPIRIVA capsules in the HANDIHALER device.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Paradoxical Bronchospasm:

Inform patients that SPIRIVA HANDIHALER can produce paradoxical bronchospasm. Advise patients that if paradoxical bronchospasm occurs, patients should discontinue SPIRIVA HANDIHALER.

Worsening of Narrow-Angle Glaucoma:

Instruct patients to be alert for signs and symptoms of narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs and symptoms develop.

Inform patients that care must be taken not to allow the powder to enter into the eyes as this may cause blurring of vision and pupil dilation.

Since dizziness and blurred vision may occur with the use of SPIRIVA HANDIHALER, caution patients about engaging in activities such as driving a vehicle or operating appliances or machinery.

Worsening of Urinary Retention:

Instruct patients to be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Not for Acute Use:

Instruct patients that SPIRIVA HANDIHALER is a once-daily maintenance bronchodilator and should not be used for immediate relief of breathing problems (i.e., as a rescue medication).

Instructions for Administering SPIRIVA HANDIHALER:

Instruct patients on how to correctly administer SPIRIVA capsules using the HANDIHALER device [see *Patient Counseling Information (17)*]. Instruct patients that SPIRIVA capsules should only be administered via the HANDIHALER device and the HANDIHALER device should not be used for administering other medications. Remind patients that the contents of SPIRIVA capsules are for oral inhalation only and must not be swallowed.

Instruct patients always to store SPIRIVA capsules in sealed blisters and to remove only one SPIRIVA capsule immediately before use or its effectiveness may be reduced. Instruct patients to discard unused additional SPIRIVA capsules that are exposed to air (i.e., not intended for immediate use).

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

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