



Verona Pharma

CLINICAL STUDY PROTOCOL

**A PHASE IIB, RANDOMIZED, DOUBLE BLIND, PLACEBO
CONTROLLED DOSE RANGING STUDY TO ASSESS THE EFFECT OF
RPL554 IN PATIENTS WITH MODERATE TO SEVERE COPD**

STUDY NO. RPL554-CO-203

Version: 2.0
Date: 18 April 2017
Phase: IIb
**Investigational
Medicinal Product: RPL554**
EudraCT Number: 2016-005205-40

**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**


RPL554-CO-203

Version 2.0

18 April 2017

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THIS DOCUMENT HAS BEEN APPROVED BY VERONA PHARMA PLC:

Name and Title	Signature	Date
Kenneth Newman MD, MBA Chief Medical Officer		APRIL 18, 2017

INVESTIGATOR SIGNATURE PAGE

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

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

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Synopsis and section 4.1, Inclusion #3, first sentence and last paragraph.

Amended from:

3. If male: unless surgically sterile, must agree to meet the following from the first dose up to 1 month after the last dose of study medication: Amended to:

3. If male: unless surgically sterile, must agree to meet the following from the first dose up to the Telephone Follow-up, 2 weeks after the last dose of study medication:

Amended from:

If female: be of non-childbearing potential, or use a highly effective form of contraception as defined in Appendix I. Female patients of childbearing potential must have a negative pregnancy test at Visit 1 and Visit 2 prior to randomization.

Amended to:

If female: be of non-childbearing potential, or use a highly effective form of contraception as defined in Appendix I. Female patients of childbearing potential must use this contraceptive from first dose until the Telephone Follow-up (2 weeks after final dose) and have a negative pregnancy test at Visit 1 and Visit 2 prior to randomization.

Synopsis and section 4.1, Inclusion #4, first, third and fourth bullets.

Amended from:

- Heart rate between 40 and 90 beats per minute
- QRS interval ≤ 140 msec
- PR interval ≤ 240 msec Amended to:
- Heart rate between 50 and 90 beats per minute
- QRS interval ≤ 120 msec
- PR interval ≤ 200 msec

Synopsis and section 4.1, Inclusion #12. Amended from:

Smoking history of ≥ 10 pack years.

Amended to:

Current and former smokers with a smoking history of ≥ 10 pack years.

Section 5.8, Blinding, fourth paragraph.

Amended from:

The blind should be broken only if specific emergency treatment would be dictated by knowing the treatment status of the patient. If the blind needs to be broken, the Investigator should contact the Sponsor.

Amended to:

The blind should be broken only if specific emergency treatment would be dictated by knowing the treatment status of the patient. If the blind needs to be broken, the Investigator should

contact the Sponsor as soon as feasible. The investigator can unblind the investigational product immediately if he/she feels it is necessary without prior contact to the sponsor. However, the investigator should promptly document and explain to the sponsor any premature unblinding.

Section 5.8 Blinding, third paragraph Amended

from:

Note: Patients will also be aware of the appearance when pouring study medication into the nebulizer. Therefore, they should be instructed not to inform site personnel of the appearance of their study medication.

Amended to:

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

Section 6.4.3 Post-Dose Assessments Amended

from:

- Vital signs at 1, 2 and 3 hours

Amended to:

- Vital signs at 30 minutes and 1, 2 and 3 hours

Section 6.5.1 Pre-Dose Assessment:

The following bullets have been added:

- 12-lead ECG □ Vital signs

Section 6.5.3 Post-Dose Assessments Amended

from:

- Vital signs at 1, 2, 4, 6, 8 and 12 hours

Amended to:

- Vital signs at 30 minutes and 1, 2, 4, 6, 8 and 12 hours

Section 9.2.2.5 Efficacy

The following paragraph has been added:

Sites will be consolidated to the country level, which will be used as a fixed factor in all analyses in order to help reduce the variability in data. At least for the primary variable, secondary analyses investigating impact of country will be performed. Depending on differences in variance structure between countries, either separate models will be applied by country to estimate the treatment effect within each stratum or a full model including a

treatment by country interaction term will be used to provide these estimates. No formal treatment by country test is planned.

Section 9.2.2.5 Efficacy Amended

from:

Testing for efficacy will start with the highest dose of RPL554 versus placebo. If a statistically significant difference is found, the testing will proceed with the next highest dose, and so on. Secondly, the various doses of RPL554 will be compared. Appropriate measures will be taken to control for the type I error rate in these hypothesis tests. The Statistical Analysis Plan will provide details of the multiplicity adjustment method(s) used.

Amended to:

Testing for efficacy will start with the highest dose of RPL554 versus placebo. If a statistically significant difference is found, the testing will proceed with the next highest dose, and so on. Secondly, the various doses of RPL554 will be compared. Appropriate measures will be taken to control for the type I error rate in these hypothesis tests. A closed testing procedure to test active dose vs. placebo will be used for the primary endpoint. The study is not powered for pairwise differences between active doses. Thus, dose-response is best investigated in a secondary analysis fitting an appropriate dose-response model to the data. The Statistical Analysis Plan will provide additional details of the multiplicity adjustment method(s) used.

Section 9.2.3 Handling of Withdrawals or Missing Data The

following paragraph was added:

Relevant pharmacodynamic parameters will be calculated for each visit and then missing visit values imputed using the LOCF technique applied to these parameters. Since peak FEV₁ will always be the maximum FEV₁ value within 3 hours, only one non-missing post-dose assessment is needed to estimate the peak.

Synopsis and Section 9.3, Determination of Sample Size, third sentence.

Amended from:

This detectable limit has been considered sufficient to conclusively identify a minimal effective dose of RPL554, also in case of loss of at most 10% patients due to withdrawal.

Amended to:

This detectable limit has been considered sufficient to conclusively identify a minimal effective dose of RPL554.

Appendix I, title Amended

from:

Birth Control Methods Which May Be Considered As Highly Effective Amended

to:

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

Appendix I, body of appendix

The following has been added:

I. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with one of the following:

- Documented hysterectomy □ Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

2. Premenarchal

3. Postmenopausal female

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

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

SYNOPSIS

Title of Study:	A Phase IIb, randomized, double blind, placebo controlled, dose ranging study to assess the effect of RPL554 in patients with moderate to severe COPD.
Protocol Number:	RPL554-CO-203
EudraCT Number:	2016-005205-40
Phase:	IIb
Sponsor:	Verona Pharma plc
Study Center(s):	Approximately 45
Planned Study Period:	June 2017 to January 2018
Objectives:	<p>Primary Objective</p> <ul style="list-style-type: none"> To investigate the effect of RPL554 or placebo administered by nebulizer on change from baseline in peak forced expiratory volume in 1 second (FEV₁) (maximum over 3 hours following dosing) over 4 weeks when administered to patients with moderate to severe Chronic Obstructive Pulmonary Disease (COPD) <p>Secondary Objectives</p> <ul style="list-style-type: none"> To investigate the effect of RPL554 or placebo administered by nebulizer on change from baseline in morning trough FEV₁ over 4 weeks when administered to patients with moderate to severe COPD To investigate the bronchodilator effect of RPL554 or placebo administered by nebulizer on AUC_{0-12 hours} FEV₁ after 4 weeks of dosing To investigate the single-dose bronchodilator effect of RPL554 or placebo on peak and average FEV₁ at Visit 2 (first dose) To investigate the bronchodilator effect of RPL554 or placebo on peak and average FEV₁ over 3 hours at Visits 3 to 6 (Weeks 1 to 4) To investigate the effects of RPL554 or placebo on COPD symptoms, as measured by daily diary (E-RS™ from the Exacerbations of Chronic Pulmonary Disease Tool Patient-Reported Outcome [EXACT-PRO]), the Baseline Dyspnea Index (BDI)/ Transition Dyspnea Index (TDI), St George's Respiratory Questionnaire (SGRQ-C), Medical Research Council (MRC) scale, and patient global assessment of change (PGAC) To investigate the safety of RPL554 when administered for 4 weeks in patients with COPD, as measured by adverse events, electrocardiograms (ECGs), Holter monitoring and vital signs To compare the amount of rescue albuterol/salbutamol use required <p>Exploratory Objectives</p> <ul style="list-style-type: none"> To compare peak and area under the curve (AUC)_{0-12 hour} FEV₁ at the final study visit (Visit 6) to Baseline (Day 1) To correlate trough pharmacokinetics with pharmacodynamic effects

Study Design and Methodology:	This is a Phase IIb, randomized, double blind, placebo controlled, parallel group study to investigate the effects of 4 weeks of treatment with nebulized RPL554 (at different dose levels) in patients with moderate to severe COPD. It is planned to enroll approximately 400 patients at approximately 45 centers in the United States of America (U.S.) and European Union (EU). The study comprises six visits: screening (Visit 1), randomization (Visit 2), and weekly visits for 4 weeks (Visit 3 to Visit 6). Patients will be screened for eligibility (Visit 1), including a reversibility test with albuterol/salbutamol between 7 and 14 days before the first dose of study medication.
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Study Procedures:	<p>Eligible patients will be randomized pre-dose at Visit 2. Patients will receive a single dose of RPL554 (one of four active strengths) or placebo and have spirometry performed over 12 hours. They will then be dispensed RPL554 (the same active strength) or placebo to be used twice daily via a Pari LC Sprint nebulizer. The patient will be instructed in the use of the nebulizer and will take the second dose of Day 1 (Visit 2) in the clinic. At each visit the study medication will be administered in the clinic with spirometry measured for 3 hours after dosing. The final visit (Visit 6) will have spirometry performed for 12 hours after dosing, and end of study procedures performed.</p> <p>The following will be performed at Visits 2 and 6:</p> <ul style="list-style-type: none"> • Measurements of lung function (FEV₁ and forced vital capacity [FVC]) pre-dose and up to 12 hours post-dose • 12 lead ECG at pre-dose and 2 hours post dose • Vital sign (supine) measurements pre-dose and up to 12 hours post-dose • Completion of questionnaires (BDI [Visit 2], TDI [Visit 6], SGRQ-C, global assessment of change, and MRC breathlessness scale). These questionnaires, except for BDI, are also completed at Visit 4. <p>At Visits 3 to 5 patients will have:</p> <ul style="list-style-type: none"> • RPL554 or placebo administered in-clinic with spirometry performed pre-dose and up to 3 hours post-dose • 12 lead ECG pre-dose and 2 hours post-dose • Vital sign (supine) measurements pre-dose and up to 3 hours post-dose <p>Adverse events will be recorded throughout the study. A follow-up telephone call will occur 2 weeks after the final visit.</p>
Number of Patients Planned:	400
Main Criteria for Eligibility:	<p><i>Inclusion Criteria</i></p> <ol style="list-style-type: none"> 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. <u>If male:</u> unless surgically sterile, must agree to meet the following from the first dose up to the Telephone Follow-up, 2 weeks after the last dose of study medication: <ul style="list-style-type: none"> • Not donate sperm • <i>Either:</i> 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) <i>Or:</i> use a condom with all sexual partners. If the partner is a female of childbearing potential the condom must be used with spermicide and a second reliable form of contraception must also be used (e.g. diaphragm/cap with spermicide, established hormonal contraception, intra-uterine device) <p><u>If female:</u> be of non-childbearing potential, or use a highly effective form of contraception as defined in Appendix I. Female patients of childbearing potential must use this contraceptive from first dose until the Telephone Follow-up (2 weeks after final dose) and have a negative pregnancy test at Visit 1 and Visit 2 prior to randomization.</p>

	<p>4. Have a 12-lead ECG recording at screening (Visit 1) showing the following (and no changes at Visit 2 deemed clinically significant by the Investigator):</p> <p><input type="checkbox"/> Heart rate between 50 and 90 beats per minute</p> <ul style="list-style-type: none"> • QT interval corrected for heart rate using Fridericia's formula (QTcF) interval ≤ 450 msec for males and ≤ 470 msec for females • QRS interval ≤ 120 msec • PR interval ≤ 200 msec • No clinically significant abnormality including morphology (e.g. left bundle branch block, atrioventricular nodal dysfunction, ST segment abnormality consistent with ischemia). <p>5. Capable of complying with all study restrictions and procedures, including ability to use the study nebulizer correctly.</p> <p>6. Body mass index (BMI) between 18 and 35 kg/m² (inclusive) with a minimum weight of 45 kg.</p> <p>7. COPD diagnosis: Patients with a clinical 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 (Visit 1).</p> <p>8. Ability to perform acceptable and reproducible spirometry. Post-bronchodilator (albuterol/salbutamol four puffs) spirometry at screening (Visit 1) must demonstrate a:</p> <ul style="list-style-type: none"> • Post-bronchodilator FEV₁/FVC ratio of ≤ 0.70 • Post-bronchodilator FEV₁ ≥ 40 % and ≤ 80% of predicted normal. <p>9. Clinically stable COPD in the 4 weeks prior to screening (Visit 1) and randomization (Visit 2).</p> <p>10. A chest X-ray (posterior-anterior) at screening, or in the 12 months prior to screening, showing no abnormalities which are both clinically significant and unrelated to COPD.</p> <p>11. Meet the concomitant medication restrictions and be expected to do so for the rest of the study.</p> <p>12. Current and former smokers with a smoking history of ≥ 10 pack years.</p> <p>13. Capable of withdrawing from long acting bronchodilators, until the end of the treatment period, and short acting bronchodilators for 8 hours prior to administration of study medication.</p> <p>Exclusion Criteria</p> <ol style="list-style-type: none"> 1. A history of life-threatening COPD including Intensive Care Unit admission and requiring intubation. 2. COPD exacerbation requiring oral steroids in the 3 months prior to screening (Visit 1) or prior to randomization (Visit 2). 3. A history of one or more hospitalizations for COPD in the 6 months prior to screening (Visit 1). 4. Lower respiratory tract infection treated with antibiotics within 3 months of screening or prior to randomization (Visit 2). 5. Evidence of cor pulmonale or clinically significant pulmonary hypertension. 6. Other respiratory disorders: Patients with a current diagnosis of asthma, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, interstitial lung diseases, known alpha-1 antitrypsin deficiency or other active pulmonary diseases. 7. Previous lung resection or lung reduction surgery.
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	<ol style="list-style-type: none"> 8. Oral therapies for COPD (e.g. oral steroids, theophylline, and roflumilast) in the 3 months prior to screening (Visit 1) and throughout the study. 9. Pulmonary rehabilitation, unless such treatment has been stable for 4 weeks prior to Visit 1) and remains stable during the trial. 10. A history of, or reason to believe a subject has, drug or alcohol abuse within the past 3 years. 11. Received an experimental drug within 30 days or five half-lives of Visit 2, whichever is longer. 12. Prior exposure to RPL554. 13. Women who are pregnant or breast-feeding. 14. Patients with a history of chronic uncontrolled disease including, but not limited to, endocrine, active hyperthyroidism, neurological, hepatic, gastrointestinal, renal, hematological, urological, immunological, or ophthalmic diseases that the Investigator believes are clinically significant. 15. Documented cardiovascular disease: arrhythmias, unstable angina, recent or suspected myocardial infarction within 6 months prior to screening, congestive heart failure, a history of unstable or uncontrolled hypertension, or has been diagnosed with hypertension in last 3 months. 16. Use of beta blockers. 17. Major surgery (requiring general anesthesia) in the 6 weeks prior to screening (Visit 1), lack of full recovery from surgery at screening (Visit 1), or planned surgery through the end of the study. 18. History of malignancy of any organ system within 5 years, with the exception of localized skin cancers (basal or squamous cell). 19. Clinically significant abnormal values for safety laboratory tests (hematology, biochemistry or urinalysis) at screening, as determined by the Investigator. 20. A disclosed history or one known to the Investigator, of significant non-compliance in previous investigational studies or with prescribed medications. 21. Requirement for oxygen therapy, even on an occasional basis. 22. Any other reason that the Investigator considers makes the subject unsuitable to participate. 23. Known hypersensitivity to RPL554 or its excipients/components. 24. Abnormal clinically significant 12 lead Holter findings, including but not limited to: <ul style="list-style-type: none"> • Premature ventricular contraction (PVCs) >1000 in 24-hour period • Sustained ventricular tachycardia >6 beats • Atrial fibrillation with rapid ventricular response (>100 bpm) • Atrial flutter • Sinus pause >2 seconds
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Study Medications:	<p>All study medications will be administered using the inhaled route.</p> <p>Patients will be randomized to one of the following groups:</p> <p>RPL554 0.75 mg twice daily</p> <p>RPL554 1.5 mg twice daily</p> <p>RPL554 3.0 mg twice daily</p> <p>RPL554 6.0 mg twice daily</p> <p>Placebo twice daily</p> <p>Study medication will be blinded using a double blind technique.</p> <p>All study medication will be administered via a nebulizer.</p> <p>The study medication (RPL554 or placebo) will be administered using a standard jet nebulizer.</p>
	<p>The RPL554 formulation is a sterile suspension supplied as unit dose glass vials of sterile stock suspensions of micronized 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.</p>
Duration of Treatment:	<p>The approximate planned duration for each patient will be up to 42 days: 2 to 14 days screening, followed by 28 days of treatment.</p>
Criteria for Evaluation:	<p>Treatments will be compared using (additive) analysis of covariance models adjusting for treatment, country/center and, if appropriate, baseline. Active treatments will first be compared to placebo using a closed test procedure (within substance) starting with the highest dose.</p>
Statistical Methods:	<p>The standard deviation for peak FEV₁ is estimated to be 250 mL. With a 2-sided test at a 5% significance level and 80 evaluable patients per group, there will be an 80% power to detect a true difference of 111 mL between any two treatments. This detectable limit has been considered sufficient to conclusively identify a minimal effective dose of RPL554. Thus 80 patients per group will be randomized.</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
BDI	Baseline dyspnea index
BMI	Body mass index
C _{max}	Maximum concentration
COPD	Chronic obstructive pulmonary disease
CI	Confidence interval
eCRF	Electronic Case report form
E _{av}	Average effect
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
E _{max}	Maximum effect
ERS	European Respiratory Society
ETFE	Ethylene tetrafluoroethylene
EU	European Union
EXACT-PRO	Exacerbations of Chronic Pulmonary Disease Tool Patient-Reported Outcome
FEV ₁	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
FVC	Forced vital capacity
g	Acceleration due to gravity
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
h	Hours
HIPAA	Health Insurance Portability and Accountability Act

HRT	Hormone replacement therapy
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroid
IUPAC	International Union of Pure and Applied Chemistry
kg	Kilograms
LABA	Long acting beta ₂ -agonist
LAMA	Long acting muscarinic antagonist
LOCF	Last observation carried forward
LPS	Lipopolysaccharide
MAD	Multiple ascending dose(s)
MedDRA	Medical Dictionary for Regulatory Activities
m	Meters
mg	Milligrams
mL	Milliliters
MRC	Medical Research Council scale
msec	milliseconds
N	Number of patients
ng	Nanograms
NHANES III	National Health and Nutrition Examination Survey III
NT-proBNP	N-terminal pro b-type natriuretic peptide
PDE	Phosphodiesterase
PGAC	Patient Global Assessment of Change
PID	Patient identification number
pMDI	Pressurized metered dose inhaler
PVC	Premature ventricular contraction
QP	Qualified person
QTcF	QT interval corrected for heart rate using Fridericia's formula

SAE	Serious adverse event
SAD	Single ascending dose(s)
SAS	Statistical analysis software
SD	Standard deviation
SOC	System organ class
SGRQ-C	St George's Respiratory Questionnaire – COPD specific
SUSAR	Suspected, unexpected serious adverse reaction
TDI	Transition Dyspnea Index
t_{\max}	Time to maximum concentration
U.S	United States of America
WOCBP	Women of Childbearing Potential

1 INTRODUCTION

1.1 Disease and Study Medication Review

RPL554, a small molecule isoquinoline 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 (Abbott-Banner et al., 2014). Pharmacological evidence from preclinical experiments with dual PDE3/4 inhibitors suggests that RPL554 may have potential therapeutic activity in allergic asthma, COPD, cystic fibrosis and allergic rhinitis (BoswellSmith et al., 2006; Calzetta et al., 2013; Calzetta et al., 2015; Turner et al., 2016; Venkatasamy et al., 2016).

PDE4 inhibitors (administered orally) have exhibited anti-inflammatory actions; however, they have been associated with unfavorable gastrointestinal side effects such as nausea, emesis, diarrhea, abdominal pain, loss of appetite and weight loss (Harbinson et al., 1997; van Schalkwyk et al., 2005; Compton et al., 2001; Rabe et al., 2005; Rennard et al., 2006; Calverley et al., 2007; Gamble et al., 2003; Grootendorst et al., 2007). Dual PDE3/PDE4 inhibitors (administered by inhalation) have exhibited both bronchodilator and anti-inflammatory actions, with a more favorable side effect profile (Ukena, et al., 1995). It is plausible that increased efficacy with reduced side effects may be achievable with administration of a dual PDE3/4 inhibitor by the inhaled route compared to orally administered PDE3 or PDE4 inhibitors. Furthermore, it has 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 the novel dual PDE3/4 inhibitor RPL554 have been evaluated in eight completed studies in healthy subjects, patients with mild to moderate persistent asthma and those with allergic rhinitis and COPD (Franciosi et al., 2013). These studies are described in detail in the Investigator's Brochure. For all these completed clinical studies, RPL554 was formulated as a nebulized solution of RPL554 in citrate/phosphate buffered saline at pH 3.2. Systemic exposure following inhalation using this solution formulation was low and somewhat variable, with maximum concentration (C_{max}) values following administration ranging from about 0.9 ng/mL 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 nebulized solution was well tolerated. Adverse events were generally mild and generally of equal frequency between placebo and active treatment groups. RPL554 produced a rapid bronchodilation in both COPD and asthmatic patients, and increased the provocative concentration of methacholine chloride by 1.5 doubling doses compared with placebo (95% 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 been re-formulated in a neutral pH phosphate buffered suspension formulation for nebulization.

The suspension formulation has been tested in three completed studies. Study RPL554-007-2014 was a Phase I randomized, double-blind, placebo-controlled study in which single ascending doses (SAD) in the range of 1.5 mg to 24 mg were administered to 35 healthy subjects, multiple ascending doses (MAD) in the range of 6 mg to 24 mg twice daily for up to 5.5 days were administered to 21 healthy subjects and MAD in the range of 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).

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 to moderate chronic asthma. Patients received four single doses of RPL554 (0.4 mg, 1.5 mg, 6 mg and 24 mg), two doses of nebulized albuterol/salbutamol (2.5 mg and 7.5 mg) and placebo in a randomized sequence. RPL554 produced a dose-dependent bronchodilation with a magnitude that was comparable to a maximal dose of albuterol/salbutamol, but with fewer of the well described albuterol/salbutamol side effects (e.g. hypokalemia, tachycardia, tremor and palpitations) (Bjermer et al., 2016).

Study RPL554-009-2015 was a Phase II randomized, 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 albuterol/salbutamol (200 µg), ipratropium (40 µg) or placebo using a pressurized metered dose inhaler (pMDI) followed immediately by nebulized RPL554 (6 mg) or placebo. RPL554 alone was as effective as standard of care (two puffs of either albuterol/salbutamol or ipratropium pMDI) as a bronchodilator, and importantly produced significant additive bronchodilation (peak and average over 8 hours) when dosed with either albuterol/salbutamol or ipratropium ($p<0.001$). Indeed, there was an approximately 60% additional increase in peak forced expiratory volume in 1 second (FEV₁) in COPD patients administered RPL554 6 mg in addition to two puffs of either albuterol/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 or adverse events of concern.

The pharmacokinetics of RPL554, following single nebulized inhaled doses of this suspension formulation, were characterized 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 MAD 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 volunteers, which is consistent with the expected reduced lung deposition in patients with obstructive lung disease. Overall, the studies performed with the inhaled nebulized suspension formulation of RPL554 have shown reproducible pharmacokinetic behavior between studies and across patient cohorts.

The purpose of this study is to investigate the dose response of RPL554 in patients with COPD over 4 weeks. This length of time should allow for study of the bronchodilator response, measured predominantly by the peak FEV₁, and the anti-inflammatory response, as measured predominantly by trough FEV₁.

1.2 [REDACTED]

2 OBJECTIVES

2.1 Primary Objective

- To investigate the effect of RPL554 or placebo administered by nebulizer on change from baseline in peak FEV₁ (maximum over 3 hours following dosing) over 4 weeks when administered to patients with moderate to severe COPD

2.2 Secondary Objectives

- To investigate the effect of RPL554 or placebo administered by nebulizer on change from baseline in morning trough FEV₁ over 4 weeks when administered to patients with moderate to severe COPD
- To investigate the bronchodilator effect of RPL554 or placebo administered by nebulizer on AUC_{0-12 hours} FEV₁ after 4 weeks of dosing
- To investigate the single-dose bronchodilator effect of RPL554 or placebo on peak and average FEV₁ at Visit 2 (first dose)
- To investigate the bronchodilator effect of RPL554 or placebo on peak and average FEV₁ over 3 hours at Visits 3 to- 6 (Weeks 1 to 4)
- To investigate the effects of RPL554 or placebo on COPD symptoms, as measured by daily diary (E-RS from the Exacerbations of Chronic Pulmonary Disease Tool Patient-Reported Outcomes [EXACT-PRO]), the Baseline Dyspnea Index [BDI]/Transition Dyspnea Index [TDI], St George's Respiratory Questionnaire – COPD specific [SGRQ-C], Medical Research Council [MRC] scale, and patient global assessment of change (PGAC)
- To investigate the safety of RPL554 when administered for 4 weeks in patients with COPD, as measured by adverse events, electrocardiograms (ECGs), Holter monitoring and vital signs
- To compare the amount of rescue albuterol/salbutamol use required

2.3 Exploratory Objectives

- To compare peak and AUC_{0-12 hour} FEV₁ at the final study visit (Visit 6) to Baseline (Day 1)
- To correlate trough pharmacokinetics with pharmacodynamic effects

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan Description

This is a Phase IIb, randomized, double-blind, placebo-controlled, parallel-group study to investigate the effect of nebulized RPL554 in patients with moderate COPD over 4 weeks. It is planned to enroll approximately 400 patients at 45 sites. The study comprises six visits: screening (Visit 1), randomization (Visit 2), and 4 weekly visits (Visit 3 to Visit 6).

Patients will be screened for eligibility (Visit 1), including a reversibility test with albuterol/salbutamol, between 7 and 14 days before the first dose of study medication. After the screening visit, patients will be instructed to wash out any long acting bronchodilators (long acting beta₂-agonists [LABA] and/or long acting muscarinic antagonists [LAMA]) but can continue on an inhaled corticosteroid at the same dose. Albuterol/salbutamol may be used on a regular or as needed basis, but must be held for at least 8 hours before a study visit. Albuterol/salbutamol should not be used after administration of study medication for the duration of the clinic visit, unless absolutely necessary for relief of symptoms.

Eligible patients will then return for Visit 2. The pre-dose FEV₁ must be within 20% of the predose FEV₁ at the screening visit. Patients will be assessed for inclusion into the study, and if appropriate will be randomized to one of the five treatment arms. They will receive the first two doses of study medication (RPL554 or placebo) in the clinic (morning and evening) and have spirometry performed for 12 hours. [REDACTED] Patients will be discharged from the clinic, having been instructed to use the study medication on a twice daily basis.

Patients will return for three interim, weekly visits. At each visit, patients will return used and unused study medication and receive new study medication from the unblinded study staff. The first dose of the newly dispensed study medication will be administered in the clinic with spirometry performed for 3 hours after dosing.

At the final study visit (Visit 6), patients will be resident at the study center from the morning until at least 12 hours after dosing to allow for monitoring of lung function and study closeout procedures. A follow-up phone call will occur 2 weeks after the final study visit as a safety follow-up.

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

A total of 400 COPD patients, either male or female, aged 40 to 75 years (inclusive) will be randomized. The purpose of the study is to investigate the dose-dependent effect of RPL554 on the lung function of patients with COPD. The dose-dependent effects of RPL554 will also be examined with regards to symptom improvement and safety measures.

Twice daily nebulized doses of RPL554 or placebo will be administered for 4 weeks after randomization. The study uses a parallel group design with four doses of RPL554 to allow for an examination of any dose dependent effects on efficacy and safety. This design makes it possible to obtain unbiased inferences about differences between treatments. Treatments will be administered double-blind with the Investigator and patient unaware of the treatment identity to further minimize any potential bias in the overall assessment of treatment effect and safety.

3.3 Planned Duration of the Study

The approximate planned duration for each patient will be up to 42 days: 7 to 14 days screening, followed by up to 28 days of treatment. There will also be a follow-up phone call 14 days after the final study visit.

3.4 Definition of the End of the Study

The end of the study is defined as the date of the follow-up phone call 2 weeks after the final study visit of the last enrolled patient in the study.

4 SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

Eligible patients must meet all of the following criteria:

1. Sign an informed consent document indicating they understand the purpose of and procedures required for the study and are willing to participate.
 2. Male or female aged between 40 and 75 years inclusive, at the time of informed consent.
 3. If male: unless surgically sterile, must agree to meet the following from the first dose up to the Telephone Follow-up, 2 weeks after the last dose of study medication: ☐ Not donate sperm
 - *Either:* be sexually abstinent in accordance with a patient's usual and preferred lifestyle (but agree to abide by the contraception requirements below should their circumstances change)
- Or:* use a condom with all sexual partners. If the partner is a female of childbearing potential the condom must be used with spermicide and a second reliable form of contraception must also be used (e.g. diaphragm/cap with spermicide, established hormonal contraception, intra-uterine device)
- If female: be of non-childbearing potential, or use a highly effective form of contraception as defined in Appendix I. All female patients of childbearing potential must use this contraceptive from first dose until the Telephone Follow-up (2 weeks after final dose) and have a negative pregnancy test at Visit 1 and Visit 2 prior to randomization.
4. Have a 12-lead ECG recording at screening (Visit 1) showing the following (and no changes at Visit 2 deemed clinically significant by the Investigator): ☐ Heart rate between 50 and 90 beats per minute
 - QT interval corrected for heart rate using Fridericia's formula (QTcF) interval ≤ 450 msec for males and ≤ 470 msec for females
 - QRS interval ≤ 120 msec
 - PR interval ≤ 200 msec
 - No clinically significant abnormality including morphology (e.g. left bundle branch block, atrioventricular nodal dysfunction, ST segment abnormalities consistent with ischemia).
 5. Capable of complying with all study restrictions and procedures, including ability to use the study nebulizer correctly.
 6. Body mass index (BMI) between 18 and 35 kg/m² (inclusive) with a minimum weight of 45 kg.
 7. COPD diagnosis: Patients with a diagnosis of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (Celli and MacNee, 2004) with symptoms compatible with COPD for at least 1 year prior to screening (Visit 1).
 8. Ability to perform acceptable and reproducible spirometry. Post-bronchodilator (albuterol/salbutamol four puffs) spirometry at screening (Visit 1) must demonstrate a:
 - Post-bronchodilator FEV₁/forced vital capacity (FVC) ratio of ≤ 0.70
 - Post-bronchodilator FEV₁ ≥ 40 % and ≤ 80 % of predicted normal

9. Clinically stable COPD in the 4 weeks prior to screening (Visit 1) and randomization (Visit 2).
10. A chest X-ray (posterior-anterior) at screening, or in the 12 months prior to screening showing no abnormalities which are both clinically significant and unrelated to COPD.
11. Meet the concomitant medication restrictions and be expected to do so for the rest of the study.
12. Current and former smokers with a smoking history of ≥ 10 pack years.
13. For patients taking long acting bronchodilators, capable of withdrawing from these medications, as defined in Section 5.9.1, until the end of the treatment period, and short acting bronchodilators for 8 hours prior to administration of study medication.

4.2 Exclusion Criteria

Patients presenting with any of the following criteria may not be enrolled:

1. A history of life-threatening COPD including Intensive Care Unit admission and requiring intubation.
2. COPD exacerbation requiring oral steroids in the 3 months prior to screening (Visit 1) or prior to randomization (Visit 2).
3. A history of one or more hospitalizations for COPD in the 6 months prior to screening (Visit 1).
4. Lower respiratory tract infection treated with antibiotics within 3 months of screening (Visit 1) or prior to randomization (Visit 2).
5. Evidence of cor pulmonale or clinically significant pulmonary hypertension.
6. Other respiratory disorders: Patients with a current diagnosis of asthma, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, interstitial lung diseases, sleep apnea, known alpha-1 antitrypsin deficiency or other active pulmonary diseases.
7. Previous lung resection or lung reduction surgery.
8. Oral therapies for COPD (e.g. oral steroids, theophylline, and roflumilast) in the 3 months prior to screening (Visit 1) and throughout the study.
9. Pulmonary rehabilitation, unless such treatment has been stable from 4 weeks prior to Visit 1) and remains stable during the trial.
10. A history of, or reason to believe a subject has, drug or alcohol abuse within the past 3 years.
11. Received an experimental drug within 30 days or five half-lives of Visit 2, whichever is longer.
12. Prior exposure to RPL554.
13. Women who are pregnant or breast-feeding.
14. Patients with a history of chronic uncontrolled disease including, but not limited to, endocrine, active hyperthyroidism, neurological, hepatic, gastrointestinal, renal, hematological, urological, immunological, or ophthalmic diseases that the Investigator believes are clinically significant.
15. Documented cardiovascular disease: arrhythmias, unstable angina, recent or suspected myocardial infarction within 6 months prior to screening, congestive heart failure, a

- history of unstable or uncontrolled hypertension, or has been diagnosed with hypertension in last 3 months.
16. Use of beta blockers.
 17. Major surgery (requiring general anesthesia) in the 6 weeks prior to screening (Visit 1), lack of full recovery from surgery at screening (Visit 1), or planned surgery through the end of the study.
 18. History of malignancy of any organ system within 5 years, with the exception of localized skin cancers (basal or squamous cell).
 19. Clinically significant abnormal values for safety laboratory tests (hematology, biochemistry or urinalysis) at screening (Visit 1), as determined by the Investigator.
 20. A disclosed history, or one known to the Investigator, of significant non-compliance in previous investigational studies or with prescribed medications.
 21. Requirement for oxygen therapy, even on an occasional basis.
 22. Any other reason that the Investigator considers makes the subject unsuitable to participate.
 23. Known hypersensitivity to RPL554 or its excipients/components.
 24. Abnormal clinically significant 12 lead Holter findings, including but not limited to:
 - Premature ventricular contractions (PVCs) >1000 in 24 hour period
 - Sustained ventricular tachycardia >6 beats
 - Atrial fibrillation with rapid ventricular response (>100 bpm)
 - Atrial flutter
 - Sinus pause >2 seconds

4.3 Removal of Patients from Therapy or Assessment

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

4.3.1 Study Medication Discontinuation

Study medication must be discontinued for the following reasons:

- Unacceptable toxicity related to study medication
- 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
- Development of a COPD exacerbation, which necessitates use of oral or parenteral corticosteroids and/or antibiotics.
- Reduction from baseline (Visit 2) in pre-dose FEV₁ >20% that requires use of albuterol/salbutamol >12 puffs per day for at least 3 consecutive days associated with an increase in COPD symptoms.
- Pregnancy

4.3.2 Patient Withdrawal

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

If a patient withdraws following randomization, every attempt should be made to contact the patient to determine the reason for withdrawal and to complete the recording of any available pharmacodynamic 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 medication, no further follow-up is necessary.

All withdrawn patients should be contacted to have a final study visit. If it is considered by the Investigator that a patient requires greater medical supervision and/or investigations, an unscheduled visit prior to (and in addition to) the scheduled final study visit may be performed.

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

Patients with an exacerbation of COPD, defined as increased symptoms for at least 3 days and decreased lung function requiring treatment with steroids or antibiotics, should be terminated from the study and given medical care to ensure their safety. Safety measures from the final study visit should be performed, if possible.

A female patient who becomes pregnant during the study must be withdrawn immediately. The Investigator will make all reasonable efforts to ascertain the progress and outcome of the pregnancy.

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
- Insufficient Investigator oversight
- Serious failure of the Investigator to comply with the International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (GCP) or local regulations
- Submission of knowingly false information from the research facility to the Sponsor, the 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 guidelines. The decision to discontinue the study is at the discretion of the Sponsor, 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 randomize approximately 400 patients. Discontinued patients in this study will not be replaced.

5 STUDY MEDICATIONS

5.1 Study Medications Administered

In this parallel group study, patients will receive one of five possible study medications, each administered twice daily. The dose levels and concentrations are shown in Table 1.

Table 1 Study Medications in Study RPL554-CO-203

Substance	Dose Level (mg)	Concentration (mg/mL)
RPL554	0.75	0.3
RPL554	1.5	0.6
RPL554	3.0	1.2
RPL554	6.0	2.4
Placebo	N/A	N/A
Abbreviations: N/A=not applicable		

All study medications will be administered using a standard jet nebulizer as described in Section 5.4.2.

5.2 Identity of Study Medications

RPL554 and placebo are manufactured using aseptic manufacturing techniques to Good Manufacturing Practice (GMP). 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.

[REDACTED]

The placebo is the same as the RPL554 suspensions except that the active RPL554 ingredient is omitted. [REDACTED]

5.3 Preparation and Labelling

5.3.1 Nebulized RPL554 and Placebo

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

For each in-clinic nebulization, an unblinded individual will pour the liquid from the vial into the nebulizer cup and will not disclose the nature (appearance) of the study medication to the blinded Investigator and study staff.

At Visits 2 to 5, patients will be dispensed 20 vials for twice daily dosing over 7 days (six vials provided as extras). For all visits, the first dose will be used for the in-clinic nebulization; for Visit 2 only the second dose will also be given in-clinic. The final dose administered in the morning at Visit 6b (final study visit) will be individually packaged. As such, the study medication administered in the clinic will always be stored only at the study center.

5.4 Selection of Doses, Dosing Schedule and Route of Administration

5.4.1 Selection of Doses in the Study

The doses of RPL554 were selected based on the results from prior studies in healthy volunteers and patients with asthma and COPD. Study RPL554-007-2014 investigated SAD and MAD of RPL554 in healthy subjects and MAD in COPD patients. This study demonstrated that doses of up to 24 mg twice daily were well tolerated in healthy subjects, and doses up to 12 mg twice daily were well tolerated in COPD patients. No maximum tolerated dose could be defined. Following one week of dosing with 12 mg twice daily in the COPD patients there was a small increase in heart rate, although without any other safety or tolerability issues. Additionally, a single dose crossover study in asthmatics demonstrated a dose response curve for RPL554. As such, the top dose in this study is 6 mg twice daily. Furthermore, 1.5 mg has been shown to be an effective bronchodilator dose. In order to determine a minimum effective dose, a dose of 0.75 mg twice daily has also been included in this study.

5.4.2 Selection and Timing of Dose for each Patient

All doses for a given patient should be given at approximately the same time of day (± 1 hour), approximately 12 hours apart. Prior studies have demonstrated that twice daily dosing is appropriate given a terminal serum half-life of 10 to 12 hours, as well as a trough FEV₁ in study RPL554-007-2014 of 97 to 125 mL which demonstrates durability of effect over 12 hours.

5.4.2.1 Nebulized RPL554 and Placebo

The RPL554 study drug will be administered by inhalation of an aerosol generated by a reusable PARI LC Sprint[®] jet nebulizer attached to a compressor (PARI TurboBOY[®] SX in the EU, or PARI Vios[®] PRO in the U.S.). Patients will receive a compressor at the randomization visit, and a LC Sprint nebulizer at each visit.

[REDACTED]

The end time of nebulization (sputtering) of the study medication will be considered Time 0 for the purposes of scheduling all post-dose study procedures. Nebulization time should be approximately 5 minutes and may not exceed 10 minutes.

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

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

5.5 Storage

RPL554 and placebo should be stored below 25°C and should not be frozen. The expiry date will be indicated on the box label.

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

Study medications will be stored under the control of the Investigator or designee in a secure facility appropriate for the advised storage conditions. Study medications that are to be returned

by the Investigator/staff or have expired must be stored separately from the unused study medications.

5.6 Accountability

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

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

Written records must also be maintained to confirm the purpose and reason for any study medication disposal, e.g. the amount contaminated, broken, or lost, and the name/signature of the personnel reporting the event. Typically, study materials (including used vials) should be returned once final study medication accountability has been performed. If storage constraints require an earlier return of supplies, the study monitor should be contacted to make appropriate arrangements.

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

5.7 Method of Assigning Patients to Treatment Groups

All patients consented will be assigned a patient identification (PID) number upon signing of the informed consent using the following convention: XXX-YYY where XXX is the center number and YYY is the patient number (001, 002, etc.). Patients will receive one of the five different treatment options in the study (see Section 5.1). Patients will be equally randomized to one of the four doses or placebo before the first study medication administration at Visit 2. Medication identification numbers will be provided on the study medication kit.

5.8 Blinding

RPL554 and placebo will be administered double blind. The placebo is the same as the active treatment except for the omission of the active ingredient.

[REDACTED]

The blind should be broken only if specific emergency treatment would be dictated by knowing the treatment status of the patient. If the blind needs to be broken, the Investigator should contact the Sponsor as soon as feasible. The investigator may unblind the investigational product immediately if he/she feels it is necessary prior to contacting the Sponsor. However, the investigator should promptly document and explain to the Sponsor any premature unblinding.

Otherwise, all blinding will be maintained until all queries are resolved and the database is locked.

5.9 Prior and Concomitant Therapies and Medications

5.9.1 Prior and Concomitant COPD Therapies

All prior and concomitant therapies for COPD 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.

All patients will be supplied with albuterol/salbutamol to be used as per the discretion of the Investigator. The albuterol/salbutamol can be dosed on a regularly scheduled basis and/or as needed use.

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

- Oral therapies for COPD (e.g. oral steroids, theophylline and roflumilast) are not allowed in the 3 months prior to Visit 1 and throughout the study. Oral mucolytics are allowed.
- Terbutaline is not allowed beginning the day prior to Visit 1
- Long acting bronchodilators (LABAs or LAMAs) are not allowed during the study and must be withheld prior to Visit 1 as follows:
 - Once daily bronchodilators must be stopped at least 48 hours prior ○
 - Twice daily bronchodilators must be stopped at least 24 hours prior □
 - Short acting bronchodilators (albuterol/salbutamol or ipratropium) must be withheld for at least 8 hours prior to spirometry at each study visit. If this withhold is not met, the patient should be rescheduled for a repeat visit within 2 days
- Patients taking inhaled corticosteroids (ICS) may continue their medication only if the dose is stable from at least 4 weeks prior to Visit 1 and is expected to remain stable. Patients taking combination products that include ICS 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. Inhaled steroid medication should be procured via prescription for patients requiring its use; it will not be supplied by the Sponsor

Pulmonary rehabilitation programs should not be started or completed during participation in the study, although an ongoing maintenance program is acceptable in accordance with Exclusion Criterion #9. Oxygen therapy is an exclusion criterion for this study.

5.9.2 Other (non-COPD) Prior and Concomitant Medications

Patients may continue other prescribed non-respiratory therapies during the study that the Investigator considers to neither compromise subject safety nor affect study data. Beta-blockers are not allowed to be used during the study.

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

All concomitant medications must also be documented in the eCRF.

5.10 Rescue Medications

Short acting bronchodilators may be used as rescue medication. If this is inadequate for symptom control, the patient should contact the Investigator. Rescue medication use during each treatment visit must be separately documented in the eCRF (medication, dose, date and time of each administration). Protocol procedures must still continue even if rescue medication has been taken. Rescue medication (i.e. albuterol/salbutamol) use will be captured in the electronic diary (e-diary).

5.11 Treatment Compliance

Treatment compliance will be monitored in 3 ways: 1) e-diary, where the number of nebulizations per day will be recorded, 2) the number of returned used vials, and 3) trough pharmacokinetic assessments at Visits 3 and 6.

6 STUDY PROCEDURES AT EACH VISIT

The study will consist of six visits:

- Screening (Visit 1) will take place in the period between 7 and 14 days prior to the first study medication administration. This may be performed as a single visit or more than one visit. Reversibility testing can be performed at Visit 1b if necessary. Eligible patients may be rescreened 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 14 days prior to administration of study medication (i.e., randomization)
 - Five treatment visits (Visit 2 to Visit 6) each separated by 7 (± 1) days
- Repeat, rescheduled and unscheduled visits and procedures are permitted at the discretion of the Investigator (rescheduled visits are subject to the ± 1 day window mentioned above).

The schedule of assessments at each visit is shown in Table 3 and listed in Section 6.1 to Section 6.5. The study assessments are described in Section 7.

Table 2 Schedule of Assessments in RPL554-CO-203

Visit	Visit 1a Screening (Week -2 to -1)	Visit 1b (Day after Visit 1a)	Visit 2 Randomization	Visit 3 (Week 1 ±1 day)	Visit 4 (Week 2 ±1 day)	Visit 5 (Week 3 ±1 day)	Visit 6a (Day before Visit 6b)	Visit 6b End of Study (Week 4 ±1 day or early termination)	Telephone Follow-up (2 weeks after Visit 6b ±3 days)
Informed consent	X ^a								
Demographics, except body weight	X								
Body weight	X							X	
Medical/surgical & disease history	X								
Inclusion/exclusion criteria	X		X						
Physical examination	X							X	
Nebulization inhalation training			X						
Reversibility test	X								
Randomization			X						
Pregnancy test ^b	X		X	X	X	X		X	
Viral serology	X								
Study medication inhalation			X ^c	X	X	X		X	
Spirometry	X		X ^d	X ^e	X ^e	X ^e		X ^d	
Prior/concomitant medications	X		X	X	X	X		X	
Vital signs (blood pressure, pulse)	X		X ^f	X ^g	X ^g	X ^g		X ^f	
ECG (QTcF and heart rate)	X		X ^h	X ^h	X ^h	X ^h		X ^h	
Laboratory safety tests	X			X				X	
Chest X-ray	X								
Administer SGRQ-C, BDI/TDI and MRC breathlessness scale			X _i		X _i			X _i	

Abbreviations: BDI=Baseline Dyspnea Index; ECG=electrocardiogram; ICS=inhaled corticosteroids; MRC=Medical Research Council; QTcF=QT interval corrected using Fridericia's formula; PGAC=Patient Global Assessment of Change; PK=pharmacokinetics; SGRQ-C=St George's Respiratory Questionnaire-COPD specific; TDI=Transition Dyspnea Index

- (a) Informed Consent may be obtained prior to screening visit
- (b) Serum pregnancy test at Visit 1; urine pregnancy test at Visits 2-6
- (c) At Visit 2, study medication is to be administered at the study clinic twice; first, just after randomization and again 12 hours later once all assessments are complete
- (d) Spirometry at Visits 2 and 6 is performed 15 minutes pre-dose, followed by 30 minutes and 1, 2, 3, 4, 6, 8 and 12 hours post-dose
- (e) Spirometry at Visits 3, 4 and 5 is performed 15 minutes pre-dose, followed by 30 minutes and 1, 2 and 3 hours post-dose
- (f) Vital signs at Visits 2 and 6 are measured pre-dose and 30 minutes, 1, 2, 4, 6, 8 and 12 hours post-dose
- (g) Vital signs at Visits 3, 4 and 5 are measured pre-dose and 30 minutes, 1, 2 and 3 hours post-dose
- (h) ECG at Visits 2 through 6 is performed pre-dose and 2 hours post-dose
- (i) BDI administered at Visit 2, TDI administered at Visits 4 and 6
- (j) A second canister of albuterol/salbutamol may be dispensed during the study if necessary (k) Holter is to be removed 24 hours (\pm 1 hour) after placement

6.1 Pre-visit Restrictions

The following restrictions in relation to study visits 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 on at all treatments visits (Visit 2 through Visit 6). Meals will be served during Visits 2 and 6
- Patients should refrain from smoking on the day of the visit, at the very least abstain from smoking in the 2 hours prior to dosing with study medications and within 1 hour of all spirometry efforts. Whether the patient smoked should be noted in source documentation
- Patients must refrain from strenuous exercise for 72 hours prior to all study visits and should undertake no unaccustomed strenuous exercise from screening (Visit 1) until the final study visit (Visit 6)

6.2 Visit 1: Screening

Written informed consent will be obtained by the Investigator as specified in Section 10.3 prior to any study related procedures being performed. This typically will need to be performed prior to the day of the screening visit to allow for discontinuation of any prohibited medications, including the requirement to refrain from bronchodilators in accordance with Section 5.9.1.

Patients will be screened to determine eligibility against the Inclusion and Exclusion Criteria between 7 and 14 days before the first dose of study medication at Visit 2. There are no fasting requirements for the screening visit. Patients must observe the medication restrictions described in Section 5.9.1, and other restrictions described in Section 6.1.

To account for diurnal variability in pulmonary function, Visit 1 is to take place in the morning. The following assessments will be performed, generally in the order indicated: □ Obtain informed consent (if not done prior to Visit 1)

- Demographic information
- Medical/surgical and disease history
- Prior medications and therapies
- Vital signs (blood pressure and pulse rate)
- Physical examination
- 12-lead ECG
- Pre-albuterol/salbutamol spirometry
- Reversibility test (four puffs of albuterol/salbutamol)
- Post-albuterol/salbutamol spirometry – 30 minutes after albuterol/salbutamol dosing
- Blood and urine samples for laboratory safety tests and viral serology
- Serum pregnancy test (female patients of childbearing potential)
- Chest X-ray (unless historical X-ray performed in last 12 months is available)
- Questioning for adverse events (if informed consent obtained prior to Visit 1)

Patients meeting all of the Inclusion and none of the Exclusion Criteria will then have the following performed:

- Holter monitor placement (to be removed 1 day later)
- Dispensing of albuterol/salbutamol and, if applicable, inhaled steroids (see Section 5.9.1)
- Dispensing of e-diary and instructions on its use. The patient will log into the electronic Patient Reported Outcome (ePRO) device and answer all of the questions to ensure comprehension (see Section 7.2.2)

The patient will be instructed on the following:

- Return the next day for removal of Holter (noted as Visit 1B in Table 3)
- Return in 7 to 14 days for Visit 2
- Observe the medication restrictions described in Section 5.9.1, and other restrictions described in Section 6.1 Contact the site for any significant increase in COPD symptoms

6.3 Visit 2: Randomization

Patients returning for Visit 2 will be evaluated to confirm that all Inclusion and Exclusion Criteria are met. In particular, laboratory and Holter findings must show no clinically significant abnormalities, including but not limited to those described in Section 4.2.

Visit 2 shall be scheduled to begin in the morning, such that dosing occurs between 7:00 and 10:00 AM.

6.3.1 Pre-Dose Assessments

The following assessments will be performed prior to dosing:

- Confirmation that respiratory medication and other restrictions described in Section 5.9.1 and Section 6.1, respectively, were properly followed. If not, reschedule the visit for within the required window
- Collection of demographic variables (date of birth, sex, height, weight, race and smoking status)
- Questioning for adverse events
- Concomitant medication check
- Review of e-diary to confirm compliance with the device
- Urine pregnancy test (female patients of childbearing potential)
- 12-lead ECG
- Vital signs (blood pressure and pulse rate)
- Patients will complete the SGRQ-C, BDI and MRC breathlessness scale
- Spirometry at 15 minutes pre-dose; must demonstrate that the FEV₁ be within 20% of the pre-albuterol/salbutamol FEV₁ recorded at Visit 1

Patients who remain eligible will then be randomized and assigned a randomization number.

6.3.2 Study Medication Administration

Patients will be administered either RPL554 (one of four different dose levels) or placebo by the unblinded study staff member according to the randomization schedule, and again approximately 12 hours later upon completion of the assessments listed below.

[REDACTED].

6.3.3 Post-Dose Assessments

The following assessments will be performed, at the times indicated (± 10 minutes) relative to dosing:

- Spirometry at 30 minutes and 1, 2, 3, 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 hours
- Questioning for adverse events

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

- Use of the e-diary
- Return in 7 days (± 1 day) for Visit 3
- Observe the medication restrictions described in Section 5.9.1, and other restrictions described in Section 6.1
- Contact the site for any significant increase in COPD symptoms

6.4 Visits 3 through 5

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

6.4.1 Pre-Dose Assessments

The following assessments will be performed prior to dosing:

- Confirmation that respiratory medication and other restrictions described in Section 5.9.1 and Section 6.1, respectively, were properly followed. If not, reschedule the visit for within the required window
- Unblinded study staff will collect nebulizer and any used/unused study medication, and dispensing of a new box and nebulizer
- Questioning for adverse events
- Concomitant medication check
- Review of e-diary for compliance with the device and study medication
- Review nebulizer technique and maintenance
- Urine pregnancy test (female patients of childbearing potential)
- 12-lead ECG
- Vital signs (blood pressure and pulse rate)
- Visit 3 only: blood and urine samples for safety laboratory tests
- Visit 3 only: blood sample for pharmacokinetic measurement
- Visit 4 only: Patients complete SGRQ-C, TDI, MRC breathlessness scale, and PGAC questionnaire
- Spirometry at 15 minutes pre-dose

6.4.2 Study Medication Administration

Patients will be dosed with either RPL554 (one of four different dose levels) or placebo according to the randomization schedule. The first dose of the new study medication pack will be administered in the clinic by the unblinded study staff.

6.4.3 Post-Dose Assessments

The following assessments will be performed, at the times indicated (± 10 minutes) relative to dosing:

- Spirometry at 30 minutes and 1, 2 and 3 hours
- Vital signs at 30 minutes and 1, 2 and 3 hours
- 12-lead ECGs at 2 hours
- Questioning for adverse events

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

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

In addition, patients completing Visit 5 will be instructed to return in 6 days (± 1 day) for placement of a 24 hour Holter monitor (noted in Table 3 as Visit 6a).

6.5 Visit 6: End of Study

Patients completing Visit 6 will have end of study procedures performed. On the day prior to performing the assessments below, the Holter monitor will be placed on the patient (Visit 6a). Visit 6 shall occur in the morning, such that dosing occurs within 1 hour of the time of administration at Visit 2.

6.5.1 Pre-dose Assessments

The following assessments will be performed prior to dosing (Visit 6b):

- Removal of Holter monitor
- Confirmation that respiratory medication and other restrictions described in Section 5.9.1 and Section 6.1, respectively, were properly followed. If not, reschedule the visit for within the required window
- Collection of compressor, nebulizer and any unused study medication
- Collection of body weight
- Questioning for adverse events
- Concomitant medication check
- Review e-diary for compliance with the device and study medication
- Collect e-diary
- Physical examination

- Blood and urine samples for laboratory safety tests
- Blood sample for pharmacokinetic measurement
- Urine pregnancy test (female patients of childbearing potential)
- 12-lead ECG
- Vital signs
- Patients complete SGRQ-C, TDI, MRC breathlessness scale, and PGAC questionnaire
- Spirometry at 15 minutes pre-dose

6.5.2 Study Medication Administration

Patients will receive their final dose of either RPL554 or placebo using a nebulizer according to the randomization schedule. Study medication for Visit 6 is packaged separately, and is maintained on site throughout the patient's participation in the study.

6.5.3 Post-Dose Assessments

The following assessments will be performed, at the times indicated (\pm 10 minutes) relative to dosing:

- Spirometry at 30 minutes and 1, 2, 3, 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 hours
- Questioning for adverse events

Following the last post-dose assessment, patients will be replaced on their long-acting COPD medications (LAMA and/or LABA) as per the discretion of the Investigator. In addition, an appointment for a follow-up telephone call will be made.

6.5.4 Telephone Follow-up

Telephonic contact will be made with the patient 2 weeks (\pm 3 days) after the final visit in order to ascertain patient status and query about any 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 (Visit 1) as described in Section 7.3.2 to Section 7.3.5 as part of the eligibility assessment.

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 (Visit 1). Weight will be collected again at Visit 6.

7.1.2 Medical/Surgical and Disease History

A complete medical and surgical history will be taken at screening (Visit 1), including disease history which includes date of diagnosis and prior respiratory therapies.

7.1.3 Reversibility Test

Reversibility in response to albuterol/salbutamol will be assessed at screening (Visit 1) as an eligibility measure. Spirometry (FEV₁ and FVC) assessment before and after four puffs of albuterol/salbutamol are administered using a pMDI will be performed.

At both time points, three technically acceptable and reproducible measurements should be made in accordance with the requirements described in Section 7.2.1. The highest reading from each assessment will be used for calculation of predicted values and increase from baseline.

The following must be confirmed post-albuterol/salbutamol dose for inclusion:

- Post-bronchodilator FEV₁/FVC ratio of ≤ 0.70
- Post-bronchodilator FEV₁ $\geq 40\%$ and $\leq 80\%$ of predicted normal*

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

7.1.4 Screening Laboratory Eligibility Assessments

Laboratory safety assessments will be performed as described in Section 7.3.2. At screening (Visit 1) only, the blood sample collected for biochemistry assessment will also be analyzed for human immunodeficiency virus, hepatitis B and hepatitis C serology at the central laboratory. Follicle stimulating hormone (FSH) testing will be performed only if it is required to confirm post-menopausal status.

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

A chest X-ray (posterior-anterior) must be performed at screening (Visit 1) or documented with results in the 12 months prior to screening.

7.1.5 Prior and Concomitant Medications and Therapies

Prior COPD therapies and medications will be recorded at screening (Visit 1) and concomitant use during the study recorded as described in Section 5.9.1.

Other prior medications will be separately recorded at screening (Visit 1) 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 (Visit 1) with a final check of all results pre-dose at Visit 2.

7.2 Efficacy Assessments

7.2.1 Pulmonary Function Tests

Spirometry assessments (FEV₁ and FVC) will be made at the following time points at Visits 2 and 6 (± 10 minutes): pre-dose (one measurement at 15 minutes prior start of dosing) and 30 minutes and 1, 2, 3, 4, 6, 8 and 12 hours post-dose (after completion of nebulization) in accordance with ATS/ERS guidelines (Miller et al., 2005). At all time points, three technically acceptable measurements should be made and recorded. Spirometry assessments may be repeated up to eight times to obtain three acceptable readings according to ATS guidelines (Miller et al., 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. At Visits 3 to 5, spirometry will be made 15 minutes pre-dose and 30 minutes, and 1, 2 and 3 hours post-dose (\pm 10 minutes). Spirometry will be performed using equipment provided by the Sponsor and reviewed centrally, and sites will be instructed in proper use of the equipment prior to study initiation.

7.2.2 Symptom Diary

At Visit 1 an electronic symptom diary will be dispensed to the patients continuing in the study. This will use the EXACT-PRO measure to determine symptoms during the study. EXACT is an acronym to represent “The Exacerbations of Chronic Pulmonary Disease Tool” and PRO is an acronym for “Patient-Reported Outcome”. E-RS is for “Evaluating respiratory symptoms,” and uses the 11 respiratory symptom questions in the EXACT tool. There are three subscales in the measures; breathlessness, cough/sputum, and chest symptoms. The diary will be used once daily at bedtime. The diary will also collect use of albuterol/salbutamol, and time of dosing with study medication.

At screening (Visit 1), study personal will train the patients on use of the ePRO device with the EXACT instrument as follows:

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

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

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

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

7.2.4 Medical Research Council (MRC) Breathlessness Scale

The MRC uses a simple grading system to assess a patient's level of breathlessness. It is the most commonly used validated scale to assess dyspnea in daily living in chronic respiratory diseases (Mahler et al., 1988; Hajiro et al., 1998). During Visits 2, 4 and 6, patients will be

provided with the MRC (shown in Table 4) and asked on a grade of 1 to 5 how they would describe their levels of breathlessness.

Table 3 MRC Breathlessness Scale

Grade	Degree of breathlessness related to activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on the level or walking up a slight hill
3	Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace
4	Stops for breath after walking about 100 yds or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when undressing

7.2.5 Patient Global Assessment of Change

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

7.2.6 Baseline and Transitional Dyspnea Indexes (BDI and TDI)

The BDI and TDI are interviewer administered ratings of dyspnea severity. It is based on three components that evoke dyspnea in activities of daily living. The BDI is scored from 0 to 12 and is only assessed at baseline. The lower the score the worse the dyspnea severity. The TDI measures the change in dyspnea severity from the baseline as measured by the BDI. It is rated by seven grades ranging from -3 (major deterioration) to +3 (major improvement). The BDI will be performed at Visit 2 and the TDI at Visits 4 and 6.

7.3 Safety Assessments

7.3.1 Adverse Events

Recording and reporting adverse events is described in detail in Section 7.6. Standard procedures for emergency care should be followed for any individual adverse event, whenever clinically needed (decision to be taken by the Investigator).

7.3.2 Laboratory Safety Assessments

7.3.2.1 Local Assessments

All female patients will have a serum pregnancy test at screening (Visit 1) and a urine pregnancy test pre-dose at Visit 2 to Visit 6 according to the study center’s standard operating procedures (SOPs).

7.3.2.2 Central Laboratory Assessments

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

A vacutainer blood collection system will be used to collect safety laboratory blood samples; full details will be provided in the laboratory manual. Two samples will be collected at each time point, one sample for hematology using a ethylenediaminetetraacetic acid (EDTA) whole blood collection tube and one sample for biochemistry using a serum clot activator tube. A midstream urine sample will also be collected in a sterile container. Additional sample collection and handling information will be described in the laboratory manual.

Samples will be analyzed at the central laboratory for:

Hematology: hemoglobin, hematocrit, total white cell count, leukocyte differential count and platelet count

Biochemistry: creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine transaminase, gamma-glutamyl transferase, lactate dehydrogenase, creatine kinase, thyroid stimulating hormone, triiodothyronine and thyroxine, glucose, potassium, sodium, calcium, NT-proBNP, hepatitis B and C, and FSH (to confirm post-menopausal status when appropriate)

Urinalysis: leukocytes, blood, ketones, bilirubin, urobilinogen, protein and glucose using a dipstick. In the event of an abnormal dipstick urinalysis result, microscopic urinalysis may be conducted. The referral criteria will be specified in the laboratory manual

Any change in laboratory normal ranges during the trial should be forwarded to the Sponsor or designee in a timely manner.

7.3.3 Vital Signs

Blood pressure and pulse rate will be measured at screening (Visit 1) and pre-dose, 30 minutes and 1, 2, 4, 6, 8 and 12 hours post-dose at Visit 2 and Visit 6.

Blood pressure and pulse rate will be measured at pre-dose and 30 minutes, 1, 2 and 3 hours after dosing at Visits 3 to 5.

At each time point, a 10 minute window will apply and supine vital signs will be assessed while the patient has been at rest for at least 5 minutes.

7.3.4 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 (Visit 1). Results will be recorded in the eCRF as normal, abnormal not clinically significant or abnormal clinically significant. A comment will be made for any clinically significant abnormalities. The physical examination will be repeated at the end of study visit (Visit 6), and any changes only recorded.

7.3.5 12-Lead ECG

12-lead ECGs will be taken at screening (Visit 1) and pre-dose and 2 hours post-dose at all subsequent visits.

At each time point, 12-lead ECGs 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. The ECGs will be centrally collected and analyzed.

7.3.6 Holter Monitors

Holter monitors will be placed at screening (Visit 1) and at end of study (Visit 6). Patients will return to the clinic for removal of the monitors after 24 hours of data has been collected.

7.4 Pharmacokinetic Assessments

Pharmacokinetic analyses will be performed on samples taken from all patients. Blood samples (4 mL at each time point) will be collected prior to dosing at Visits 3 and 6. Samples will be collected by venipuncture in the forearm into lithium heparin tubes and then centrifuged within 15 minutes of collection. The plasma will be separated in a centrifuge at 1100g for 15 minutes and then transferred into polypropylene tubes in 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. Analyses will be performed by the pharmacokinetic central laboratory.

7.5 Appropriateness of Measurements

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

Spirometry is a standard lung function test used to screen for, and monitor, respiratory disease. Spirometry and daily calibrations will be performed in accordance with ATS/ERS task force standardization guidelines (Miller et al., 2005) using equipment provided by the spirometry vendor.

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.

7.6 Handling of Adverse Events and Pregnancies

7.6.1 Adverse Event Definitions

Adverse event is defined as any undesirable experience occurring to a patient, or worsening of patient's pre-existing condition, during a clinical study, whether or not considered related to the study medication. An adverse event may be any of the following:

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

No causal relationship with the study medication is implied by the use of the term "adverse event."

An exacerbation of a pre-existing condition or illness is defined as a more frequent occurrence or as an increase in the severity of the pre-existing condition or illness during the

study. COPD exacerbations, for the purposes of this protocol, are defined as an increase or new onset of more than one respiratory symptom (cough, sputum, sputum purulence, wheezing, or dyspnea) lasting for at least 3 days and requiring treatment with an antibiotic, systemic steroid, or both (Decramer et al., 2009).

Planned or elective surgical or invasive procedures for pre-existing conditions that have not worsened are not adverse events. However, any complication that occurs during a planned or elective surgery is an adverse event (if the event fits the serious criteria, such as an extended hospitalization, it will be considered to be serious). Conditions leading to unplanned surgical procedures may be adverse events.

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

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

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

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

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

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

7.6.2 Recording and Assessing Adverse Events

All adverse events, whether reported spontaneously by the patient, in response to open questioning on treatment days or observed by the Investigator or his/her staff, will be recorded from informed consent until the Telephone Follow-up (2 weeks after Visit 6b).

The start and stop time will be recorded and adverse events will be assessed by the Investigator for the following:

7.6.2.1 Severity

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

7.6.2.2 Chronicity

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

7.6.2.3 Causality

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

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

A guide to the interpretation of the causality question is found in Appendix II.

7.6.2.4 Action and Outcome

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

7.6.3 Reporting Procedure for SAEs

The Investigator must report all SAEs using the reporting form provided as soon as practical, no later than within 24 hours of awareness. Any SAEs notified in the 28 day period after the last dose of study medication must also be reported.

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

SAEs will be reported to the 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.

7.6.4 Management of Pregnancies

Should a female patient become pregnant or a male patient father a child during the study or in the 28 days after the end of the study, they must inform the Investigator immediately. Pregnant

female patients must discontinue study medication immediately and be withdrawn from the study. The Investigator will report this information to the Sponsor within 7 days of awareness. The Investigator will make all reasonable efforts to ascertain the progress and outcome of the pregnancy. If the outcome meets the criteria for immediate classification of a SAE (e.g. spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital anomaly, birth defect), the Investigator must follow the procedure for reporting SAEs.

8 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 10).

8.1 Audit and Inspection

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

8.2 Monitoring and Source Document Verification

The Sponsor will arrange for the study to be monitored in accordance with the principles of ICH GCP guidelines. There will be a blinded and an unblinded study monitor assigned to each site. The study monitors will be approved by the Sponsor. The frequency of monitoring visits will be determined by, among other factors, the rate of patient recruitment. During these visits, all procedures will be monitored for compliance with the protocol. Source documents will be reviewed and compared with the data entries in the eCRFs to ensure consistency.

The 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 (performed by unblinded monitor)

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) while 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 are not limited to, the following and will be identified in a source data location log:

- Screening/enrollment 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 medication accountability/inventory forms

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

8.3 Data Management and Coding

Electronic case report forms (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 onto the eCRFs using a secure internet connection. The eCRFs should be filled out completely by the Investigator or designee as stated on the delegation of responsibilities form. The eCRF system will be Food and Drug Administration Code of Federal Regulations 21 Part 11 compliant.

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

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

Data collected centrally will be transferred electronically into the study database. Discrepancies will be queried to the site and/or the laboratory until the electronic data and the database are reconciled.

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

Once the full set of eCRFs has been completed and locked, the Sponsor will authorize database lock and all electronic data will be sent to the designated statistician for analysis. Subsequent changes to the database will then only be made 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). Prior and concomitant medications and therapies will be coded according to the World Health Organization drug code. An independent coding review will be performed by the Sponsor. The clinical database (in Statistical Analysis System [SAS] format) will be transferred to the Sponsor at the end of the study.

9 STATISTICAL METHODS

9.1 Statistical and Analytical Plans

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

9.2 Populations to be Analyzed

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

The full analysis set will consist of all randomized patients with sufficient data collected after intake of study medication to compute the pharmacodynamic parameters on at least one study visit. Patients will be considered evaluable if they have at least one FEV₁ measurement after randomization.

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

9.2.1 Study Endpoints

9.2.1.1 Primary Endpoint

Change from baseline in peak FEV₁ (maximum value during 3 hours following dose) after 4 weeks of treatment.

9.2.1.2 Secondary Endpoints

- Change from baseline in morning trough FEV₁ after 4 weeks of treatment
- Change from baseline in average FEV₁ over 12 hours at Visits 2 and 6
- Change from baseline in peak and average FEV₁ over 3 hours at Visits 2 to 6
- Change from baseline in COPD symptoms, as measured by daily diary (EXACT-PRO)
- Change from baseline in the SGRQ-C and MRC breathlessness scales.
- TDI dyspnea scale
- PGAC
- Change from baseline in rescue albuterol/salbutamol use
- Safety and tolerability:
 - Continuous monitoring of adverse events
 - Laboratory safety tests (hematology, biochemistry and urinalysis)
 - 12-lead ECG (including QTcF and heart rate), supine vital signs [blood pressure and pulse rate] over 12 hours (Visits 2 and 6) or up to 3 hours (Visits 3 to 5) - Holter monitor

9.2.2 Statistical Methods

In general, unless stated otherwise, continuous variables will be summarized using descriptive statistics (number of patients [N], mean, standard deviation [SD], median, minimum and

maximum values) and for categorical (nominal) variables, the number and percentage of patients will be used.

9.2.2.1 Patient Disposition

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

9.2.2.2 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.

9.2.2.3 Demographics and Other Baseline Characteristics

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

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

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.

9.2.2.4 Extent of Exposure and Treatment Compliance

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

9.2.2.5 Efficacy

For FEV₁ the average effect (E_{av}) will be calculated as the AUC divided by the length of the time interval of interest. In addition, the peak effect on FEV₁ during these time intervals will be computed as the maximum value (E_{max}) and the trough FEV₁ as the value at 12 hours prior to next dose administration. Parameters will be calculated both over 3 hours (Visits 2 to 6) and over 12 hours (Visits 2 and 6). For withdrawn patients, values from last visit performed will be imputed. The peak FEV₁ is the highest value in the 3 hours after dosing.

Computed pharmacodynamic parameters for FEV₁ will be compared between the five study medications using (additive) analysis of covariance (ANCOVA) models with fixed factors for treatment and country(/center) and using the baseline FEV₁ (pre-dose at Visit 2) as a covariate. Parameters will be analyzed both after single-dose (Visit 2), at end-of-study (Visit 6/last visit) or as the average over Visits 3 to 6. The total score for the EXACT-PRO will be summarized for each day and the average weekly scores during the treatment period as well as the average over the full treatment period will be calculated. The average over last 7 days of the run-in period will be used as baseline.

Sites will be consolidated to the country level, which will be used as a fixed factor in all analyses in order to help reduce the variability in data. At least for the primary variable, secondary analyses investigating impact of country will be performed. Depending on differences in variance structure between countries, either separate models will be applied by country to estimate the treatment effect within each stratum or a full model including a treatment by country interaction term will be used to provide these estimates. No formal treatment by country test is planned.

The average daily use of rescue medication during the full treatment period and during each week will be calculated. The average over last 7 days of the run-in period will be used as baseline.

Average EXACT-PRO total scores, average daily use of rescue medication, SGRQ-C total scores, MRC, global assessment of change, and TDI scores will be compared between the five treatments using ANCOVA models with treatment and country(/center) as factors and using baseline as a covariate where appropriate. Subdomain scores of the EXACT-PRO and SGRQC will be summarized and subjected to exploratory analyses.

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

Testing for efficacy will start with the highest dose of RPL554 versus placebo. If a statistically significant difference is found, the testing will proceed with the next highest dose, and so on. Secondly, the various doses of RPL554 will be compared. Appropriate measures will be taken to control for the type I error rate in these hypothesis tests. A closed testing procedure to test active dose vs. placebo will be used for the primary endpoint. The study is not powered for pairwise differences between active doses. Thus, dose-response is best investigated in a secondary analysis fitting an appropriate dose-response model to the data. The Statistical Analysis Plan will provide additional details of the multiplicity adjustment method(s) used.

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

9.2.2.6 *Safety*

Safety data, including safety laboratory tests, ECG parameters, Holter monitors, vital signs and physical examinations, will be summarized by treatment group and time point, when appropriate. For continuous variables, the change from baseline (both regarding pre-dose at Visit 2 and pre-dose at each treatment visit) to each post-dose time point will also be calculated and summarized. Data will further be illustrated by shift tables (showing changes from low/normal/high) and shift plots for selected time points.

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

9.2.3 *Handling of Withdrawals or Missing Data*

Relevant pharmacodynamic parameters will be calculated for each visit and then missing visit values imputed using the LOCF technique applied to these parameters. Since peak FEV₁ will

always be the maximum FEV₁ value within 3 hours, only one non-missing post-dose assessment is needed to estimate the peak.

Patients withdrawn prior to any efficacy measures will not be included in the efficacy analyses. Detailed procedures for imputation of data will be described in the statistical analysis plan.

All available data from all patients who have received study medication will be listed and summarized. Any unscheduled or unplanned readings will be presented within the patient listings, but only the scheduled readings will be used in any summaries. If a visit is rescheduled for any reason, the rescheduled visit will be listed and summarized as the valid visit.

9.2.4 Interim Analyses

No formal interim analysis is planned for the study.

9.3 Determination of Sample Size

The standard deviation for peak FEV₁ is estimated to be 250 mL. With a 2-sided test at a 5% significance level and 80 evaluable patients per group, there will be an 80% power to detect a true difference of 111 mL between any two treatments. This detectable limit has been considered sufficient to conclusively identify a minimal effective dose of RPL554. Thus 80 patients per group will be randomized.

10 ETHICAL CONSIDERATIONS

10.1 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.

10.2 Ethics and Regulatory Approval

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

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

10.3 Informed Consent Process

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

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

10.4 Patient Confidentiality

Data collected during this study may be used to support the development, registration or marketing of the study medication. The Sponsor will control all data collected during the study, and will abide by the Health Insurance Portability and Accountability Act (HIPAA) and the EU 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 U.S. and EU. The purpose of any such transfer would be to support regulatory submissions made by the Sponsor in such countries.

10.5 Record Maintenance/Retention

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

11 FINANCE AND INSURANCE

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

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

12 PUBLICATION POLICY

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

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14 APPENDICES

Appendix I – Birth Control Methods For Women of Childbearing Potential Which May Be Considered As Highly Effective

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

I. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP:

4. Premenopausal female with one of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

5. Premenarchal

6. Postmenopausal female

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

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

II. Methods

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

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation¹:
 - oral
 - intravaginal
 - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation 1:
 - oral
 - injectable
 - implantable²

- Intrauterine device (IUD)²
- Intrauterine hormone-releasing system (IUS)²
- Bilateral tubal occlusion²
- Vasectomized partner^{2,1}
- Sexual abstinence²

¹ Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method

² Contraception methods that in the context of this guidance are considered to have low user dependency

¹ Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success

² In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject

Appendix II – Interpreting Adverse Event Causality

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

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

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

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

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

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

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