

STATISTICAL ANALYSIS PLAN

RPL554-CO-205

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

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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Abbreviations

ACS	Abnormal Clinically Significant
ALT	Alanine Amino Transferase
ANCS	Abnormal Not Clinically Significant
AEs	Adverse Events
ANCOVA	Analysis of Covariance
AST	Aspartate Amino Transferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC _{0-t}	Area under the curve over t hours
BDI	Baseline Dyspnea Index
BMI	Body Mass Index
CAT	COPD Assessment Test
CIs	Confidence Intervals
COPD	Chronic Obstructive Pulmonary Disease
CV	Coefficient of Variation
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ENR	All Patients Enrolled Set
E-RS TM : COPD	Evaluating Respiratory Symptoms for COPD
FAS	Full Analysis Set
FEV ₁	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GGT	Gamma Glutamyl Transferase
IC	Inspiratory capacity
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
Non-TEAE	Non-treatment emergent adverse event
PD	Pharmacodynamic
PGAC	Patient Global Assessment of Change
PK	Pharmacokinetic
PPS	Per-Protocol Set
PT	Preferred Term
QTcF	QT interval corrected for heart rate using Fridericia's formula
RND	All Patients Randomized Set
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan

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SAS	Statistical Analysis Software
SGRQ-C	St. George's Respiratory Questionnaire
SI	Standard International
SOC	System Organ Class
TDI	Transition Dyspnea Index
TEAE	Treatment-emergent Adverse Event
WHO	World Health Organization

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety as described in Section 9 of the study protocol. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. This statistical analysis plan (SAP) is based on protocol version 5.0, dated 22nd July 2019.

2. STUDY OBJECTIVES

2.1. Primary Objective

To investigate the bronchodilator effect of different doses of RPL554 administered by nebulizer on change from baseline in peak forced expiratory volume in 1 second (FEV₁) (maximum over 3 hours following dosing) at the final study visit (i.e., Week 4) when administered twice daily to patients with moderate to severe chronic obstructive pulmonary disease (COPD) on a background of once-daily tiotropium.

2.2. Secondary Objective

- To investigate the bronchodilator effect of RPL554 administered by nebulizer on average area under the curve AUC_{0-3h} FEV₁ at Week 4
- To investigate the bronchodilator effect of RPL554 administered by nebulizer on average AUC_{0-12h} FEV₁ at Week 4
- To investigate the effect of RPL554 administered by nebulizer on change from baseline in morning trough FEV₁ at Week 4
- To investigate the effects of RPL554 on COPD symptoms, as measured by daily diary (Evaluating Respiratory Symptoms for COPD [E-RSTM:COPD], St. George's Respiratory Questionnaire [SGRQ-C], Baseline Dyspnea Index [BDI]/Transition Dyspnea Index [TDI] and patient global assessment of change [PGAC])
- To investigate the bronchodilator effect of RPL554 administered by nebulizer on peak FEV₁, trough FEV₁ and average AUC_{0-3h} FEV₁ at Weeks 1, 2 and 3
- To investigate the bronchodilator effect of RPL554 administered by nebulizer on peak FEV₁, average AUC_{0-3h} FEV₁ and average AUC_{0-12h} FEV₁ at Day 1
- To investigate the safety of RPL554 when administered for 4 weeks in patients with COPD, as measured by adverse events (AEs), laboratory tests, 12-lead electrocardiograms (ECGs) and vital signs
- To investigate the effect of RPL554 on rescue albuterol use
- To investigate the bronchodilator effect of RPL554 administered by nebulizer on peak and average AUC_{0-3h} forced vital capacity (FVC) on Day 1 and at Weeks 1 to 4, in average AUC₀₋₁₂ FVC on Day 1 and at Week 4 and in morning trough FVC at Weeks 1 to 4.

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- To evaluate the steady state exposure of RPL554
- To evaluate the effect of RPL554 on tiotropium steady state exposure

2.3. Exploratory Objective

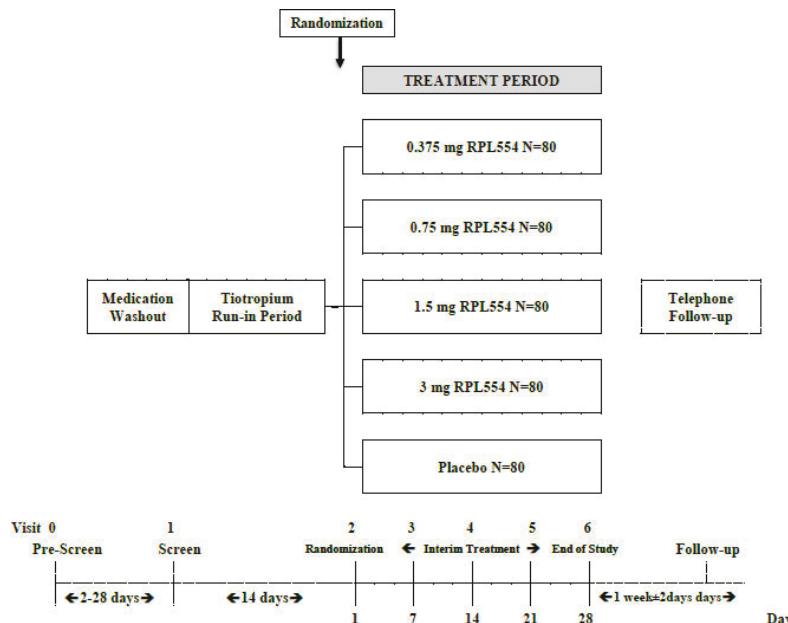
- To assess the change from baseline FEV₁ to peak and average AUC_{0-12h} FEV₁ at Week 4 compared to Day 1
- To investigate the effect of RPL554 on inspiratory capacity (IC) on Day 1 and at Week 4
- To investigate the effects of RPL554 on COPD symptoms, as measured by the COPD Assessment Test (CAT)
- To assess the effect of RPL554 on morning symptoms and activity limitation

3. STUDY DESIGN

3.1. General Description

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

Figure 1: Study Flow Chart



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At the pre-screen visit patient will be asked to sign the informed consent, will receive their patient identification number and commence washout of prohibited medications. Patients will be dispensed rescue medication to be used as needed for increased pulmonary symptoms during the screening run-in and treatment periods.

After patients provide informed consent and following at least a 48-hour washout of all long-acting bronchodilators, they will be screened for eligibility including a reversibility test (spirometry both pre- and post-four puffs of albuterol). Eligible patients will enter a 14-day run-in and be dispensed open-label tiotropium (Spiriva® Respimat) and an electronic diary (e-diary) for recording symptoms, assessing rescue usage and confirming twice daily dosing with study treatment. Starting the day after Screening (Visit 1) patients will start taking open-label tiotropium (Spiriva® Respimat®) once daily in the morning.

At Day 1 patients will be re-assessed for eligibility according to the Randomization Criteria, which can be found in Section 4.3 of the study protocol. Eligible patients will be stratified based on the reversibility to albuterol, as determined at Screening (“reversible”, “non-reversible”), then randomized to one of the five treatment groups within each reversibility stratum. After randomization, patients will take their tiotropium dose 2 minutes prior to their first dose of double-blind study treatment (RPL554 or placebo). Patients will remain in the clinic for 12 hours to undergo serial spirometry and other assessments. They will then take their second dose of study treatment in the evening prior to clinic discharge. Patients will return to the clinic for 3 weekly visits. In between visits, patients will take the study treatment twice a day (morning and evening) and tiotropium once a day in the morning, in the same order as described above.

Patients will be instructed to withhold study treatment, tiotropium and rescue medication prior to study visits. Rescue medication will need to be withhold prior to the visit for at least 6 hours.

Approximately 400 patients with COPD aged 40 to 80 years (inclusive) will be randomized equally to receive RPL554 (four possible doses) or placebo (Figure 1). Study treatment will be administered double-blind to minimize any potential bias in the overall assessment of treatment effect and safety.

3.2. Schedule of Events

Schedule of events can be found in Section 6.0 of the study protocol.

3.3. Changes to Analysis from Protocol

No changes to the analysis outlines in the protocol are planned.

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4. PLANNED ANALYSES

A final analysis after database lock is planned for this study.

4.1. Data Monitoring Committee (DMC)

There will be no data monitoring committee (DMC) for this study.

4.2. Interim Analysis

There will be no formal, unblinded interim analysis for this study. To assess the plausibility of the assumptions in the sample size calculation, peak FEV₁, trough FEV₁, AUC₀₋₃ FEV₁ and AUC_{0-12h} FEV₁ will be calculated on blinded data after completion of 125 patients. If the estimated standard deviation has an increase of 12% or less, then there will be no revised sample size made. However, if the estimated standard deviation has an increase of 20% or more, a revised sample size estimation using the new standard deviation and the previously assumed difference of 93 mL will be performed. If the increase in estimated standard deviation will be between 12% and 20% then a decision to review the sample size will be taken based on further examination of the data.

4.3. Final Analysis

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following sponsor authorization of this SAP (and associated output shells), database lock, analysis sets and unblinding of treatment.

5. ANALYSIS SETS

Agreement and authorization of patients included/ excluded from each analysis set will be conducted prior to the unblinding of the study.

Analyses will be performed for the population sets described in Table 1.

Table 1: Use of the analysis set

	All Patients Enrolled Set	All Patients Randomized Set	Full Analysis Set	Per-Protocol Analysis Set	Safety Analysis Set	PK data Set
Disposition of patients	X					
Protocol deviations	X					
Demographic and other baseline characteristics		X				
Medical history		X				
Prior and concomitant medication		X			X	
Treatment compliance and extent of exposure					X	
Efficacy: Primary endpoint			X	X		
Efficacy: Secondary endpoints			X	X		
Efficacy: Exploratory endpoints			X			
Sensitivity Analyses (incl. primary and selected secondary endpoints) *			X			
Safety					X	
Pharmacokinetic						X

* ANCOVA analyses of the primary endpoint (change from baseline FEV₁ to peak FEV₁ at Week 4), and key secondary endpoints (change from baseline FEV₁ to average AUC_{0-12h} FEV₁ at Week 4 and change from baseline in total E-RS™:COPD score at Week 4).

5.1. All Patients Enrolled Set [ENR]

The all patients enrolled (ENR) set will contain all patients who provide informed consent for this study. Depending on the data that is being analysed, patients will either be classified according to randomized treatment or actual treatment received, specified in the relevant section.

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5.2. All Patients Randomized Set [RND]

The all patients randomized (RND) set will contain all patients in the ENR set who are randomized to study treatment. For analyses and displays based on the RND set, patients will be classified according to randomized treatment.

5.3. Full Analysis Set [FAS]

The full analysis set (FAS) will contain all patients in the RND set who have collected sufficient data after intake of study treatment to compute any of the FEV₁ parameters (including peak FEV₁, trough FEV₁, AUC_{0-12h} FEV₁ and AUC_{0-3h} FEV₁) on at least one occasion. Patients will be classified according to randomized treatment.

5.4. Per-Protocol Set [PPS]

The per-protocol set (PPS) will contain all patients in the FAS set who had no major protocol deviations considered to influence the treatment effect of RPL554. Protocol deviations will be agreed and documented prior to database lock and unblinding. Patients will be classified according to randomized treatment.

5.5. Safety Analysis Set [SAF]

The safety analysis set (SAF) will contain all patients in the RND set who received at least one dose of study treatment. Patients will be classified according to actual treatment received.

5.6. PK data Set [PKS]

The pharmacokinetic (PK) data set (PKS) will contain all patients in the RND set who have blood sampling performed and a quantitative value of tiotropium and/ or RPL554 concentration determined. Patients will be classified according to actual treatment.

6. GENERAL CONSIDERATIONS

6.1. Reference Start Date and Period Day

The reference start date is defined as the day of the first dose of study treatment (RPL554 or placebo) and will appear in every listing where an assessment date or event date appears.

If the date of the event is on or after the reference start date, then:

Study Day = (date of event – reference start date) + 1.

If the date of the event is prior to the reference start date, then:

Study Day = (date of event – reference start date).

In the situation where the event date is partial or missing, Study Day and any corresponding durations will appear partial or missing in the listings, unless otherwise stated.

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6.2. Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to study treatment start date (including unscheduled assessments). In the case where the last non-missing measurement and the study treatment start date coincide, the measurement will be considered pre-baseline, unless time is present. If time of the assessment is on or after the study treatment start date, then the assessment is not considered baseline. AEs and medications commencing on the reference start date will be considered post-baseline.

6.3. Retests and Unscheduled Visits

Retests, reschedules and unscheduled visits are permitted at the discretion of the Investigator.

All the data available, including unscheduled or unplanned readings will be presented within the patient listings, however only scheduled readings will be used in the summaries.

6.4. Windowing Conventions

Each visit will have ± 1 day window. No visit windowing will be applied during the analysis for patients that have completed the study, and therefore the data will be presented as per the visit reported in the database.

For the discontinued patients End of Study (EOS) visit will be windowed to the corresponding visit, based on the study day, for questionnaire, spirometry and rescue medication data. The rules for the windowing are as follows:

- For questionnaires that only happen at certain visits, windowing will only be done for those corresponding visits.
 - o For SGRQ-C and CAT:
 - Day 1 = Day 1
 - Week 2 = after day 1 and up to and including day 16
 - Week 4 = after day 16 and up to and including day 30
 - o For TDI and PGAC:
 - Week 2 = after day 1 and up to and including day 16
 - Week 4 = after day 16 and up to and including day 30
 - o For rest of the questionnaires requiring windowing:
 - Day 1 = Day 1
 - Week 1 = after day 1 and up to and including day 9
 - Week 2 = after day 9 and up to and including day 16
 - Week 3 = after day 16 and up to and including day 23
 - Week 4 = after day 23 and up to and including day 30
- For spirometry raw data and derived data that happens at every visit, windowing will be done as per the corresponding visits.
 - o Day 1 = Day 1

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- Week 1 = after day 1 and up to and including day 9
- Week 2 = after day 9 and up to and including day 16
- Week 3 = after day 16 and up to and including day 23
- Week 4 = after day 23 and up to and including day 30
- For spirometry derived data that only happen at certain visits, windowing will be done for the corresponding visits.
 - For morning trough:
 - Week 1 = after day 1 and up to and including day 9
 - Week 2 = after day 9 and up to and including day 16
 - Week 3 = after day 16 and up to and including day 23
 - Week 4 = after day 23 and up to and including day 30
 - For AUC_{0-12h}:
 - Day 1 = Day 1
 - Week 4 = after day 1 and up to and including day 30
- For rescue medication data, windowing will be done as per the corresponding visits.
 - Day 1 = Day 1
 - Week 1 = after day 1 and up to and including day 9
 - Week 2 = after day 9 and up to and including day 16
 - Week 3 = after day 16 and up to and including day 23
 - Week 4 = after day 23 and up to and including day 30

6.5. Statistical Tests and Summaries

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

The default significance level will be 5%; confidence intervals (CIs) will be 95% and all hypothesis testing will be done using two-sided alternative hypotheses, unless otherwise specified.

6.6. Common Calculations

- Change from baseline: Test Value at Visit X – Baseline Value
- Percentage change from baseline:

$$\frac{\text{Test Value at Visit X} - \text{Baseline Value}}{\text{Baseline Value}} * 100\%$$

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6.7. Actual Treatment

Once the study unblinds, the patient's actual treatment will be assigned based on the most frequent dose they have received throughout the study. The external vendor, Cenduit, will provide the Material List document after confirmation of a Database Lock. This document will contain the kit numbers, which will be merged with the site data to the dosage that was dispensed at each visit.

If a patient takes more than one dose and the ratio of patient taking them is the same, then assigning actual treatment will follow the two rules:

- RPL554 overrides Placebo
- Higher dose overrides lower dose, i.e. if a patient takes for 50% of the time 1.5 mg dose and for another 50% of the time 0.75 mg dose, then the patient would be assigned 1.5 mg as their actual treatment.

6.8. Software Version

All analyses will be conducted using SAS 9.4.

7. STATISTICAL CONSIDERATIONS

7.1. Adjustments for Covariates and Factors to be Included in Analyses

The following covariates and factors will be used in the analyses. For details of their inclusion in the models, see the specific analysis section.

- Fixed effects: treatment (RPL554 0.375 mg, RPL554 0.75 mg, RPL554 1.5 mg, RPL554 3 mg, Placebo), visit (Day 1, Weeks 1, 2, 3 and 4), visit*treatment, actual reversibility strata (reversible, non-reversible)
- Random effect – patient
- Covariate – baseline

7.2. Missing data

Missing data will only be imputed for the calculation of average (AUC) effects for FEV₁ and FVC, which is described in Section 16.4.

For the sensitivity analysis using analysis of covariance (ANCOVA), missing data will be imputed using the last observation carried forward (LOCF) method prior to analysis described in Section 16.4.

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7.3. Multiple Comparisons/ Multiplicity

To address multiplicity in the analysis of the endpoints, statistical testing of the PD parameters and questionnaire scores will be done in a hierarchical order. Firstly, the 3 mg dose will be compared to placebo. If significant then the 1.5 mg dose will be compared to placebo. If found significant, the next lower dose will be compared to placebo. This process will continue until either all doses are compared to placebo, or if one of the comparisons is found to not be significant. There will also be a pairwise comparison between all RPL554 doses, where all doses are compared with each other, as shown in Table 2 in Section 16.1.2.

7.4. Examination of Subgroups

The subgroup analysis will be performed for smoking status, chronic bronchitis and actual reversibility.

The subgroups will be analysed using an MMRM approach, as described in Section 16.1.2 for the primary endpoint, with separate models for the different strata. Reversible patients are those who are reversible to albuterol ($\geq 12\%$ and ≥ 200 mL increase in FEV₁), as defined in Section 5.7 of the study protocol and Section 10 of this Statistical Analysis Plan.

8. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The shells document provided with this SAP describes the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All patients who provide informed consent will be accounted for in this study. Patient disposition and withdrawals, and protocol deviations, including inclusion and exclusion criteria will be presented for RND set. Reasons for exclusion from each analysis set will be presented for the ENR set with patients classified according to randomized treatment.

Protocol deviations will be defined in a separate document. The list will be finalized before database lock.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be listed for the ENR set, with patients classified according to randomized treatment, and summarized for the RND set.

No statistical testing will be carried out for demographic or other baseline characteristics.

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The following demographic and other baseline characteristics will be reported for this study:

- Age (years) - calculated relative to date of consent
- Age category (<65 years and \geq 65 years)
- Gender
- Ethnicity
- Race
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m²)
- Reversibility status (reversible or non-reversible) – planned and actual
- Modified Medical Research Council (mMRC) questionnaire scores
- Pre- and post-bronchodilator FEV₁ (both in litres and in percentage of predicted normal)
- Post-bronchodilator FEV₁/FVC
- FEV₁ actual reversibility (in mL and as a percentage)
- Time since initial diagnosis of COPD (years)
- Chronic Bronchitis (yes/no)
- Smoking status (current smoker (yes/no), number of packs per day, number of years smoking, and smoking exposure in pack-years)

10.1. Derivations

- BMI (kg/ m²) = weight (kg)/ height (m)²
- Time since initial diagnosis of COPD = (date of consent - date first diagnosed)/ 365.25
- Smoking exposure (pack-years) = number of packs per day * number of years smoking

Reversibility status is calculated based on pre-dose and post-dose FEV₁ values taken at Screening. If patient has increase of \geq 12% and \geq 200mL then patient is reversible, else patient is non-reversible.

Actual reversibility strata will be decided on the value calculated pre-rounding, however rounded reversibility values will be presented in the outputs. See Appendix 3 for the rounding rules that are used by the Vendor.

10.2. mMRC

Modified Medical Research Council (mMRC) questionnaire is used to assess a patient's level of breathlessness and the score will be listed. The scores range from 0 to 4, with the following definitions:

0 = "I only get breathless with strenuous exercise",

1 = "I get short of breath when hurrying on the level or walking up a slight hill",

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2 = “I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level”,

3 = “I stop for breath after walking about 100 meters or after a few minutes on the level”,

4 = “I am too breathless to leave the house, or I am breathless when dressing or undressing”.

11. SURGICAL AND MEDICAL HISTORY

Surgical and Medical History information will be listed and summarized for the ENR set.

- Surgical History will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 22.0.
 - Data captured on the ‘Surgical Procedure History’ page of the electronic case report form (eCRF) will be presented by System Organ Class (SOC) and Preferred Term (PT).
- Medical History will be coded using the MedDRA central coding dictionary, Version 22.0.
 - Medical History conditions are defined as those conditions which stop prior to or at Screening.
 - Concomitant illnesses are identified as “Ongoing” at Screening.
 - Data captured on the ‘Medical History’ page of the eCRF will be presented by SOC and PT.
- Patients with multiple events within a SOC/PT will only be counted once for that category.

12. PRIOR AND CONCOMITANT THERAPIES AND MEDICATIONS

Prior and concomitant medications will be coded using the World Health Organization (WHO) drug code and summarized by therapeutic subgroup (Anatomical Therapeutic Chemical Classification System (ATC) level 2). Potential therapeutic subgroups include ICS, LABA, LAMA or combinations thereof, which are defined in a separate spreadsheet provided by the medic.

Prior medications will be listed for ENR set with patients classified according to randomized treatment and summarized for the RND set. Concomitant medications will be listed for ENR set with patients classified according to actual treatment received and summarized for the SAF set.

See Appendix 2 for handling of partial dates for medications. In the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified by the worst case; i.e. concomitant.

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- ‘Prior’ medications are medications which started prior to the first dose of study treatment and stopped prior to or on the first dose of study treatment.
- ‘Concomitant’ medications are defined as medications with onset dates on or after the first dose of study treatment and on or before last dose of study treatment, or medications with onset dates prior to first dose of study treatment without a stop date or with a stop date after first dose of study treatment.
- ‘Post treatment’ medications are defined as medications with an onset date after the date of last dose of study treatment.

Patients taking COPD medications prior to the study will be listed by therapeutic class for the ENR set, classified according to randomized treatment, and summarized by therapeutic class for the RND set.

Patient with multiple medications within an ATC level/therapeutic subgroup will only be counted once for that level.

12.1. Derivations

Time since first diagnosed with COPD = (Date of informed consent – Date of COPD first diagnosed + 1) / 365.25.

13. STUDY TREATMENT EXPOSURE

Exposure to study treatment will be presented for the SAF set.

The date of first and last study treatment administration will be taken from the e-Diary entry. The number of vials dispensed and returned will be taken from “Drug Accountability” page in the eCRF.

13.1. Derivations

The RPL554 exposure will be calculated as:

Duration of exposure (in days) to study treatment:
(stop date – start date) +1

Total exposure (in mg):
(Number of vials dispensed - Number of vials returned) x Content of each vial in mg

The mean duration of exposure in days and the mean exposure in mL will be summarized by treatment group.

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14. STUDY TREATMENT COMPLIANCE

Compliance to study treatment and tiotropium will be summarized and listed for the SAF.

14.1. Derivations

Treatment compliance will be summarized by treatment group in 2 ways:

- $100 * ((\text{total number of vials dispensed} - \text{total number of vials returned}) / (\text{expected number of vials to be taken during the study}))$
- Drug intake as recorded in the e-diary: percent of 'yes' responses. The denominator is the number of records for which the patient provided an answer (Yes or No) to drug intake questions (morning and evening) in the e-diary.

15. E-DIARY COMPLIANCE

Compliance to e-diary will be summarized and listed for the SAF.

15.1. Derivations

E-diary compliance for study treatment will be summarized by treatment group, for the duration of the treatment, as per the following:

$100 * ((\text{total number of e-diary entries for study treatment}) / (\text{expected number of e-diary entries for study treatment during the study}))$

Each patient should have a morning and evening dose, which should be recorded in the e-diary, including the dosing at site visits, however only dosing not at the site visit will be included in the compliance calculation. At Week 4 visit there should only be morning dose recorded.

Number of e-diary entries will be calculated as per the following:

$[(\text{reference end date} - \text{reference start date}) * 2 - 1 \text{ evening dose}] - \text{expected number of CRF entries}$

The 1 evening dose will be subtracted for the completed patients.

Expected number of CRF entries for study treatment during the study will be 5 for all patients that have completed the study. In cases where patient discontinues early the following strategy explained below will be used.

1. Count how many entries there are in the "Drug Exposure" CRF dataset.
2. Select how many site visits patient should have based on the following window for each visit:
 - a. Calculate reference end day = reference end date - reference start date + 1
 - b. 0 site visits if reference end day is missing
 - c. 1 site visit if $1 \leq \text{reference end day} \leq 7$

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- d. 2 site visits if $8 \leq \text{reference end day} \leq 14$
- e. 3 site visits if $15 \leq \text{reference end day} \leq 21$
- f. 4 site visits if $22 \leq \text{reference end day}$

3. Choose the minimum number between points 1 and 2.

16. EFFICACY OUTCOMES

16.1. Primary Efficacy

16.1.1. Primary Efficacy Variables & Derivations

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

16.1.2. Primary Analysis of Primary Efficacy Variables

Peak FEV_1 will be summarised as actual value at Week 4 and change from baseline FEV_1 to peak FEV_1 at Week 4 using descriptive statistics for all treatment groups.

Peak FEV_1 will be computed as the maximum value in the 3 hours after dosing. Baseline FEV_1 is the latest measurement taken before study drug on the day of first dosing, i.e. 30 minutes pre-dose at Day 1.

The primary objective of this study is to test the hypothesis that there is a difference between different dose levels of study treatment (RPL554) in comparison with placebo, all administered by nebulizer and added on to tiotropium. The change from baseline FEV_1 to peak FEV_1 will be compared between the treatments using a mixed model for repeated measures (MMRM) with fixed effects for treatment, visit and treatment by visit interaction, patient as random effect and baseline as covariate. An unstructured covariance structure will be used to model the within-patient errors. If the model does not converge a compound symmetry covariance structure will be used. Kenward-Roger method will be used to estimate the model degrees of freedom.

Treatment comparisons will be summarised using mean effect differences with 95% CI and associated 2-sided p-values.

Firstly, RPL554 treatments will be compared to placebo using a closed testing procedure. The testing will begin with the highest dose (3 mg) compared to placebo. If found statistically significant then the lower dose (1.5 mg) will be compared to placebo. If found significant then the next lower dose will be compared to placebo until either all doses are compared to placebo, or a result is found to be non-significant and therefore the comparison ends. Secondly, the doses will be compared in a pairwise fashion as shown in Table 2, below.

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Table 2: Pairwise comparison between the RPL554 treatment groups:

RPL554 dose	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
0.375 mg	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

The primary efficacy analysis will be performed on the FAS set. The analysis will also be repeated for the subgroups specified in Section 7.4.

A bar chart to present the least squares mean change from baseline FEV₁ to peak FEV₁ for Day 1, Weeks 1 to 4 (based on the MMRM analysis) will be created.

16.2. Secondary Efficacy

The secondary efficacy endpoints include:

- Change from baseline FEV₁ to average AUC_{0-3h} FEV₁ on Day 1 and at Weeks 1 to 4
- Change from baseline FEV₁ to average AUC_{0-12h} FEV₁ on Day 1 and at Week 4
- Change from baseline FEV₁ to peak FEV₁ on Day 1 and at Weeks 1 to 3
- Change from baseline FEV₁ to morning trough FEV₁ at Weeks 1 to 4
- Change from baseline (i.e., mean over the last 7 days of run-in) to the mean weekly values over Weeks 1 to 4 in COPD symptoms, as measured by daily diary (E-RSTM:COPD)
- Change from baseline in the SGRQ-C questionnaire at Weeks 2 and 4
- TDI questionnaire at Weeks 2 and 4
- PGAC questionnaire at Weeks 2 and 4
- Change from baseline (i.e., mean over the last 7 days of run-in) to the mean weekly values over Weeks 1 to 4 in the number of puffs of rescue medication
- Change from baseline FVC to peak FVC on Day 1 and at Week 4
- Change from baseline FVC to average AUC_{0-3h} FVC on Day 1 and at Week 4
- Change from baseline FVC to average AUC_{0-12h} FVC on Day 1 and at Week 4
- Change from baseline FVC to morning trough FVC at Weeks 1 to 4
- Proportion of patients with an improvement from baseline in SGRQ-C total score of 4 or more

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- Trough plasma concentration of tiotropium on Day 1 and at Week 2, and trough plasma concentration of RPL554 at Week 2
- Safety and tolerability:
 - Continuous monitoring of AEs
 - Laboratory safety tests (hematology, blood chemistry and urinalysis)
 - 12-lead ECG (including the QT interval corrected for heart rate using Friderica's formula (QTcF) and heart rate), supine vital signs (blood pressure and pulse rate)

16.2.1. Secondary Efficacy Variables & Derivations

16.2.1.1. PULMONARY FUNCTION TESTS

16.2.1.1.1. SPIROMETRY

Spirometry (FEV₁ and FVC) will be performed at Screening and the following time points during each treatment:

- Day 1 and Week 4 (End of Study): 30 minutes pre-dose; 30 minutes and 1, 2, 4, 6, 8 and 12 hours post-dose.
- Week 1 – Week 3: 30 minutes pre-dose; 30 minutes and 1, 2 and 3 hours post-dose.

At each time point, three acceptable measurements of FEV₁ and FVC will be recorded and the highest reading from each time point will be used in all summaries and analyses. Each measurement will be graded based on the quality of the measurement. Grades “Acceptable” and “Borderline Acceptable” will be used in the analyses, as these will indicate usable measurements. Grade “Unacceptable” will not be used in the analysis, as the measurement will be identified as poor quality.

Morning trough FEV₁ is the last value collected prior to the morning dose.

Peak, average and trough FEV₁ and FVC will be summarized as actual value and change from baseline FEV₁ and FVC (e.g. change from baseline FEV₁ to peak/average/trough FEV₁).

16.2.1.1.2. AUC_{0-T}

The average effect will be calculated as the AUC divided by the length of the time interval of interest (for example, 12 hours for AUC_{0-12h} or 3 hours for AUC_{0-3h}). AUC will be calculated using the trapezoidal method, as follows:

$$AUC = \frac{1}{2} \sum_{i=1}^{n-1} (T_{i+1} - T_i) (C_{i+1} + C_i)$$

Where T_i is the ith time value, C_i is the ith concentration value, n is the number of time values. The change from the baseline FEV₁ to average FEV₁ (AUC) will be summarised and analysed.

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If two last data points are missing the AUC is set to missing, that is for AUC_{0-12h} we require at least up to 8 hours of assessments and for AUC_{0-3h} we require at least up to 2 hours of assessments. If first measurement for the calculation of the AUC is missing, then the AUC will not be calculated.

16.2.1.2. *DIARY DATA*

16.2.1.2.1. *E-RSTM: COPD*

Evaluating Respiratory Symptoms for COPD (E-RSTM: COPD) data will be collected within EXACT-PRO questionnaire (consisting of 14 questions), as shown in the Appendix 4. Please note that items 3, 8, 9, 10, 11 and 14 have separate scoring instructions, namely with the same raw score being assigned to several answer options. E-RSTM: COPD consists of 11 questions, with subdomains of: Breathlessness, Cough and Sputum, and Chest Symptoms. This data will be collected everyday throughout the duration of the study.

Calculating the score

E-RS subdomains:

- Breathlessness – items 7, 8, 9, 10 and 11 (score range: 0-17)
- Cough and Sputum – items 2, 3 and 4 (score range: 0-11)
- Chest Symptoms – items 1, 5 and 6 (score range: 0-12)

Total and subdomain scores are derived weekly as the mean over total number of days between previous visit (inclusive) and the following visit, using only days where data was recorded. For the last visit, when patient completes the study the derivation will use days between previous visit (inclusive) and the following/last visit (inclusive). Baseline is the mean over the 7 days prior to the first intake of study treatment, using only days where data was recorded. If less than 4 days of data are available for the week, the weekly mean is set to missing, e.g. if data is entered for less than 4 days between Visits 2 and 3 then no result will be presented for Week 1. Furthermore, all questions need to be answered to be evaluable for that day.

If a patient discontinued then use treatment study end date, as the date of their last expected visit.

The EXACT-PRO total score will be calculated by first summing all raw scores and then looking up the corresponding EXACT-PRO total score in the table described in the Appendix 5.

E-RS subdomain score is calculated as the sum from the relevant questions.

16.2.1.2.2. *SGRQ-C*

St. George's Respiratory Questionnaire – COPD specific (SGRQ-C) is a questionnaire consisting of 14 questions, split into two parts. Part 1 consists of the first 7 questions and is related to the Symptoms subdomain. The remaining 7 questions are in Part 2, which are related to the Activity and Impacts subdomains. Each possible answer to each question has a weight assigned described in the Appendix 6.

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Calculating the score

Subdomains:

- Symptoms – items 1 to 7
- Activity – items 9 and 12
- Impacts – items 8, 10, 11, 13 and 14

The score for each component is calculated separately by dividing the summed weights by the maximum possible weight for that component and expressing the result as a percentage. A positive component has a non-zero response. It is not possible to have missing items in the questionnaire, as the data is collected in the e-diary which doesn't allow patients to skip between items.

$$Score = 100 * \frac{\text{Sum of weights from all positive items in that component}}{\text{Sum of maximum weights for all items in that component}}$$

The total score is calculated similarly

$$Score = 100 * \frac{\text{Sum of weights from all positive items in that questionnaire}}{\text{Sum of maximum weights for all items in that questionnaire}}$$

The higher the score the more severe impact of COPD on patient's life.

16.2.1.2.3.□□□□□ BDI/TDI

BDI and TDI are questionnaires that focus on three subdomains: Functional impairment, Magnitude of task and Magnitude of effort. BDI is collected at baseline (Day 1) and TDI is collected post-baseline (Weeks 2 and 4).

Subdomain score is calculated as the sum from the related questions.

Total score is calculated as the sum of the subdomain scores.

If at least one of the scores is missing, then total score is set to missing.

16.2.1.2.4.□□□□□ PGAC

Patient Global Assessment of Change (PGAC) is a single question assessment to determine whether patients have noticed a change in their breathing since the start of the study.

16.2.1.2.5.□□□□□ CAT

CAT is designed to assess further the COPD symptoms. There are 8 subdomains, each having only one question and these include Cough, Mucus, Chest Tight, Breathless, Limited Activities, Confident, Sleep and Energy. Each question is scored 1-5. The higher the score the more severe impact of COPD on patient's life.

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16.2.1.3. COPD EXACERBATIONS

Patients with at least one AE meeting both the following criteria will be included in the analysis of exacerbations:

- MedDRA LLT = "COPD exacerbation"
- Use of a systemic steroid (ATC2=H02) at or after the AE date of onset and before the end date, lasting for at least 3 days

16.2.1.4. RESCUE MEDICATIONS

Rescue medication use will be presented for the FAS set.

Baseline use of rescue medication is the mean over the last 7 days of run-in phase, using only days where data was recorded:

$$\frac{\text{Sum of number of puffs taken}}{\text{days recorded}}$$

Use of medication per visit is calculated as the mean use daily over total number of days between previous visit (inclusive) and the following visit, e.g. Week 1 is defined as the period between Visit 2 and Visit 3, calculated only based on the days data was recorded/verified. For the last visit, when patient completes the study the derivation will use days between previous visit (inclusive) and the following/last visit (inclusive).

If less than 4 days of data are available for the week, the weekly mean is set to missing, e.g. if data is entered for less than 4 days between Visits 2 and 3 then no result will be presented for Week 1.

If a patient discontinued then use treatment study end date, as the date of their last expected visit. This will be documented in the "Rescue Medication" page of the eCRF, as well as in the "Rescue Medication Use" diary entry.

The rescue medication use will be confirmed in the diary using the following rules:

1. If patient has put in rescue medication use then analyse as expected
2. If patient has not put in rescue medication use, then to confirm that there was no diary compliance issue, or IT issue, question "No Rescue Medication Confirmation" will be checked to make sure it is filled in correctly.
3. If patient has not put in rescue medication use and question "No Rescue Medication Confirmation" was not filled in correctly then this will be treated as diary compliance or IT issue and therefore this day will not be used as the day recorded for the weekly means calculation.

16.2.2. Analysis of Secondary Efficacy Variables

PD parameters (trough FEV₁, peak FEV₁, FEV₁ AUC_{0-T}, trough FVC, peak FVC and FVC AUC_{0-T}), rescue medication, average weekly E-RSTM:COPD, SGRQ-C, TDI and PGAC scores will be analysed using an MMRM approach, as described in Section 16.1.2 for the primary endpoint. The change from baseline will be analysed for all endpoints except TDI and PGAC. The BDI will be used as baseline for TDI. The baseline term will not be included in the MMRM analysis of PGAC.

For exploratory purposes, the subdomain scores of E-RSTM:COPD and SGRQ-C will also be summarised and analysed in the same way.

A plot of the mean change from baseline FEV₁ to each post-dose FEV₁ result over time will be created by visit and treatment group.

The number of patients experiencing at least one COPD exacerbation and the number of exacerbations will be summarized by treatment group.

Individual questions for E-RS and SGRQ-C questionnaires will be listed.

A plot of the least squares means change from baseline to total score E-RS over time will be presented (based on the MMRM analysis).

Furthermore, an analysis of the proportion of responder patients, with an improvement from baseline in SGRQ-C total score of 4 or more, will be summarised by visit and treatment group and analysed using logistic regression. The model for each visit will include randomised treatment groups and actual reversibility strata as factors. Patients with a missing response, either due to withdrawal or that the SGRQ-C questionnaire was not filled in properly, will be assumed to be a non-responder.

A bar chart of the percentage of responders at each visit will also be presented by treatment group.

Total score will be used for the TDI analysis; BDI and TDI total and subdomain scores will be listed.

The secondary efficacy analyses (excluding the PK summaries) will be performed on the FAS set. The PK results will be summarised for the PKS set.

The analyses of the secondary safety endpoints are described in Section 17.

16.3. Exploratory Efficacy

The exploratory endpoints include:

- Change in peak FEV₁ from Day 1 to Week 4
- Change in average AUC_{0-12h} FEV₁ from Day 1 to Week 4

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- Change from baseline in IC on Day 1 and at Week 4
- Change from baseline in the CAT questionnaire at Weeks 2 and 4
- Change from baseline (i.e. mean over the last 7 days of run-in) to the mean weekly values over Weeks 1 to 4 in morning symptoms
- Change from baseline (i.e. mean over the last 7 days of run-in) to the mean weekly values over Weeks 1 to 4 in morning activity limitations
- Proportion of patients with an improvement from baseline in CAT total score of 4 or more

16.3.1. Exploratory Efficacy Variables & Derivations

Peak FEV₁ is defined in Section 16.2.1.1.1. AUC_{0-T} will be derived as detailed in Section 16.2.1.1.2.

16.3.1.1. *DIARY DATA*

16.3.1.1.1. MORNING SYMPTOMS

Morning symptoms are scored based on the overall COPD symptom severity in the early morning before the first dose of COPD treatment. COPD symptoms include: cough, wheezing, shortness of breath, tightness in chest, chest congestion, difficulty bringing up phlegm. Patients will be asked to rate their symptoms between 0 to 4, 0="no symptoms" and 4="severe symptoms".

Weekly means are calculated as per method detailed in section 16.2.1.2.1.

16.3.1.1.2. MORNING ACTIVITY LIMITATIONS

Morning activity limitations are scored based on the activity limitations in the early morning before the first dose of COPD treatment. Morning activities will include: showering, making breakfast, dressing, etc. Patients will be asked to rate their activity limitations between 0 to 4, 0="I do not have any difficulty in performing" and 4="I have great difficulty in performing".

Weekly means are calculated as per method detailed in section 16.2.1.2.1.

16.3.2. Analysis of Exploratory Efficacy Variables

Peak FEV₁, CAT scores, morning symptoms and morning activity limitations will be analysed using an MMRM approach, as described in Section 16.1.2.

Due to AUC_{0-12h} FEV₁ only being derived for Day 1 and Week 4, an ANCOVA analysis of the change from baseline will be performed with fixed effects for treatment and actual reversibility strata, and baseline as a covariate. Each measurement will be graded based on the quality of the measurement. Grades "Acceptable" and "Borderline Acceptable" will be used in the analyses, as

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these will indicate usable measurements. Grade “Unacceptable” will not be used in the analysis, as the measurement will be identified as poor quality.

Total score data will be used for the CAT questionnaire analysis.

An analysis of the proportion of patients with an improvement from baseline in CAT total score of 4 or more will be summarised by visit and treatment group and analysed using logistic regression. The model will include randomised treatment groups and actual reversibility strata as factors. Patients with a missing response will be assumed to be a non-responder. Also, total score and subdomain scores will be listed. A plot of the least square means change from baseline in total score over time will be presented (based on the MMRM analysis).

Due to IC only being collected on Day 1 and at Week 4 for two timepoints 30 minutes pre-dose and 2 hours post-dose, an ANCOVA analysis of the change from baseline (Day 1, 30 minutes pre-dose) to remaining 3 timepoints will be performed with fixed effects for treatment and actual reversibility strata, and baseline as a covariate. Each measurement will be graded based on the quality of the measurement. Grades “Acceptable” and “Borderline Acceptable” will be used in the analyses, as these will indicate usable measurements. Grade “Unacceptable” will not be used in the analysis, as the measurement will be identified as poor quality.

16.4. Missing Data Methods for Efficacy Variables

Data for calculation of average (AUC) effects for FEV₁ will be imputed if the pre-dose is not missing. This will be done using the following method:

- ‘bounded’ missing data will use interpolation through the trapezoidal method described in section 16.2.1.1.2,
- ‘unbounded’ missing data will not be imputed
 - If last measurement is missing, then the AUC will be calculated up to the point where data is not missing, however if two or more last measurements will be missing, then the AUC will be set to missing.
 - If first measurement is missing, the AUC will not be calculated and set to missing.

For the analysis of responder on SGRQ-C and CAT missing responses will be treated as indicating non-responders in the analysis.

All other missing data, including for when pre-dose is missing, will not be imputed.

For the sensitivity and interim analysis missing data will be imputed using LOCF method. In cases where patient discontinues early and has spirometry data reported at the EOS visit, the following strategy explained below will be used.

1. Check the visit day at which EOS visit was performed against the following window for

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each visit:

- a. Day 1 = Day 1
- b. Week 1 = after day 1 and up to and including day 9
- c. Week 2 = after day 9 and up to and including day 16
- d. Week 3 = after day 16 and up to and including day 23
- e. Week 4 = after day 23 and up to and including day 30

2. Set the value for the corresponding visit, and any subsequent visits, to be the value from EOS. If the corresponding visit has a measurement already, then the next available visit must be used for EOS.
3. If there are missing values before the EOS corresponding visit, we would impute using LOCF in the usual manner.

In the case where patient discontinues early and did not have spirometry data recorded at the EOS visit, or cases of missing data for patients who did not discontinue early, LOCF will be applied in the usual manner.

16.5. Sensitivity analysis for Efficacy Variables

Sensitivity analyses will be done for the primary endpoint (change from baseline FEV₁ to peak FEV₁ at Week 4) and for key secondary endpoints (change from baseline FEV₁ to average AUC_{0-12h} FEV₁ at Week 4, and change from baseline in total E-RSTM:COPD score at Week 4). An ANCOVA approach will be used to compare treatment groups, with fixed factors for treatment and actual reversibility strata, and the baseline result as a covariate. RPL554 treatments will be compared to placebo and to each other, as described in Section 16.1.2.

As a sensitivity analysis, the primary analysis (i.e. MMRM) of the efficacy endpoints described above will be repeated on the PPS set.

Furthermore, an analysis of the proportion of patients with an improvement from baseline in SGRQ-C total score of 4 or more will be summarised by visit and treatment group and analysed using logistic regression. The model will include randomised treatment groups and actual reversibility strata as factors. Patients with a missing response will be handled according to last known responder status (LOCF).

Any missing data post-baseline will be imputed using the LOCF method described in Section 16.4.

Sensitivity analysis, with respect to impact of rescue use during clinic visits, will only be performed if at least one patient is excluded from this analysis due to taking rescue medication within 6 hours of spirometry test. Patient can only be excluded from the analysis if enough of the spirometry tests are affected for the function tests not being able to be calculated, i.e. if first

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FEV₁ measurement is affected by the rescue medication then AUC cannot be calculated for that visit.

This additional sensitivity analysis, taking into account rescue medication, will be performed for a secondary endpoint, change from baseline FEV₁ to average AUC_{0-12h} FEV₁ at Week 4.

16.6. Interim Analysis

To check the assumptions in the sample size calculation, as detailed in Section 9.5 of the study protocol, a blinded sample size-re-estimation is planned after 125 patients who have been randomized, have collected sufficient data after intake of study treatment to compute any of the FEV₁ parameters and either completed the study or had early termination. Analyses will be based on data that is as clean as possible at the time of the data cut-off.

Two different models will be fitted to the data and both will estimate blinded standard deviation which will be compared to the standard deviation assumption of 200 mL included in the original sample size calculation. Using each of these blinded estimates of the standard deviation, the original sample size calculation, based on a two-sample t-test, will be repeated for each of the following scenarios.

- Calculation 1 – unknown sample size (per treatment group), known detectable treatment difference (93 mL) and power (80%)
- Calculation 2 – unknown power (%), known detectable treatment difference (93 mL) and sample size (73 per treatment group)
- Calculation 3 – Unknown detectable treatment difference (mL), known power (80%) and sample size (73 per treatment group)

The ANCOVA analysis will be performed on the following endpoints. The MMRM analysis will be performed for the first endpoint only:

- Change from baseline FEV₁ to peak FEV₁ at Visit 6
- Change from baseline FEV₁ to average AUC_{0-3h} FEV₁ at Visit 6
- Change from baseline FEV₁ to average AUC_{0-12h} FEV₁ at Visit 6
- Change from baseline FEV₁ to morning trough FEV₁ at Visit 6

16.6.1. Blinded ANCOVA analysis

To analyse the four endpoints above, an ANCOVA approach will be used with a fixed factor for reversibility strata, and the baseline result as a covariate. Any missing data at Visit 6/Week 4 will be imputed using the LOCF method described in Section 16.4.

The ANCOVA model will use the square root of mean square error to estimate the blinded standard deviation.

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16.6.2. Blinded MMRM analysis

To analyse the change from baseline FEV₁ to peak FEV₁, an MMRM approach will be used with a fixed factor for visit, patient as a random effect, and the baseline result as a covariate. An unstructured covariance structure will be used to model the within-patient errors. If the model does not converge a compound symmetry covariance structure will be used. Kenward-Roger method will be used to estimate the model degrees of freedom.

Sample size calculation is based on the number of patients with available data at Visit 6/week 4 included in the analysis, therefore any assessment of sample size based on MMRM should also consider the drop-out rate observed in the study.

The MMRM model will use the square root of variance representing Visit 6/Week 4 taken from variance-covariance matrix to estimate the blinded standard deviation.

17. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF set, unless otherwise stated.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified within the relevant section.

17.1. Adverse Events

AEs will be listed for ENR set, with patients classified according to actual treatment received, and summarized for SAF set.

AEs will be coded using the MedDRA central coding dictionary, Version 22.0.

Treatment emergent adverse events (TEAEs) are defined as all AEs which start after the first dose of study treatment or start prior to first dose of study treatment and worsen, based on the investigator's assessment of severity, on or after first dose of study treatment.

Non-treatment emergent adverse events (non-TEAEs) are defined as AEs that start prior to first dose of study treatment and end prior to first dose of study treatment, or do not worsen, based on the investigator's assessment of severity, on or after first dose of study treatment.

In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

If any AE records contain only partial dates, these will be handled by imputation, as described in the Appendix 2.

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An overall summary of the number of patients with at least one event in each of the categories listed below will be provided as specified in the templates. In addition, the number of patients with each of the following AE events will be presented by SOC and PT and summarized by treatment group:

- TEAE
- TEAEs leading to discontinuation of study treatment
- TEAEs causally related to study treatment
- TEAEs by maximum severity
- Serious TEAEs
- Serious TEAEs causally related to study treatment
- Serious TEAEs by maximum severity
- Serious TEAEs leading to discontinuation of study treatment
- TEAEs with an outcome of death

AEs will be identified by using the 'Adverse Events' page of the eCRF. Listings will include TEAEs and Non-TEAEs.

17.1.1. Severity

Severity is classed as mild/ moderate/ severe. TEAEs starting after the first dose of study treatment with a missing severity will be classified as severe. If patient reports a TEAE more than once within that SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

17.2. Laboratory Evaluations

Results from the central laboratory will be included in the reporting of this study for Hematology, Blood Chemistry, Urinalysis and Viral Serology. Measurements and timepoints for each laboratory assessment can be found in Table 3.

Presentations will use standard international (SI) Units.

The handling of re-tests and unscheduled measurements is detailed in Section 6.3.

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Table 3: Laboratory Assessments

Laboratory Assessment	Measurements	Time points
Hematology	hemoglobin, hematocrit, total white cell count, leukocyte differential count and platelet count	Screening and at the End of Study visit
Blood Chemistry	creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine transaminase, gamma-glutamyl transferase, lactate dehydrogenase, creatine kinase, thyroid stimulating hormone*, triiodothyronine and thyroxine*, glucose, potassium, sodium and calcium	Screening and at the End of Study visit
Urinalysis	leukocytes, blood, ketones, bilirubin, urobilinogen, protein and glucose	Screening and at the End of Study visit
Viral Serology	human immunodeficiency virus, hepatitis B and hepatitis C serology	Screening

*Will only be measured at Screening.

The following summaries will be provided for laboratory data (Hematology, Blood Chemistry and Urinalysis), summarised by treatment group:

- Shift tables representing changes from Low/Normal/High, determined by reference normal range.
- Listings of patients meeting markedly abnormal criteria after the first dose

Change from baseline table by post-dose time-point of collection for continuous variables will be summarised by treatment group for Hematology and Blood Chemistry.

Viral Serology data will be listed.

17.2.1. Laboratory Markedly Abnormal Criteria

Markedly abnormal quantitative safety (and other) laboratory assessments will be identified in accordance with the predefined markedly abnormal criteria as presented in Table 4. All laboratory parameter results will be listed.

Table 4: Markedly abnormal ranges for clinical laboratory parameters

Parameter	Markedly Abnormally High Criteria
Alanine Amino Transferase (ALT)	>3 times Upper Limit of Normal Range
Alkaline Phosphatase	>3 times Upper Limit of Normal Range
Aspartate Amino Transferase (AST)	>3 times Upper Limit of Normal Range
Creatinine	>221 µmol/L
Gamma Glutamyl Transferase (GGT)	>3 times Upper Limit of Normal Range
Total Bilirubin	>3 times Upper Limit of Normal Range

17.3. ECG Evaluations

12-lead ECG will be centrally collected at Screening, pre-dose and 2 hours post-dose for Day 1, Weeks 1 and 4. Details regarding retests and unscheduled measurements can be found in Section 6.3.

The following ECG parameters will be reported for this study:

- Heart Rate (bpm)
- PR Interval (msec)
- RR Interval (msec) [derived]
- QRS Interval (msec)
- QT Interval (msec)
- QTcF Interval (msec) [derived]
- Overall assessment of ECG (Investigator's judgment):
 - Normal
 - Abnormal, Clinically Significant (ACS)
 - Abnormal, Not Clinically Significant (ANCS)

The following summaries will be provided for ECG data, summarised by treatment group:

- Change from baseline table by post-dose time-point of collection for continuous variables
- Shift tables representing changes from Normal/ ACS/ ANCS, using Vendor's criteria
- Listings of patients meeting markedly abnormal criteria after the first dose

17.3.1. ECG Specific Derivations

The following ECG parameters are derived in the eCRF using the formulae shown below. To derive them, the parameters used will need to be collected at the same assessment, as per the "ECG" page of the eCRF.

- RR Interval

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- $RR \text{ (msec)} = 1000 * \frac{60}{HR \text{ (bpm)}}$
- Fridericia's Correction (msec)
 - $QTcF \text{ (msec)} = \frac{QT \text{ (ms)}}{\sqrt[3]{RR \frac{ms}{1000}}}$

17.4. Vital Signs

The following Vital Signs measurements will be reported for this study:

- Supine Systolic Blood Pressure (mmHg)
- Supine Diastolic Blood Pressure (mmHg)
- Supine Pulse Rate (bpm)
- Body weight (kg)
- BMI (kg/m²)

Blood pressure and Pulse Rate are measured in a following way:

- Screening
- Day 1 and Week 4 (End of Study)– pre-dose and 30 minutes, 1, 2, 4, 6, 8 and 12 hours post-dose
- Week 1 – Week 3 – pre-dose and 30 minutes, 1, 2 and 3 hours post-dose

BMI is calculated at Screening and End of Study visit using height measured at Screening, and body weight measured at Screening and End of Study visit.

The following summaries will be provided for Vital Signs data, summarised by treatment group:

- Change from baseline table by post-dose time-point of collection for continuous variables
- Shift tables representing changes from Normal/ Low/ High, defined in the Table 5.
- Listings of patients meeting markedly abnormal criteria after the first dose

A plot over time will be presented for all vital signs by treatment group and visit.

17.4.1. Vital Signs Markedly Abnormal Criteria

Markedly abnormal quantitative vital signs measurements will be identified in accordance with the predefined markedly abnormal criteria found in Table 5.

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Table 5: Markedly Abnormal Post-Baseline Vital Signs

Vital Sign Parameter	Abnormally Low	Abnormally High
Heart Rate (bpm)	<ul style="list-style-type: none"> - A decrease from Baseline of ≥ 30 - Value ≤ 50 	<ul style="list-style-type: none"> - An increase from Baseline of ≥ 30 - Value ≥ 110
Systolic blood pressure (mmHg)	<ul style="list-style-type: none"> - A decrease from Baseline of ≥ 40 - Value ≤ 90 	<ul style="list-style-type: none"> - An increase from Baseline of ≥ 40 - Value ≥ 180
Diastolic blood pressure (mmHg)	<ul style="list-style-type: none"> - A decrease from Baseline of ≥ 20 - Value ≤ 50 	<ul style="list-style-type: none"> - An increase from Baseline of ≥ 20 - Value ≥ 105
Body weight (kg)	Loss of $\geq 5\%$	Gain of $\geq 5\%$

17.5. Physical Examination

This examination will be performed on major body systems at Screening and at the End of Study visit, and will include the nose, throat, skin, thyroid gland, neurological system, respiratory system, cardiovascular system, abdomen (liver and spleen), lymph nodes and extremities. These will be identified by using the 'Full Physical Examination' page of the eCRF. All these assessments will be recorded as Normal, ANCS or ACS, and ACS results will be described.

The following summaries will be provided for physical examination data, summarised by treatment group:

- Shift tables representing changes from Normal/ ACS/ ANCS
- Listings of patients meeting markedly abnormal criteria after the first dose

17.6. Pharmacokinetics

Pre-dose PK blood samples are collected on Day 1 and at Week 2 and will be used to assess RPL554 steady-state exposure (at Week 2), and tiotropium steady-state exposure prior to and following 14 days of treatment with RPL554 (Day 1 and Week 2).

A correlation plot between PK concentration and change from baseline FEV₁ to pre-dose FEV₁ at Week 2 (morning trough) will be created by treatment group.

The plasma concentrations of tiotropium and RPL554 will be provided by an outside vendor, LGC.

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18. REFERENCES

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APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

Dates & Times

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

Spelling Format

English US.

Presentation of Treatment Groups

For outputs, treatment groups will be represented as follows and in that order:

Treatment Group	For Tables, Listings and Figures
RPL554 0.375 mg	RPL554 0.375 mg
RPL554 0.75 mg	RPL554 0.75 mg
RPL554 1.5 mg	RPL554 1.5 mg
RPL554 3 mg	RPL554 3 mg
Placebo	Placebo

Decimal Places

The decimal places for this study will use the following rules, unless otherwise stated.

Value = x dp

Mean = x+1 dp

Standard Deviation = x+2 dp

Median = x+1 dp

Q1/Q3 = x+1 dp

Minimum/Maximum = x dp

CI = x+1 dp

For spirometry data we will present outputs with decimal places for value as follows:

- Values in litres = 3dp
- Values in millilitres = 0dp
- Percentage values = 1dp

P-values will be presented to 4dp.

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Presentation of Visits

For outputs, visits will be represented as follows and in that order, unless otherwise specified:

Long Name (default)	Short Name
Pre-Screening	Pre-Screening
Screening	Screening
Baseline	Baseline
Day 1	Day 1
Week 1	Week 1
Week 2	Week 2
Week 3	Week 3
Week 4	Week 4
Follow-up	FUP

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):

- Randomized treatment group (or treatment received if it's a safety output)
- Centre-patient ID,
- Treatment day (where applicable),
- Date and time (if applicable),
- For listings where non-randomized patients are included, these will appear in a category after the randomized treatment groups labelled 'Not Randomized'.

Tables

All tables presenting multiple events that map to a SOC and PT will be counted only once, per unique patient, for incidence counts. Events will be presented in descending frequency of SOC and PT (unless otherwise indicated in the template).

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APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

Algorithm for Treatment Emergence of Adverse Events:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
<hr/>		
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
<hr/>		
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
<hr/>		
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day

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START DATE	STOP DATE	ACTION
		of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date and stop date <= study med start date, assign as prior If start date >= study med start date and stop date <= end of treatment, or start date < study med start date and stop date >= study med start date, assign as concomitant If start date > end of treatment, assign as post study
	Partial	If start date < study med start date and stop date <= study med start date, assign as prior If start date >= study med start date and stop date <= end of treatment, or start date < study med start date and stop date >= study med start date, assign as concomitant If start date > end of treatment, assign as post study
	Missing	If stop date is missing could never be assumed a prior medication If start date < end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
Partial	Known	<p>Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then:</p> <p>If start date < study med start date and stop date <= study med start date, assign as prior</p> <p>If start date >= study med start date and stop date <= end of treatment, or start date < study med start date and stop date >= study med start date, assign as concomitant</p> <p>If start date > end of treatment, assign as post study</p>
	Partial	<p>Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:</p> <p>If start date < study med start date and stop date <= study med start date, assign as prior</p> <p>If start date >= study med start date and stop date <= end of treatment, or start date < study med start date and stop date >= study med start date, assign as concomitant</p> <p>If start date > end of treatment, assign as post study</p>
	Missing	<p>Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then:</p> <p>If stop date is missing could never be assumed a prior medication</p> <p>If start date < end of treatment, assign as concomitant</p> <p>If start date > end of treatment, assign as post treatment</p>
Missing	Known	<p>If stop date <= study med start date, assign as prior</p> <p>If stop date > study med start date, assign as concomitant</p> <p>Cannot be assigned as 'post treatment'</p>

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START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date <= study med start date, assign as prior If stop date > study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

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APPENDIX 3. REVERSIBILITY ROUNDING CRITERIA

If a calculation yields a result that would suggest more precision than the measurements from which it originated, "rounding off" to the proper number of significant figures is required. Based on statistical probability, the following rounding rules must be applied:

If the digit following the last significant figure is less than 5, the number is rounded down to the present value of the last significant figure.

THE NUMBER BEFORE ROUNDING	ROUNDING TO 3 SIGNIFICANT FIGURES
6.2317 g	6.23 g
193.499 mL	193 mL

If the digit following the last significant figure is greater than 5, add one (1) to the preceding digit. This will round the number up.

THE NUMBER BEFORE ROUNDING	ROUNDING TO 4 SIGNIFICANT FIGURES
48.738 g	48.74 g

If it is 5 and other nonzero digits follow after that, add one (1) to the preceding digit. This will also round the number up.

THE NUMBER BEFORE ROUNDING	ROUNDING TO 4 SIGNIFICANT FIGURES
1786.519 mL <small>↖ Last significant figure is followed by a five (5) followed by a nonzero digit.</small>	1787 mL

If the digit following the last significant figure is exactly 5, the number is rounded off to the nearest even digit.

THE NUMBER BEFORE ROUNDING	ROUNDING TO 2 SIGNIFICANT FIGURES
7.35 g	7.4 g
36.5 mL <small>↖ The digit following the last significant figure is <u>exactly</u> 5 so we round to the nearest even number.</small>	36 mL

APPENDIX 4. ANNOTATED EXACT FOR RAW SCORE ASSIGNMENT

1. Did your chest feel congested today?	0.Not at all 1.Slightly 2.Moderately 3.Severely 4.Extremely
2. How often did you cough today?	0.Not at all 1.Rarely 2.Occasionally 3.Frequently 4.Almost constantly
3. How much mucus (phlegm) did you bring up when coughing today?	0.None at all 1.A little 2.Some 2.A great deal 3.A very great deal
4. How difficult was it to bring up mucus (phlegm) today?	0.Not at all 1.Slightly 2.Moderately 3.Quite a bit 4.Extremely
5. Did you have chest discomfort today?	0.Not at all 1.Slight 2.Moderate 3.Severe 4.Extreme
6. Did your chest feel tight today?	0.Not at all 1.Slightly 2.Moderately 3.Severely 4.Extremely
7. Were you breathless today?	0.Not at all 1.Slightly 2.Moderately 3.Severely 4.Extremely

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8. Describe how breathless you were today	0.Unaware of breathlessness 1.Breathless during strenuous activity 2.Breathless during light activity 3.Breathless when washing or dressing 3.Present when resting
9. Were you short of breath today when performing your usual personal care activities like washing or dressing?	0.Not at all 1.Slightly 2.Moderately 3.Severely 3.Extremely 4.Too breathless to do these
10. Were you short of breath today when performing your usual indoor activities like cleaning or household work?	0.Not at all 1.Slightly 2.Moderately 3.Severely 3.Extremely 3.Too breathless to do these
11. Were you short of breath today when performing your usual activities outside the home such as yard work or errands?	0.Not at all 1.Slightly 2.Moderately 3.Severely 3.Extremely 3.Too breathless to do these
12. Were you tired or weak today?	0.Not at all 1.Slightly 2.Moderately 3.Severely 4.Extremely
13. Last night, was your sleep disturbed?	0.Not at all 1.Slightly 2.Moderately 3.Severely 4.Extremely
14. How scared or worried were you about your lung problems today?	0.Not at all 1.Slightly 2.Moderately 3.Severely 3.Extremely

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APPENDIX 5. RAW SUMMED SCORE TO SCALE CONVERSION TABLE FOR EXACT TOTAL SCORE

Raw Summed Score	EXACT Total Score	Raw Summed Score	EXACT Total Score
0	0	26	50
1	8	27	51
2	13	28	52
3	17	29	53
4	20	30	54
5	23	31	55
6	25	32	57
7	27	33	58
8	28	34	59
9	30	35	60
10	31	36	61
11	33	37	63
12	34	38	64
13	36	39	65
14	37	40	67
15	38	41	68
16	39	42	70
17	40	43	72
18	41	44	73
19	42	45	75
20	43	46	77
21	44	47	80
22	46	48	83
23	47	49	87
24	48	50	92
25	49	51	100

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APPENDIX 6. SGRQ-C ITEM WEIGHTS

Question	Answers	Weight
Part 1		
Question 1: I cough		
	Most days	80.6
	Several days	46.3
	With chest infections	28.1
	Not at all	0.0
Question 2: I bring up phlegm (sputum)		
	Most days	76.8
	Several days	47.0
	With chest infections	30.2
	Not at all	0.0
Question 3: I have shortness of breath		
	Most days	87.2
	Several days	50.3
	Not at all	0.0
Question 4: I have attacks of wheezing		
	Most days	86.2
	Several days	71.0
	A few days	45.6
	With chest infections	36.4
	Not at all	0.0
Question 5: How many attacks of chest trouble have you had		
	3 or more	80.1
	1 or 2 attacks	52.3
	None	0.0
Question 6: How often do you have good days (with little chest trouble)		
	None	93.3
	A few	76.6
	Most are good	38.5
	Every day	0.0
Question 7: If you have a wheeze, is it worse in the morning?		
	No	0.0
	Yes	62.0
Part 2		

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Question 8: How would you describe your chest condition?	The most important problem I have	82.9
	Causes me a few problems	34.6
	Causes no problem	0.0
Question 9: Questions about what activities usually make you feel breathless	Getting washed or dressed	82.8
	Walking around the home	80.2
	Walking outside on the level	81.4
	Walking up a flight of stairs	76.1
	Walking up hills	75.1
Question 10: More questions about your cough and breathlessness	My cough hurts	81.1
	My cough makes me tired	79.1
	I get breathless when I talk	84.5
	I get breathless when I bend over	76.8
	My cough or breathing disturbs my sleep	87.9
	I get exhausted easily	84.0
Question 11: Questions about other effects your chest trouble may have on you	My cough or breathing is embarrassing in public	74.1
	My chest trouble is a nuisance to my family, friends or neighbors	79.1
	I get afraid or panic when I cannot get my breath	87.7
	I feel that I am not in control of my chest problem	90.1
	I have become frail or an invalid because of my chest	89.9
	Exercise is not safe for me	75.7
	Everything seems too much of an effort	84.5
Question 12: Questions about how activities may be affected by your breathing	I take a long time to get washed or dressed	74.2
	I cannot take a bath or shower, or I take a long time	81.0
	I walk more slowly than other people, or I stop for rests	71.7

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	Jobs such as housework take a long time, or I have to stop for rests	70.6
	If I walk up one flight of stairs, I have to go slowly or stop	71.6
	If I hurry or walk fast, I have to stop or slow down	72.3
	My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, play bowls or play golf	74.5
	My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	71.4
Question 13: We would like to know how your chest trouble actually affects your daily life	I cannot play sports or games	64.8
	I cannot go out for entertainment or recreation	79.8
	I cannot go out of the house to do the shopping	81.0
	I cannot do housework	79.1
	I cannot move far from my bed or chair	94.0
Question 14: Tick the statement which you think best describes how your chest affects you	It does not stop me doing anything I would like to do	0.0
	It stops me doing one or two things I would like to do	42.0
	It stops me doing most of the things I would like to do	84.2
	It stops me doing everything I would like to do	96.7