STATISTICAL ANALYSIS PLAN – PART A

RPL554-DP-201

A Phase II, Randomized Study to Assess the Pharmacokinetics, Safety and Pharmacodynamics of Single and Repeat Doses of RPL554 Administered by Dry Powder Inhaler in Patients with COPD

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STATISTICAL ANALYSIS PLAN – PART A SIGNATURE PAGE

Statistical Analysis Plan V1.0 – Part A (Dated 19DEC2018) for Protocol RPL554-DP-201.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan – Part A, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	19DEC2018	Nicholas Roubinis	Not Applicable – First Version

TABLE OF CONTENTS

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety and pharmacokinetic (PK)/pharmacodynamic (PD) data for Part A of protocol RPL554-DP-201. 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 the protocol version 1.0, dated 02OCT2018. The study will consist of two parts (A and B) and Part A will be described in this SAP while a separate SAP for Part B will be created prior to the start of Part B. Only the protocol sections applicable to Part A will be described in this SAP.

2. STUDY OBJECTIVES FOR PART A

2.1. PRIMARY OBJECTIVE

The primary objective of Part A is to investigate the PK profile of single doses of RPL554, administered by dry powder inhaler (DPI), in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

2.2. SECONDARY OBJECTIVES

The secondary objectives of this part are as follows:

- To investigate the safety and tolerability of single doses of RPL554 administered by DPI, including effects on peak pulse and heart rate.
- To investigate the bronchodilator effect of single doses of RPL554 administered by DPI, in terms of peak FEV_1 (forced expiratory volume in one second), average FEV_1 area under the curve $(AUC)_{0\text{-}4h}$ and average FEV_1 $AUC_{0\text{-}12h}$.

3. STUDY DESIGN

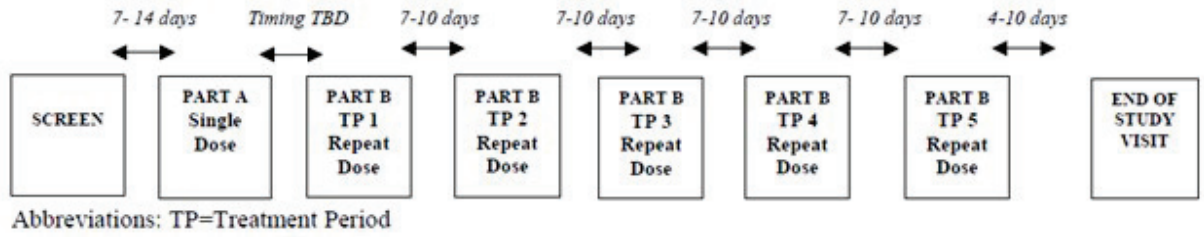
3.1. GENERAL DESCRIPTION

This is a Phase II, randomized, double-blind, placebo-controlled, two-part study. Part A is a parallel group, single dose assessment of RPL554 administered by DPI to evaluate the safety and terminal PK profile of a range of doses of RPL554. Five dose levels, 150 µg, 500 µg, 1500 µg, 3000 µg and 6000 µg were selected, covering a 40-fold increase in doses. A total of approximately 36 COPD patients (as defined by the American Thoracic Society [ATS]/European Respiratory Society [ERS] guidelines with symptoms compatible with COPD for at least 1 year prior to Screening) aged 40 to 80 years (inclusive) will be randomized at up to 2 sites in the Unites States (US). At the end of Part A, the database will be locked and the data unblinded and analyzed prior to commencing Part B. Up to four active doses will be selected for Part B, which will include all Part A patients. Part B is designed as a complete block crossover, repeat dose assessment of RPL554 administered by DPI to evaluate the steady state efficacy/PD effect of the doses compared to the effect with placebo DPI. The patients in Part B will undergo up to five treatment periods.

In Part A, patients will be screened for eligibility, including a reversibility test with albuterol between 7 and 14 days before the single dose of study treatment. Eligible patients will then be given a single dose of RPL554 or placebo and assessed for 12 hours. They will then return to the clinic the following day for a 24-hour post-dose assessment of PK and lung function.

In Part B, the patients from Part A will be randomly assigned in crossover fashion to one of 4 treatment sequences (if there are 4 treatment groups in Part B), or 10 treatment sequences (if there are 5 treatment groups in Part B) each consisting of up to five 1-week treatment periods separated by a 7 to 10-day washout. Each treatment period consists of 6 days of twice daily doses of RPL554, and a single morning dose on Day 7. In each treatment period, patients will undergo assessments over 12 hours on Days 1 and 7. Figure 1 below and Figure 1 in the protocol summarize these details.

Figure 1 Study Flow Chart



3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 6 of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

Not applicable.

4. PLANNED ANALYSES

There are no data monitoring committee (DMC) or formal interim analyses to be performed for this study. The study will consist of two separate and independent analyses, Part A and Part B. At the end of each part, the database will be locked and unblinded, and the analyses for each part will be performed.

4.1. DATA MONITORING COMMITTEE (DMC)

There will be no DMC analyses for this study.

4.2. INTERIM ANALYSIS

No formal interim analysis is planned for the study.

4.3. PART A ANALYSIS

All Part A analyses identified in this SAP will be performed by IQVIA Biostatistics following Database Lock on a clean database:

- All outstanding data issues and queries resolved.
- All irresolvable data issues documented in the Data Handling Report (DHR) from Data Management.
- All coding of medications and adverse events (AEs) completed.
- Serious AE (SAE) reconciliation completed.
- All reconciliation of vendor data with electronic case report form (eCRF) data completed successfully.
- Analysis sets authorized.

It should be noted that the main teams performing the Part A analysis will remain blinded at the time of the Part A database lock. This is to avoid any potential risk they could trace what study medication a patient might be receiving in Part B (e.g. if they know they experienced certain AEs while on one treatment in Part A and identify this in Part B).

All verbatim text from the eCRF will be presented in outputs "as is" with no "manual hard coding" corrections for such data. Also, PK analysis will be performed by another party (third party vendor), however details of this analysis will be specified in this SAP.

5. ANALYSIS SETS

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

unblinding of the study for Part A.

5.1. ALL PATIENTS ENROLLED SET [ENR]

The all patients enrolled (ENR) set will contain all patients who provide informed consent for this study.

5.2. ALL PATIENTS RANDOMIZED SET [RND]

The all patients randomized (RND) set will contain all patients who provide informed consent and who are randomized to study medication. For analyses and displays based on RND, patients will be classified according to randomized treatment.

5.3. SAFETY ANALYSIS SET [SAF]

The safety analysis set (SAF) will contain all patients in the RND set who received the single dose of study medication during Part A. Patients will be classified according to actual treatment received. If there is any doubt whether a patient was treated or not, they will be assumed treated for the purposes of analysis.

5.4. FULL ANALYSIS SET [FAS]

The full analysis set (FAS) will contain all patients in the RND set with data collected after intake of study medication to compute the pharmacodynamic parameters (FEV_1 measurements pre-dose and at least one post-baseline). For analyses and displays based on FAS, patients will be classified according to actual treatment received.

5.5. PHARMACOKINETICS [PK] ANALYSIS SET

The PK analysis set will contain all patients in the RND analysis set who have a blood sampling performed after the single dose of RPL554 and PK parameter data. The PK analysis set will be determined by a third-party vendor and the data will be provided to IQVIA.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. Reference start date is defined as the day of the single dose of study medication 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 date, then:

- Study day = (date of event – reference date) + 1.

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

- Study day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and study day, and any corresponding durations will be presented based on the imputations specified in Appendix 2; Partial Date Conventions.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the single dose assessment (including unscheduled assessments). For FEV_1 and forced vital capacity (FVC), baseline is defined as the average of the two pre-dose assessments (at 1-hour [±5 minutes] and immediately [within 5 minutes] pre-dose).

6.3. REPEAT/RESCHEDULE, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. If a visit is repeated/rescheduled due to variability in FEV_1 or other reason, the repeated/rescheduled visit, will be listed and summarized as the valid visit (same visit number assigned). Unscheduled measurements will not be included in by-visit summaries, but will contribute to the endpoint value. For example, if an unscheduled visit occurred at 10 hours post-dose on the day of the single dose, then this value will be considered in the calculation of the average FEV_1 over 12 hours ($AUC_{0\text{-}12h}$ FEV_1). Any unscheduled or unplanned readings will be presented within the patient listings.

Early termination data will be mapped according to the visit number the termination occurred for by-visit summaries. In Part A early terminations can occur at Screening, Day 1 and Day 2. If termination is between Part A and Part B, data are to be considered in the Part B SAP. Subject will be a completer of Part A.

Listings will include scheduled, unscheduled, repeat/reschedule and early discontinuation data.

6.4. WINDOWING CONVENTIONS

No visit windows will be applied in this study and the scheduled assessments will be reported and analyzed as per eCRF collection.

6.5. STATISTICAL TESTS

The default significant level will be (5%); confidence intervals will be 95% and all tests will be 2-sided, unless otherwise specified in the description of the analyses. All significant p-values (i.e. < 5%) will be flagged by means of a "*" for ease of review.

For presentation of summary statistics for quantitative and qualitative variables see Appendix 1; Programming conventions for outputs.

6.6. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Test value at post-dose timepoint – baseline value.

For quantitative measurement values of FEV_1 and FEV_1 AUCs will be calculated based on:

- The highest FEV_1 reading from each assessment.
- The baseline value (average of the two pre-dose values [at 1-hour {±5 minutes} and immediately {within 5 minutes}} pre-dose) must be within ± 20% of the pre-albuterol value at Screening; otherwise, the patient will be a screen failure.

Peak effect will be calculated as:

- Maximum value in the first 4 hours after dosing.

Average effect will be calculated as:

- FEV_1 AUC divided by the length of the time interval of interest.

Log-transformations will be performed on FEV_1 data:

- FEV_1 will be analyzed using multiplicative models, which means that data will be logged prior to analysis. The results will then be back-transformed to linear scale (treatment differences will thus be ratios of geometric means).

6.7. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following covariates are used in the analyses. For details of their inclusion in the models, see the specific analysis section.

- Randomized treatment (fixed).
  - RPL554 150µg
  - RPL554 500µg
  - RPL554 1500µg
  - RPL554 3000µg
  - RPL554 6000µg
  - Placebo

- Baseline value of analyzed variable (covariate).

7.2. MULTICENTER STUDIES

This study will be conducted at up to 2 study centers, in the US.

7.3. MISSING DATA

Missing safety data will not be imputed, apart from partial date imputations as specified in Appendix 2.
Missing efficacy data will be handled as described in Section 15.1.2 and Section 15.2.2 of this SAP.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

Significance of treatment effect will be tested for the primary and secondary efficacy endpoints in Part A and will be done for each of the doses of RPL554 against placebo, starting with the highest dose (6000 µg). To this end, the fixed-sequence testing approach (Maurer et al., 1995; Westfall & Krishen, 2001) will be used.

For the endpoints, let i = 0, 1, 2, 3, 4 and 5 represent increasing dose levels, 0 denoting placebo. Also, let μ_i, i = 0, 1, 2, 3, 4 and 5 denote the mean change from baseline for the endpoint of interest for placebo and each increasing active dose level, respectively. The null hypotheses are defined as: H_i: $\mu_j - \mu_0 = 0$ and will be tested against the 2-sided alternative K_i: $\mu_j - \mu_0 \neq 0$, j = 1, 2, 3, 4 and 5.

Finally, let p_1, p_2, p_3, p_4, p_5 denote the marginal p-values obtained from the statistical tests associated with H_1, H_2, H_3, H_4, H_5(obtained from the model).
The fixed-sequence testing will begin with the null hypothesis corresponding to the highest dose versus placebo. If a statistically significant difference is found at the 2-sided α level of 5%, the testing will proceed with the next highest dose. Otherwise, testing stops, and the remaining null hypotheses are considered as failed to reject, without testing.

This testing strategy can be written as the following stepwise algorithm:

- Step 1: If $p_5 \leq \alpha$ reject H_5 and go to Step 2. Otherwise, fail to reject H_5, H_4, H_3, H_2 and H_1 and stop.
- Step 2: If $p_4 \leq \alpha$ reject H_4 and go to Step 3. Otherwise, fail to reject H_4, H_3, H_2 and H_1 and stop.
- Step 3: If $p_3 \leq \alpha$ reject H_3 and go to Step 4. Otherwise, fail to reject H_3, H_2 and H_1 and stop.
- Step 4: If $p_2 \leq \alpha$ reject H_2 and go to Step 5. Otherwise, fail to reject H_2 and H_1 and stop.
- Step 5: If $p_1 \leq \alpha$ reject H_1. Otherwise, accept H_1.

The fixed-sequence procedure controls the family-wise error rate in the strong sense because, for each null

hypothesis, the testing is conditional upon rejecting all hypotheses earlier in the sequence (Dmitrienko, et al., 2009).

Each secondary endpoint will be tested independently and nominally following a hierarchical testing of doses like the one used for the primary endpoint.

7.5. EXAMINATION OF SUBGROUPS

No subgroup analyses will be performed for this study.

8. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.
The templates provided with this SAP describe 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, withdrawals and reasons for exclusion from each analysis set and protocol deviations, including exception to the inclusion and exclusion criteria will be presented for all patients, including those with screen failures and summarized by treatment group for the RND analysis set. Number of patients treated and discontinued will also be presented. If the patient discontinued/withdraws, he/she will be allocated to the single dose treatment group administered.

All protocol deviations collected in Part A will be divided into critical, major or minor categories and will be assigned to the single dose treatment group. These which will be summarized by treatment and presented in a listing for the RND analysis set. Protocol deviations affect the integrity of the drug activity data and will be obtained by the

clinical research associates (CRAs) and documented in the clinical trial management system (CTMS).
Each protocol deviation is categorized into one of the following types, based on CTMS:

1. Informed Consent Criteria
2. Eligibility and Entry Criteria
3. Concomitant Medication Criteria
4. Laboratory Assessment Criteria
5. Study Procedures Criteria
6. Serious Adverse Event Criteria
7. Randomization Criteria
8. Visit Schedule Criteria
9. Investigation Product (IP) Compliance
10. Efficacy Criteria
11. Administrative Criteria
12. Source Document Criteria
13. Regulatory or Ethics Approvals Criteria
14. Other Criteria

Preliminary assignment to each analysis population, therefore whether a patient is included/excluded in each analysis population (excluding the PK analysis population) will be recorded in an EXCEL sheet by the IQVIA Biostatistician, with the reason for exclusion from each population indicated. The EXCEL sheet should then be authorized by means of a customer authorization form (CAF) and prior to the Database Lock of the study.

10. DEMOGRAPHIC AND OTHER SCREENING CHARACTERISTICS

Demographic data and other baseline characteristics (including screening disease characteristics) will be presented for all analysis sets (RND, SAF, FAS, PK), by treatment groups, if the analysis sets differ to each other. If these are the same, as is expected for Part A, the presentation will be limited to just the RND analysis set, or to those that are

different. No statistical testing will be carried out for demographic or other baseline characteristics. The following demographic and other baseline characteristics will be reported for Part A:

- Age (years)
- Sex
- Childbearing potential
- Race
- Ethnicity
- Height (inches)
- Weight (pounds)
- BMI (kg/m^2)
- Pre (prior to dosing at baseline)/post (post dosing at baseline) bronchodilator FEV_1 (both in liters and in percentage of predicted normal)
- Post-bronchodilator FEV_1/FVC
- FEV_1 reversibility test (mL and %)

10.1. DERIVATIONS

- Age (years) = (Informed consent date – date of birth)
- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$

Demographic and other screening characteristics recorded on the eCRF will be used as is on the eCRF, without any derivations or adjustments.

11. SURGICAL, MEDICAL AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE/SMOKING HISTORY

Surgical and Medical History information will be presented in table summaries and listings, for the RND analysis

set.

- Surgical History will be coded by Medical Dictionary for Regulatory Activities (MedDRA) dictionary using the version specified in the data management plan.
  - Surgical History conditions are defined as those conditions which stop prior to or at Screening.
  - Data captured on the Surgical Procedure History page of the eCRF will be presented by SOC (System Organ Class) and PT (Preferred Term).
- Medical History will be coded by MedDRA dictionary using the version specified in the data management plan.
  - Medical History conditions are defined as those conditions which stop prior to or at Screening.
  - Data captured on the Medical History page of the eCRF will be presented by SOC and PT.
- COPD/Smoking History data captured on the COPD and Smoking History page of the eCRF will be presented for the RND analysis set.
  - COPD history (Duration of COPD [calculated relative to date of first diagnosis {Randomization date – first COPD diagnosis date}], date of most recent exacerbation, known to have chronic bronchitis/emphysema)
  - Smoking history (current or former smoker, number of packs per day, number of years smoking and number of pack-years [calculated as number of packs per day x number of years smoking])

12. MEDICATIONS

Medications will be coded using the World Health Organization – Drug Dictionary (WHO-DD) version specified in the data management plan and will be presented in a listing by Anatomical Therapeutic Chemical (ATC) (the 1st level of the ATC code) and PT for the RND analysis set. Certain medications (or a special grouping of medications) will be classified in a list during the study and signed-off prior to lock by a medical advisor. As this list, may change prior to sign-off they will not be defined in this section of the SAP. Potential medications include, but are not limited to, inhaled corticosteroids (ICS), LAMAs (long-acting muscarinic antagonists), LABAs (long-acting beta2-agonists) etc.

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.

- 'Prior' medications are medications which started and stopped in the 3 months prior to the single dose of study medication and are recorded at Screening.
- 'Concomitant' medications are medications which:
  - Had an onset date on or after the single dose of study medication.
  - AND ended on or after the date of single dose of medication or were ongoing at the end of Part A.
  - A patient can report more than 1 concomitant medication with the same PT.

Prior and concomitant medications will be presented in a listing only, by treatment group.

Rescue medications will be recorded on the Rescue Medication/Rescue Medication Canister Collection/Rescue Medication Canister Dispensed/Rescue Medication Canister Weight pages of the eCRF. These are short acting bronchodilators and will be sourced by the study center and dispensed at the Screening visit and end of Part A (Day 2). Rescue medication used during study visits will be documented on the eCRF pages. Protocol procedures must continue even if rescue medication has been taken. Salbutamol/albuterol is to be used for primary rescue use.

Rescue medications used during study visits (by recording the time it was dispensed and collected) and the amount taken between Day 1 and Day 2 (by recording the weight of the canisters), will be presented in a listing for the RND analysis set.

13. STUDY MEDICATION EXPOSURE

Date and time of exposure to the single dose of study medication and the date of completion/discontinuation will be presented in a listing for the SAF analysis set. Duration of exposure will not be calculated as this is expected to be one day for all patients in Part A. The information to be listed will be taken from the Drug Exposure and Disposition eCRF pages.

14. STUDY MEDICATION COMPLIANCE

All administration of study treatment will be done at the clinic under supervision of the study staff; therefore, no formal analysis of compliance will be performed.

15. EFFICACY OUTCOMES

15.1. PRIMARY EFFICACY

15.1.1. PRIMARY EFFICACY VARIABLE(S) & DERIVATION(S)

- Not applicable – The primary endpoint of Part A will be described in Section 17.

15.1.2. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLE(S)

Not applicable.

15.1.3. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE(S)

Not applicable.

15.2. SECONDARY EFFICACY

The secondary efficacy analyses will be performed for the FAS.

15.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

15.2.1.1. Change in baseline in average FEV_1 of $AUC_{0\text{-}4h}$ (Average FEV_1 over 4 hours) after single dose (Secondary variable 1)

Average FEV_1 after single dose is defined as the $AUC_{0\text{-}4h}$ FEV_1 collected, divided by the length of the time (in hours). $AUC_{0\text{-}4h}$ FEV_1 is derived using the following formula:

$$AUC = \frac{1}{2}(t_1 - t_0)(y_1 + y_0) + \frac{1}{2}(t_2 - t_1)(y_2 + y_1) + \cdots + \frac{1}{2}(t_i - t_{i-1})(y_i + y_{i+1})$$

where *i* are the number of intervals, t_i are the time values or time intervals (in actual hours) between assessments and y_i the FEV_1 values at t_i. The AUC result will then be divided by the actual time (the time elapsed since dosing, until the time of assessment) at 4-hour assessment (as this can occur ± 10 minutes) to obtain the average FEV_1. For analysis purposes, it will be assumed that the pre-dose value (immediately pre-dose) occurred at time 0 when computing PD parameters. If a patient misses hour 2 and 4 then the $AUC_{0\text{-}4}$ is set to missing.

Descriptive statistics (see Appendix 1 [Programming conventions for outputs]) for $AUC_{0\text{-}4}$ will be presented for all patients assigned to FAS, at each assessment and change from baseline at each assessment as relevant. All summaries will be presented for each treatment group. In addition, a figure (bar graph) representing mean change from baseline FEV_1 to FEV_1 $AUC_{0\text{-}4}$ by treatment will be presented, including the standard error of the mean.

Change from baseline FEV_1 to FEV_1 $AUC_{0\text{-}4}$ will be derived to test the hypothesis described in Section 15.2.3 with baseline defined as the average of the FEV_1 pre-dose assessments (-60 minutes and -5 minutes) collected.

15.2.1.2. Change in baseline in average FEV_1 $AUC_{0\text{-}12h}$ (Average FEV_1 over 12 hours) after single dose (Secondary variable 2)

$AUC_{0\text{-}12h}$ FEV_1 after single dose is defined and derived similarly to secondary endpoint above (see Section 15.2.1.1), but over 12-hours post-dose. If patient misses hours 11.5 and 12 then the $AUC_{0\text{-}12h}$ is set to missing.

15.2.1.3. Change from baseline in peak FEV_1 (measured in first 4 hours) after single dose (Secondary variable 3)

Peak FEV_1 is measured in the first 4 hours after single dose. It is collected on the Spirometry Study measurements eCRF page.

Three acceptable readings are performed at each of the timepoints in first 4 hours after the single dose (5, 15 and 30 minutes and 1, 1.5, 2 and 4 hours) and the highest of the 3 is used for analysis purposes. Hence peak FEV_1 is derived as the highest of all these readings.

Descriptive statistics (see Appendix 1 [Programming conventions for outputs]) for peak FEV_1 will be presented for all patients assigned to FAS, at each assessment and change from baseline as relevant. All summaries will be presented for each treatment group. In addition, a figure (bar graph) representing mean change from baseline FEV_1 to peak FEV_1 by treatment will be presented, including the standard error of the mean. A figure also displaying the mean change over time on Day 1 will be presented.

Change from baseline FEV_1 to peak FEV_1 (over 4 hours) will be derived to test the hypothesis described in Section 15.2.3 with baseline defined as the average of the FEV_1 pre-dose assessments (-60 minutes and -5 minutes) collected.

15.2.2. Missing Data Methods for Secondary Efficacy Variable(s)

No imputation will be applied.

15.2.3. Analysis of Secondary Efficacy Variables

The secondary variables will be analyzed by comparing the RPL554 treatment groups to each other and placebo by rejecting the null hypothesis described below at significance level α=0.05 level (2-sided):

$H_0: \mu_j = \mu_0$ versus $H_1: \mu_j \neq \mu_0$

where μ_j and μ_0 are the mean change from Baseline for each parameter (Peak FEV_1, $AUC_{0\text{-}4h}$ and $AUC_{0\text{-}12h}$) after single dose for each respective dose of RPL554 and placebo.

ANCOVA analyses will be implemented using the SAS® procedure MIXED as follows:

```
PROC MIXED DATA = …;
       CLASS TREATMENT;
       MODEL CHG = TREATMENT BASELINE;
       LSMEANS TREATMENT / CL DIFF;
RUN;
```

where CHG = difference in log (parameter) – log (baseline parameter) i.e. log (parameter / baseline parameter)
TREATMENT = treatment group (Respective dose of RPL554, 150µg, 500µg, 1500µg, 3000µg and 6000µg and placebo)
BASELINE = log (baseline parameter)

The primary comparison will be the contrast (difference in least squares mean [LSMEAN]) between 6000µg RPL554 and placebo. The parameter value and its baseline will be log-transformed prior to analysis using natural logarithm. The difference between the two (log [parameter] – log [baseline parameter] equals log (parameter / baseline parameter). The covariate, baseline parameter, will also be log transformed. Therefore, the LSMEAN statement between treatments in the above PROC MIXED will provide the log of the contrasts. Prior to presentations, the antilog of these point estimates and associated 95% confidence intervals will be performed, giving ratios of geometric means on the linear scale. The 2-sided p-value for the exponential (exp)least squares mean, exp(LSM), ratio between each of the 2 treatment groups and placebo will be reported.

Summary statistics for each parameter (Peak FEV_1, $AUC_{0\text{-}4h}$ and $AUC_{0\text{-}12h}$) will be presented for baseline, at point of interest and change from baseline by treatment group on patients with both assessments, on the original scale.

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF.
There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

16.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded by MedDRA dictionary using the version specified in the data management plan.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the single dose of study medication, based on the investigator assessment of severity. TEAEs will be assigned to treatment groups based on actual treatment received.

See Appendix 2 for handling of partial dates for AEs. 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.

An overall summary of number of patients within each of the categories described in the sub-section below, will be provided as specified in the templates.

Listings will include TEAEs and Non-TEAEs.

16.1.1. ALL TEAES

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and broken down further by maximum severity and relationship to study medication.

16.1.1.1. Severity

Severity is classed as mild/ moderate/ severe (increasing severity). TEAEs starting after the single dose of study medication with a missing severity will be classified as severe. If a 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.

16.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as "yes" or "no". A related TEAE is defined as a TEAE with a relationship to study medication as "yes". TEAEs with a missing relationship to study medication will be regarded as relationship = "yes" to study medication. If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study medication will be used in the corresponding relationship summaries.

16.1.2. TEAEs Leading to Discontinuation of Study

TEAEs leading to discontinuation from the study will be identified by using the question "Did the AE cause the Patient to discontinue from the study?" from the AE page of the eCRF.

For TEAEs leading to discontinuation from the study, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

16.1.3. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the eCRF. A summary of serious TEAEs by SOC and PT will be prepared, similarly to Section 16.1.1 and Section 16.1.2.

16.1.4. Adverse Events Leading to Death

TEAEs leading to Death are those events which are recorded as "Death" on the Adverse Events page of the eCRF. A

summary of TEAEs leading to death by SOC and PT will be prepared.

16.2. LABORATORY EVALUATIONS

Results from the local laboratory will be included in the reporting of this study for hematology, blood chemistry, urinalysis and viral serology. A list of laboratory assessments to be included in the outputs is included in the protocol, Sections 7.4.3.1, 7.4.3.2,7.4.3.3 and 7.1.4 for hematology, blood chemistry, urinalysis and viral serology, respectively. Presentations will use International system (SI) units.
Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.
The following summaries will be provided for laboratory data:

- Actual results at Screening.
- Incidence of abnormal values at Screening according to normal range criteria
- Listing of all laboratory evaluations and abnormal values at Screening.

16.2.1. LABORATORY REFERENCE RANGES AND MARKEDLY ABNORMAL CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

In addition to the high and low quantitative laboratory assignments (as identified by means of the laboratory reference ranges), markedly abnormal quantitative blood chemistry values per the table below will also be identified by the Investigator.

	Blood Chemistry – Markedly Abnormal Definition
Alanine Aminotransferase (ALT)	> 3 x ULN
Alkaline Phosphatase (ALP)	> 3 x ULN
Aspartate Aminotransferase (AST)	> 3 x ULN
Creatinine	> 221 µmol/L
Gamma Glutamyl Transferase (GGT)	> 3 x ULN
Bilirubin (TBL)	> 3 x ULN

ULN: Upper limit of normal. ALT: Alanine aminotransferase. AST: Aspartate aminotransferase.

ALP: Alkaline phosphatase. TBL: Total bilirubin.

16.3. ECG EVALUATIONS

Overall results from the local ECG (Electrocardiogram) lab will be included in the reporting of this study. The overall assessment of ECG parameters will be reported for this study:

- Normal
- Abnormal not Clinically Significant (ANCS)
- Abnormal Clinically Significant (ACS)
- Incomplete
- Uninterpretable

The following summaries will be provided for quantitative ECG data, for example heart rate:

- Actual assessments at screening, baseline (pre-dose of single dose) and each post-dose timepoint (1, 2, 4 and 8 hours)
- Change from Baseline at each post-dose timepoint assessment
- Shift of overall assessment baseline to post-dose timepoints according to Normal, ANCS and ACS overall

assessment criteria
- Listing of all ECG evaluations and abnormal values

Peak heart rate after single dose is defined as the maximum value measured in the first 4 hours post-dose. Peak heart rate and change from baseline to peak will be summarized similarly to Section 15.2.1.3, including the figure presentations. In addition, hypothesis testing as per Section 15.2.3, will be repeated for this endpoint.

16.4. 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)

The following summaries will be provided for vital signs data:
- Actual assessments at screening, baseline (pre-dose of single dose) and each post-dose timepoint (1, 2, 4, 8, 12 and 24 hours [Day 2])
- Change from Baseline at each post-dose timepoint assessment
- Incidence of markedly abnormal values based on the criteria presented in the table below:

	Low	**High**
Systolic blood pressure (mmHg)	≤ 90 mmHg or decrease from Baseline of ≥ 20 mmHg	≥ 180 mmHg, or increase from Baseline of ≥ 20 mmHg
Diastolic blood pressure (mmHg)	≤ 50 mmHg or decrease from Baseline of ≥ 20 mmHg	≥ 105 mmHg, or increase from Baseline of ≥ 20 mmHg
Pulse rate (bpm)	≤ 50 bpm or decrease from Baseline of ≥ 20 bpm	≥ 110 bpm or increase from Baseline of ≥ 20 bpm

Peak supine pulse rate after single dose is defined as the maximum value measured in the first 4 hours post-dose. Peak pulse rate and change from baseline to peak will be summarized similarly to Section 15.2.1.3, including the figure presentations. In addition, hypothesis testing as per Section 15.2.3, will be repeated for these endpoints.

16.5. PHYSICAL EXAMINATION

The following summaries will be provided for the full physical examination data, covering major body systems (nose, throat, skin, thyroid gland, neurological system, respiratory system, cardiovascular system, abdomen [liver and spleen], lymph nodes and extremities):

- Incidence of abnormalities at screening

The following summaries will be provided for a brief physical examination to be also performed, on skin, respiratory system, cardiovascular system, and abdomen (liver and spleen):

- Incidence of abnormalities pre-dose.

16.6. OTHER SAFETY ASSESSMENTS

Chest X-ray and inhalation training results will be presented in a listing only. In addition, screening serum and urine pregnancy test results, as well as pregnancy report data (current pregnancy, pregnancy history and details of the mother), will be listed for women of childbearing potential at Screening.

17. PHARMACOKINETIC EVALUATIONS

The primary endpoints of the study are the PK parameters $AUC_{0\text{-}12h}$ and $AUC_{0\text{-}t}$, maximum concentration (C_{max}), time to maximum concentration (t_{max}) and half-life. PK concentrations are measured at the time of the single dosing and are collected on the Pharmacokinetic Samples eCRF page. Based on this information the PK parameters are then

derived.

AUC_{0-t} represents the area under the plasma concentration curve from time 0 to last observed value above the lower limit of quantification and AUC_{0-12h} represents the area under the plasma concentration curve from time 0 to 12 hours. C_{max} denotes the highest plasma concentration measured and t_{max} denotes the timepoint corresponding to C_{max}. Half-life is the time required for the concentration to reduce to half its initial value, estimated as ln (2)/λ_z.

Descriptive statistics (see Appendix 1 [Programming conventions for outputs]) for the AUC parameters, C_{max}, t_{max} and half-life will be presented for all patients assigned to the PK analysis set for each treatment group.

Dose-normalization, the process of dividing the parameters by the administered dose, will be performed for each PK dose-dependent parameter (AUC_{0-t}, AUC_{0-12h}, C_{max}). No imputations for missing data will be applied.
The Power Model: log(Yk)= β x log(Dk) + εk where D is the total number of doses, N are the total number of doses k=1,..,D. Yk is the measured response variable, AUCs or C_{max} on the kth dose. ε_k is the error will be applied to assess dose proportionality. Dose proportionality requires β to be close to unity for dose dependent parameters. The estimate of β together with appropriate confidence interval (β_L, β_U) can be used to quantify the degree of non-proportionality. Analysis will be implemented using the SAS® procedure MIXED as follows:

```
PROC MIXED DATA = …;
       CLASS PATIENT;
       MODEL PARAMETER = TREATMENT;
       ESTIMATE 'LOGTREATMENT – 1 unit' TREATMENT 1/CL ALPHA=0.1;
       ODS OUTPUT ESTIMATES = ESTIMATE;
       ODS OUTPUT SOLUTIONR = SOLUTION;
RUN;
```

where `PATIENT` = patient ID
`PARAMETER` = separate models for each of the log(parameters): log(AUC_{0-12h}) log(AUC_{0-t}) and log(C_{max})
`TREATMENT` = log (treatment group [RPL554 treatment groups])

Summary statistics (For AUC and C_{max} parameters: n, geometric mean, coefficient of variation [CV], minimum, maximum and median and for t_{max} parameter: n, arithmetic mean, standard deviation, minimum, maximum and median) will also be presented.

18. REFERENCES

Dobson, A. J. (2002). *An introduction to generalized linear models, 2nd ed.* Chapman & Hall/CRC.

Dmitrienko, A., Bretz, F., Westfall, P. H., Troendle, J., Wiens, B. L., Tamhane, A. C., & Hsu, J. C. (2009). *Multiple testing methodology. Multiple Testing Problems in Pharmaceutical Statistics*. Chapman and Hall/CRC Press, New York.

Maurer, W., Hothorn, L. A., & Lehmacher, W. (1995). Multiple Comparisons in Drug Clinical Trials and Preclinical Assays: A-priori ordered Hypotheses. *Testing Principles in Clinical and Preclinical Trials (J. Vollmar, editor) STuttgart, Gustav Fisher Verlag*, 3-18.

SAS Institute, Inc. (1999). *SAS Procedures Guide, version 8.* Cary, NC: SAS Institute.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA OUTPUT CONVENTIONS

Outputs will be presented according to the following:

TABLE AND LISTING OUTPUT CONVENTIONS

General:

• The first row in the body of the table or listing should be blank
• The left-hand column should start in column 1. No indenting or centering of the output should occur.
• Rounding should be done with the SAS function ROUND.
• Numbers in tables should be rounded, not truncated.
• Alphanumeric output should be left aligned.
• Numbers should be decimal point aligned.
• Whole numbers should be right aligned.
• Text values should be left aligned.
• The first letter of a text entry should be capitalized
• Listings of adverse events, concomitant medications, medical histories etc. should be sorted in chronological order, with earliest adverse event, medication or history coming first.
• The study drug should appear first in tables with treatments as columns
• In general, only present totals (across treatment groups) at baseline/randomization, and do not present them post randomization, unless the customer specifically requests it.
• All listing outputs should be sorted (preferably by Treatment, Site Number and Patient Number).
• Exponentiation will be expressed using a superscript with ODS RTF.
• All variables that are output in the CRF (which have data present) should appear in the listings, along with all derived data appearing in the corresponding tables

• The width of the entire output should match the linesize.

Univariate Statistics:

• Statistics should be presented in the same order across tables (i.e., n, Mean, SD, Minimum, Median, Maximum and equivalently, n, GeoMean, CV, Minimum, Median, Maximum)

• Table statistics should line up under the N part of the (N=XXX) in the table header. All decimal points should line up. If the minimum and maximum are output on 1 line as Minimum, Maximum then the comma should line up with the decimal point.

• If the original data has N decimal places, then the summary statistics should have the following decimal places:

Minimum and maximum: N

Mean, median and CV%: N + 1

SD: N + 2

Frequencies and percentages (n and %):

• Percent values should be reported inside parentheses, with 1 space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:

77 (100.0%)

50 (64.9%)

0 (0.0%)

• Percentages will be reported to 1 decimal place, except percentages <100.0% but >99.9% will be presented as '>99.9%' (e.g., 99.99% is presented as >99.9%); and percentages < 0.1% will be presented as '<0.1%' (e.g., 0.08% is presented as <0.1%). Rounding will be applied after the <0.1% and >99.9% rule.

e.g. (<0.1%)

(6.8%)

(>99.9%)

Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively

small).

• Where counts are zero, percentages of 0.0% should appear in the output.

Confidence Intervals:

• As a rule, confidence intervals are output to 1 place more than the raw data, and standard deviations and standard errors to 2 places more than the raw data

• Confidence intervals should be justified so that parentheses displayed on consecutive lines of a table "line up".

• Boundary values of confidence intervals should be separated by a comma.

• Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place.

• An example is given below:

(-0.12, -0.10)

(9.54, 12.91)

P-values:

• P-values should be reported to 3 decimal places, except values <1.000 but >0.999 will be presented as '>0.999' (e.g., 0.9998 is presented as >0.999); and values <0.001 will be presented as '<0.001' (e.g., 0.0009 is presented as <0.001). Rounding will be applied after the <0.001 and >0.999 rule

Ratios:

• Ratios should be reported to 1 more decimal place than the original data.

Spacing:

• There must be a minimum of 1 blank space between columns (preferably 2)

Denominators:

• If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number "n".

• Alternatively, a footnote should be included in each table with percentages to indicate the denominator for percentages.

Missing values

• A "0" should be used to indicate a zero frequency.

• A blank will be used to indicate missing data in an end-of-text table or patient listing.

FIGURE OUTPUT CONVENTIONS

• Figures should be provided in RTF files generated by SAS.
• Should contain the title or footer.
• The image should be clear and of high quality when viewed in the Word document, and when printed.
• In general, boxes around the figures should be used.

DATES & TIMES

Depending on data available, dates and times will take the form DDMMMYYY THH:MM:SS.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

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

Treatment Group	For Tables, Graphs and Listings
RPL554 150 µg double blind	RPL554 150µg
RPL554 500 µg double blind	RPL554 500µg

Treatment Group	For Tables, Graphs and Listings
RPL554 1500 µg double blind	RPL554 1500µg
RPL554 3000 µg double blind	RPL554 3000µg
RPL554 6000 µg double blind	RPL554 6000µg
Placebo	Placebo
Non-randomized (where applicable)	Non-randomized

PRESENTATION OF VISITS

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

Long Name (default)	Short Name
Screening	Scr
Day 1	Day 1
Day 2	Day 2

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), first by active dose [by ascending dose group] and then placebo.
Center-patient ID,
Date (where applicable),
For listings where non-randomized patients are included, these will appear in a category after the randomized treatment groups labeled 'Non-randomized'.

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
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
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

START DATE	STOP DATE	ACTION
		If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
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 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 stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study

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 and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	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
Partial	Known	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: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
	Partial	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: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	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: 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
Missing	Known	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'
	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

STATISTICAL ANALYSIS PLAN – PART B

RPL554-DP-201

A Phase II, Randomized Study to Assess the Pharmacokinetics, Safety and Pharmacodynamics of Single and Repeat Doses of RPL554 Administered by Dry Powder Inhaler in Patients with COPD

AUTHOR: NICHOLAS ROUBINIS / JENNIFER ALLSOPP

VERSION NUMBER AND DATE: V2.0, 08JUL2019

STATISTICAL ANALYSIS PLAN – PART B SIGNATURE PAGE

Statistical Analysis Plan V2.0 – Part B (Dated 08JUL2019) for Protocol RPL554-DP-201.

	Name	Signature	Date
Author:	Jennifer Allsopp		
Position:	Biostatistician II		
Company:	IQVIA		

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan – Part B, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:	Mark Shaw		
Position:	Associate Director		
Company:	IQVIA		
Approved By:	Reynold Daniel		
Position:	Sr. Clinical Trial Manager		
Company:	Verona Pharma		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	21JUN2019	Nicholas Roubinis / Jennifer Allsopp	Not Applicable – First Version
2.0	08JUL2019	Jennifer Allsopp	Update treatment sequences from blinded sequences to unblinded sequences.

TABLE OF CONTENTS

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety and pharmacokinetic (PK)/pharmacodynamic (PD) data for Part B of protocol RPL554-DP-201. 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 the protocol version 2.0, dated 12FEB2019. The study will consist of two parts (A and B) and Part B will be described in this SAP. Only the protocol sections applicable to Part B will be described in this SAP.

2. STUDY OBJECTIVES FOR PART B

2.1. PRIMARY OBJECTIVE

The primary objective of Part B is to investigate the bronchodilator effect of repeat doses of RPL554 administered by DPI (Dry powder inhaler), assessed in terms of peak FEV_1 (forced expiratory volume in one second).

2.2. SECONDARY OBJECTIVES

The secondary objectives of this part are as follows:

- To investigate the safety and tolerability of repeat doses of RPL554 administered by DPI.
- To investigate the bronchodilator effect of RPL554 administered by DPI, in terms of average FEV_1 area under the curve $(AUC)_{0\text{-}4h}$, average FEV_1 $AUC_{0\text{-}12h}$ and trough FEV_1.
- To determine the onset of action of RPL554 administered by DPI.
- To evaluate the PK profile of RPL554 administered by DPI.
- To evaluate the amount of rescue medication use during treatment periods.

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives of this part are as follows:

- To assess the dose response of RPL554 on peak and FEV1 $AUC_{0\text{-}12h}$ after morning dose on Day 7, and morning trough FEV_1 prior to the last dose on Day 7.
- To examine the effect of RPL554 administered by DPI on a Likert dyspnea scale.

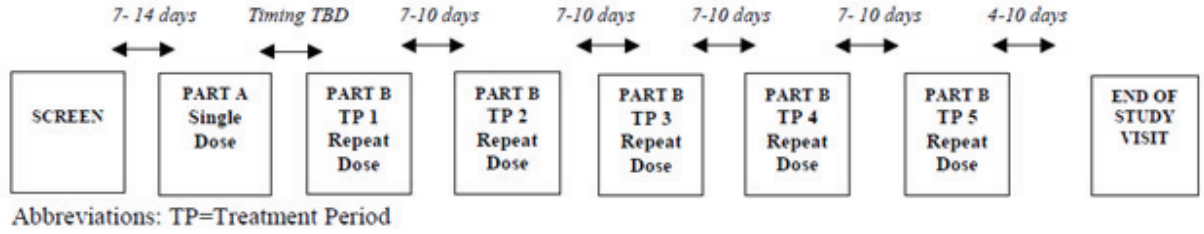
3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a Phase II, randomized, double-blind, placebo-controlled, two-part study. Part A was a parallel group, single dose assessment of RPL554 administered by DPI to evaluate the safety and terminal PK profile of a range of doses of RPL554. Five dose levels, 150 µg, 500 µg, 1500 µg, 3000 µg and 6000 µg were selected, covering a 40-fold increase in doses. A total of approximately 36 COPD patients (as defined by the American Thoracic Society [ATS]/European Respiratory Society [ERS] guidelines with symptoms compatible with COPD for at least 1 year prior to Screening) aged 40 to 80 years (inclusive) were randomized at one site in the Unites States (US). At the end of Part A, the database was locked and the data unblinded and analyzed prior to commencing Part B. Four dose levels, 150 µg, 500 µg, 1500 µg, 3000 µg were selected for Part B, using the same Part A patients. Part B is designed as a crossover, repeat dose assessment of RPL554 administered by DPI to evaluate the steady state efficacy/PD effect of the four RPL554 doses compared to the effect with placebo DPI. The patients in Part B will be expected to complete five treatment periods.

In Part B, the patients from Part A will be randomly assigned in crossover fashion to one of 10 treatment sequences (see Appendix 1; Presentation of Treatment Sequences) each consisting of five 1-week treatment periods separated by a 7 to 10-day washout. Each treatment period consists of 6 days of twice daily doses of RPL554, and a single morning dose on Day 7. In each treatment period, patients will undergo assessments over 12 hours on Days 1 and 7. Figure 1 below summarizes these details.

Figure 1 Study Flow Chart



3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 6 of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

None.

4. PLANNED ANALYSES

There are no data monitoring committee (DMC) or formal interim analyses to be performed for this study. The study will consist of two separate and independent analyses, Part A and Part B. At the end of each part, the database will be locked and unblinded, and the analyses for each part will be performed.

4.1. DATA MONITORING COMMITTEE (DMC)

There will be no DMC analyses for this study.

4.2. INTERIM ANALYSIS

No formal interim analysis is planned for the study.

4.3. PART B ANALYSIS

All Part B analyses identified in this SAP will be performed by IQVIA Biostatistics following Database Lock on a clean database:

- All outstanding data issues and queries resolved.
- All irresolvable data issues documented in the Data Handling Report (DHR) from Data Management.
- All coding of medications, medical history and adverse events (AEs) completed.
- Serious AE (SAE) reconciliation completed.
- All reconciliation of vendor data with electronic case report form (eCRF) data completed successfully.
- Analysis sets authorized.

It should be noted that the main teams that performed the Part A analysis remained blinded at the time of the Part A database lock. This was to avoid any potential risk they could trace what study medication a patient might be receiving in Part B (e.g. if they know they experienced certain AEs while on one treatment in Part A and this was identifiable in Part B).

All verbatim text from the eCRF will be presented in outputs "as is" with no "manual hard coding" corrections for such data. Also, PK analysis will be performed by another party (third party vendor), and details of this analysis will not be specified in this SAP.

5. ANALYSIS SETS

Agreement and authorization of patients included/excluded from each analysis set will be conducted prior to the unblinding of the study for Part B.
In the case of dosing errors leading to duplication of treatment period or that treatment during period is undetermined, the period data for a patient could be excluded from the analysis. These will be agreed and documented prior to unblinding.

5.1. PART A COMPLETERS SET

This set will contain all patients who completed Part A of the study.

5.2. ALL PATIENTS RANDOMIZED SET IN PART B [RND]

The all patients randomized (RND) set will contain all patients who completed Part A and who are randomized to study medication in Part B (two randomizations are expected for this study, one for each part). For analyses and displays based on RND, patients will be classified per randomized sequence/treatment.

5.3. 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 medication during Part B. Patients will be classified per actual sequence/treatment received. If there is any doubt whether a patient was treated or not, they will be assumed treated for the purposes of analysis. If a patient is treated based on a non-pre-specified sequence, which is not one of the 10 listed treatment sequence, this will be reported as 'Undefined' for analysis by actual sequence/ treatment per Appendix 1; Presentation of Treatment Sequences. For analysis by treatment group a patient should be counted once for each time a specific treatment was received.

5.4. FULL ANALYSIS SET [FAS]

The full analysis set (FAS) will contain all patients in the RND set with sufficient data (pre-dose and at least one post-dose assessment of spirometry) collected after intake of study medication to compute the pharmacodynamic parameters (FEV_1, FRC measurements) on at least 2 treatment periods in Part B. For analyses and displays based on FAS, patients will be classified per randomized sequence/treatment.

5.5. COMPLETERS ANALYSIS SET [CAS]

The completers analysis set (CAS) will contain all patients in the SAF analysis set who complete all treatment

periods i.e., a patient who receives a first and last dose intake plus 1 day for all 5 treatment periods per schedule of events (see section 6 of the protocol for schedule details).

5.6. PHARMACOKINETICS [PK] ANALYSIS SET

The PK analysis set will contain all patients in the RND analysis set who have a blood sampling performed after at least one dose of RPL554 in Part B and with data sufficient to calculate PK parameter data.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study day will be calculated from the reference start date (treatment period [TP] 1, day 1) and will be used to show start/stop day of assessments and events. Relative day will be calculated from the reference start date (each TP, day 1) and will be used to show start/stop day of assessments and events relative to each treatment period. Reference start date is defined as the day of the study medication 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 date, then:

- Study day = (date of event – reference date) + 1.

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

- Study day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and study day, and any corresponding durations will be presented based on the imputations specified in Appendix 2; Partial Date Conventions.

6.2. BASELINE

Baseline definitions are related to the treatment period the patient enters. For majority of endpoints (primary endpoint, relevant secondary/exploratory endpoints and safety endpoints assessed post-dose in the treatment periods), this will be the pre-dose assessment on Day 1 of each treatment period (treatment period 1 to treatment period 5). Baseline pre-dose FEV_1/FVC will be derived from 3 acceptable readings (performed up to 8 times to obtain these), with the highest result from each assessment being used for analysis. For safety assessments with pre-dose assessments, baseline will be defined as the pre-dose assessment for each treatment period.

6.3. REPEAT/RESCHEDULE, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. If a visit is repeated/rescheduled due to variability in FEV_1 or other reason, the repeated/rescheduled visit, will be listed and summarized as the valid visit (same visit number assigned). Unscheduled measurements will not be included in by-visit summaries, but will contribute to the endpoint value. For example, if an unscheduled visit occurred at 10 hours post-dose on Day 1, then this value will be considered in the calculation of the average FEV_1 over 12 hours ($AUC_{0\text{-}12h}$ FEV_1). Any unscheduled or unplanned readings will be presented within the patient listings.

Early termination data will be mapped according to the visit number the termination occurred for by-visit summaries. If termination is between the end of Part A and the beginning of Part B, data are to be considered in the Part B SAP and patient is considered a Part A completer.

Listings will include scheduled, unscheduled, repeat/reschedule and early discontinuation data.

6.4. WINDOWING CONVENTIONS

No visit windows will be applied in this study and the scheduled assessments will be reported and analyzed as per eCRF collection.

6.5. STATISTICAL TESTS

The default significant level will be (5%); confidence intervals will be 95% and all tests will be 2-sided, unless otherwise specified in the description of the analyses. All significant p-values (i.e. < 5%) will be flagged by means of a "*" for ease of review.

For presentation of summary statistics for quantitative and qualitative variables see Appendix 1; Programming conventions for outputs.

6.6. COMMON CALCULATIONS

Assessments assigned to treatment periods:

- Based on the day of assessment relative to the start date of each treatment period as defined by the first treatment administration for that specific treatment period:
    - Treatment period 1
    - Treatment period 2
    - Treatment period 3
    - Treatment period 4
    - Treatment period 5

For quantitative measurements, change from baseline will be calculated as:

- Test value at post-dose timepoint – baseline value.

For quantitative measurement values of FEV_1 and FEV_1 AUCs will be calculated based on:

- The highest FEV_1 reading from each assessment.
- The baseline value (average of the two pre-dose values [at 1-hour {±5 minutes} and immediately {within 5 minutes}} pre-dose) must be within ± 20% of the pre-albuterol value at Screening; otherwise, the patient will be a screen failure.

Peak effect will be calculated as:

- Maximum value in the first 4 hours after dosing.

Average effect will be calculated as:

- FEV_1 AUC divided by the length of the time interval of interest.

Log-transformations will be performed on FEV_1 data:

- FEV_1 will be analyzed using multiplicative models, which means that data will be logged prior to analysis. The results will then be back-transformed to linear scale (treatment differences will thus be ratios of geometric means).

6.7. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following covariates are used in the analyses. For details of their inclusion in the models, see the specific analysis section.

- Randomized treatment (fixed).
  - RPL554 150µg
  - RPL554 500µg
  - RPL554 1500µg
  - RPL554 3000µg
  - Placebo
- Treatment period (fixed).
  - Treatment period 1
  - Treatment period 2
  - Treatment period 3
  - Treatment period 4
  - Treatment period 5
- Baseline value of analyzed variable (covariate).

7.2. MULTICENTER STUDIES

This study is being conducted at 1 study center in the US.

7.3. MISSING DATA

Missing safety data will not be imputed, apart from partial date imputations as specified in Appendix 2.
Missing efficacy data will be handled as described in Section 15.1.2 and Section 15.2.2 of this SAP.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

Significance of treatment effect will be tested for the primary and secondary efficacy endpoints in Part B and will be done for each of the doses of RPL554 against placebo, starting with the highest dose (3000 µg). To this end, the fixed-sequence testing approach (Maurer et al., 1995; Westfall & Krishen, 2001) will be used.

For the endpoints, let i = 0, 1, 2, 3 and 4 represent increasing dose levels, 0 denoting placebo. Also, let μ_i, i = 0, 1, 2, 3 and 4 denote the mean change from baseline for the endpoint of interest for placebo and each increasing active dose level, respectively. The null hypotheses are defined as: H_i: $\mu_j - \mu_0 = 0$ and will be tested against the 2-sided alternative K_i: $\mu_j - \mu_0 \neq 0$, j = 1, 2, 3 and 4.

Finally, let p_1, p_2, p_3, p_4 denote the marginal p-values obtained from the statistical tests associated with H_1, H_2, H_3, H_4 (obtained from the model).
The fixed-sequence testing will begin with the null hypothesis corresponding to the highest dose versus placebo. If a statistically significant difference is found at the 2-sided α level of 5%, the testing will proceed with the next highest dose. Otherwise, testing stops, and the remaining null hypotheses are considered as failed to reject, without testing.

This testing strategy can be written as the following stepwise algorithm:

- Step 1: If $p_4 \leq \alpha$ reject H_4 and go to Step 2. Otherwise, fail to reject H_4, H_3, H_2 and H_1 and stop.
- Step 2: If $p_3 \leq \alpha$ reject H_3 and go to Step 3. Otherwise, fail to reject H_3, H_2 and H_1 and stop.
- Step 3: If $p_2 \leq \alpha$ reject H_2 and go to Step 4. Otherwise, fail to reject H_2 and H_1 and stop.
- Step 4: If $p_1 \leq \alpha$ reject H_1. Otherwise, accept H_1.

The fixed-sequence procedure controls the family-wise error rate in the strong sense because, for each null hypothesis, the testing is conditional upon rejecting all hypotheses earlier in the sequence (Dmitrienko, et al., 2009).

Each secondary endpoint will be tested independently and nominally following a hierarchical testing of doses like the one used for the primary endpoint.

7.5. EXAMINATION OF SUBGROUPS

No subgroup analyses will be performed for this study.

8. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.
The templates provided with this SAP describe 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 completed Part A of the study will be accounted for in Part B of the study.

Patient disposition, withdrawals and reasons for exclusion from each analysis set will be presented for all patients, summarized by treatment sequence for the patients who completed Part A and were randomized in Part B. Number of patients treated and discontinued in each treatment period will also be presented. If the patient discontinued/withdrew, he/she will be allocated to the last treatment period attended.

All protocol deviations collected in Part B will be divided into critical, major or minor categories and will be assigned to the actual treatment group. The major and critical protocol deviations (PD) will be summarized by treatment and all PDs will be presented in a listing for the RND analysis set. Protocol deviations affect the integrity of the drug activity data and will be obtained by the clinical research associates (CRAs) and documented in the clinical trial management system (CTMS).

Each protocol deviation is categorized into one of the following types, as reported in CTMS:

1. Informed Consent Criteria
2. Eligibility and Entry Criteria
3. Concomitant Medication Criteria
4. Laboratory Assessment Criteria
5. Study Procedures Criteria
6. Serious Adverse Event Criteria
7. Randomization Criteria
8. Visit Schedule Criteria
9. Investigation Product (IP) Compliance
10. Efficacy Criteria
11. Administrative Criteria
12. Source Document Criteria
13. Regulatory or Ethics Approvals Criteria
14. Other Criteria

Assignment to each analysis set, therefore whether a patient is included/excluded in each analysis set (excluding the PK analysis set, as this set will be defined later in a separate authorization with input, as required, from the PK scientist) will be recorded in an EXCEL sheet by the IQVIA Biostatistician, with the reason for exclusion from each population indicated. The EXCEL sheet should then be authorized by means of a customer authorization form (CAF) and prior to the Database Lock of the study.

10. DEMOGRAPHIC AND OTHER SCREENING CHARACTERISTICS

Demographic data and other screening characteristics (including screening disease characteristics) will be presented for each unique set, as described in Section 5. No statistical testing will be carried out for demographic or other screening characteristics. The following demographic and other screening characteristics will be reported for Part B:

- Age (years)
- Sex
- Childbearing potential

- Race
- Ethnicity
- Height (inches)
- Weight (pounds)
- BMI (kg/m^2)
- Pre (prior to dosing at screening)/post (post dosing at screening) bronchodilator FEV_1 (both in liters and in percentage of predicted normal)
- Post-bronchodilator FEV_1/FVC
- Reversibility test (mL and %)
- Reversibility assessment performed with four puffs of Albuterol
- Met requirements of reversibility test

10.1. DERIVATIONS

Demographic and other screening characteristics recorded on the eCRF will be used as is on the eCRF, without any derivations or adjustments.

11. SURGICAL, MEDICAL AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE/SMOKING HISTORY

Surgical and Medical History information will be presented in listings, for the RND analysis set.

- Surgical History will be coded by Medical Dictionary for Regulatory Activities (MedDRA) dictionary using the version specified in the data management plan.
  - Surgical History conditions are defined as those conditions which stop prior to or at Screening.
  - Data captured on the Surgical Procedure History page of the eCRF will be presented by SOC (System Organ Class) and PT (Preferred Term).
- Medical History will be coded by MedDRA dictionary using the version specified in the data management plan.
  - Medical History conditions are defined as those conditions which stop prior to or at Screening.
  - Data captured on the Medical History page of the eCRF will be presented by SOC and PT.

- COPD/Smoking History data captured on the COPD and Smoking History page of the eCRF will be presented for each unique set, as described in Section 5.
  - COPD history (Duration of COPD (years) [calculated relative to date of first diagnosis {Randomization date, as recorded in Part A – first COPD diagnosis date}/365.25], date of most recent exacerbation, known to have chronic bronchitis/emphysema).
  - Smoking history (current or former smoker, number of packs per day, number of years smoking and number of pack-years [calculated as number of packs per day x number of years smoking])

12. MEDICATIONS

Medications will be coded using the World Health Organization – Drug Dictionary (WHO-DD) version specified in the data management plan and will be presented in a listing by Anatomical Therapeutic Chemical (ATC) (the 1st level of the ATC code) and PT for the RND analysis set. Certain medications (or a special grouping of medications) will be classified in a list during the study and signed-off prior to lock by a medical advisor. As this list, may change prior to sign-off they will not be defined in this section of the SAP. Potential medications include, but are not limited to, inhaled corticosteroids (ICS), LAMAs (long-acting muscarinic antagonists), LABAs (long-acting beta2-agonists) etc.

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

- 'Prior' medications are medications which started and stopped in the time between Part A and Part B (prior to the study medication at TP1, Day 1) and have Started prior to start of study medication? = "Yes" on the Concomitant medications eCRF page.

- 'Concomitant' medications are medications which:
  - Had an onset date on or after the start of study medication for Part B (TP1, Day 1).
  - AND ended on or after the date of medication or were ongoing at the end of Part B.
  - A patient can report more than 1 concomitant medication with the same PT.

Prior and concomitant medications will be presented in a listing only, by treatment sequence. For concomitant medications, the treatment period when the medication was taken will also be reported in the listing.

- Rescue medications will be recorded on the Rescue Medication Canister Collection/Rescue Medication Canister Dispensed/Rescue Medication Canister Weight pages of the eCRF. These are short acting bronchodilators and will be sourced by the study center and dispensed as needed during the Screening, treatment and washout periods. Rescue medication used during the study will be documented on the eCRF pages. Protocol procedures must continue even if rescue medication has been taken. Albuterol is to be used for primary rescue use, but others are also permitted (e.g. ipratropium). Rescue medications must be withheld for at least 8 hours prior to spirometry (per below), and this is to be confirmed in the eCRF at the start of each treatment period. If this withhold is not met, the patient should be rescheduled for a repeat visit within permitted windows.

Rescue medications used during study visits (by recording the time it was dispensed and collected) and the amount taken by treatment period (by recording the weight of the canister dispensed at the end of Day 1 and start of Day 7 per period), will be described in Section 15.2.1.5.

When a rescue medication is used less than 8 hours prior to study medication a sensitivity analysis will be carried out for the analysis detailed in Section 15.2.1.2 removed patients who took rescue medication. This will only be carried out if at least 1 patient has taken rescue medication less than 8-hours prior to study medications.

13. STUDY MEDICATION EXPOSURE

Exposure to study medication in days will be presented by treatment for the SAF analysis set. The date of first study medication inhalation, per treatment, will be taken from the Drug Exposure eCRF page for treatment period 1. The date of last study medication inhalation, per treatment sequence, will also be taken from the Drug Exposure eCRF page, based on the last end time of inhalation for the last treatment period of a patient.

Drug accountability i.e. the number of capsules used per treatment period, as measured on the Drug Exposure eCRF page will be summed to get the total number of capsules used and presented similarly to exposure, by treatment sequence for the SAF analysis set.

13.1. DERIVATIONS

- Duration of exposure per treatment period (days) in Part B = date of last study medication administration, per treatment – date of first study medication administration, per treatment +1.
- Duration of exposure per treatment sequence (days) in Part B = Duration of exposure for period 1 + Duration of exposure for period 2 + Duration of exposure for period 3 + Duration of exposure for period 4 + Duration of exposure for period 5.
- Drug accountability (number of capsules) = Number of capsules dispensed – number of capsules returned by treatment period.

14. STUDY MEDICATION COMPLIANCE

In Part B, patients will be dosed at the study center on the morning and evening of Day 1 and on the morning of Day 7. Patients will self-administer study medication for the other dosing times (i.e. on Days 2 through 6). Compliance will be assessed by recording the number of capsules dispensed and returned, as per drug accountability described in Section 13.

15. EFFICACY OUTCOMES

15.1. PRIMARY EFFICACY

15.1.1. PRIMARY EFFICACY VARIABLE(S) & DERIVATION(S)

The primary efficacy variable is peak FEV_1 (measured in first 4 hours after morning dosing). This will be measured after dosing on Day 7 and is collected on the Spirometry Study measurements eCRF page. The primary efficacy endpoint is change from baseline in peak FEV_1.

Three acceptable readings are performed at each of the timepoints in first 4 hours after morning dosing on Day 7 (5, 15 and 30 minutes and 1, 1.5, 2 and 4 hours) and the highest of the 3 is used for analysis purposes. Hence, peak

FEV_1 is derived as the highest of all these readings. Patients withdrawn after only one treatment period will not be included in the analysis.

Descriptive statistics (see Appendix 1 [Programming conventions for outputs]) for FEV_1 will be presented for all patients assigned to FAS, at each assessment and change from baseline at each assessment. All summaries will be presented for each treatment group by day and timepoint. In addition, a figure (bar graph) representing mean change from baseline FEV_1 to peak FEV_1 by treatment will be presented, including the standard error of the mean.

Change from baseline FEV_1 to peak FEV_1 (over 4 hours) at Day 7 will be derived to test the hypothesis described in section 15.1.3 with baseline defined as the average of the FEV_1 pre-dose assessment (-60 minutes and -5 minutes) collected on Day 1 of each treatment period. Peak FEV_1 at Day 7 is defined as the maximum post-dose value among the 5, 15, 30 minutes, 1, 1.5, 2 and 4-hour assessments collected at after morning dose on Day 7 of each treatment period.

15.1.2. Missing Data Methods for Primary Efficacy Variable(s)

No imputation will be applied.

15.1.3. Primary Analysis of Primary Efficacy Variable(s)

The primary efficacy objective of the study is to show that at least 1 RPL554 treatment group (RPL554 3000µg, RPL554 1500µg, RPL554 500µg, RPL554 150µg) will increase peak FEV_1 (change from Baseline) compared to placebo at Day 7 (measured in first 4 hours after morning dosing) by rejecting the null hypothesis described below at significance level α=0.05 level (2-sided):

$$H_0: \mu_j = \mu_0 \text{ versus } H_1: \mu_j \neq \mu_0$$

where μ_j and μ_0 are the mean change from Baseline in peak FEV_1 at Day 7 (measured in first 4 hours after morning dosing) for 1 RPL554 treatment group (RPL554 3000µg, RPL554 1500µg, RPL554 500µg, RPL554 150µg) and placebo respectively.

An ANCOVA will be used to test the hypothesis with change from baseline FEV_1 to peak FEV_1 (measured in first 4 hours after morning dosing) on Day 7 as response variable, and treatment and treatment period as fixed factors, patient as random and baseline FEV_1 as covariates. Analyses will be implemented using the SAS® procedure MIXED as follows:

```
PROC MIXED DATA = …;
       CLASS USUBJID PERIOD TREATMENT;
       MODEL CHG = TREATMENT PERIOD BASELINE;
       RANDOM USUBJID;
       LSMEANS TREATMENT / CL DIFF;
RUN;
```

where CHG = difference in log (peak FEV_1 - baseline FEV_1)

TREATMENT = treatment group (RPL554 3000µg, RPL554 1500µg, RPL554 500µg, RPL554 150µg and placebo)

PERIOD = treatment period (treatment period 1, 2, 3, 4 and 5)

BASELINE = log (baseline FEV_1)

USUBJID = subject ID

The primary comparison will be the contrast (difference in least squares mean [LSMEAN]) between RPL554 3000µg and placebo on Day 7 (in first 4 hours after morning dosing).

Peak FEV_1 and the covariate, baseline FEV_1, will be log-transformed prior to analysis using natural logarithm. The difference between the two is log (peak FEV_1) – log (baseline FEV_1). Therefore, the LSMEAN statement between treatments in the above PROC MIXED will provide the log of the contrasts. Prior to presentations, the antilog of these point estimates and associated 95% confidence intervals will be performed, giving ratios of geometric means on the linear scale. The 2-sided p-value for the exponential (exp) least squares mean, exp(LSM), ratio between each of the 2 treatment groups and placebo will be reported.

Summary statistics for FEV_1 will be presented for baseline, peak on Day 7 (in first 4 hours after morning dosing) and change from baseline to peak by treatment group on patients with both assessments, on the original scale. A figure displaying the mean change from baseline FEV_1 over time by treatment and day will also be presented.

15.2. SECONDARY EFFICACY

The secondary efficacy analyses will be performed for the FAS. Patients withdrawn after only one treatment period will not be included in the analyses of any of the secondary efficacy variables.

15.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

15.2.1.1. Change in baseline in average FEV_1 of $AUC_{0\text{-}4h}$ (Average FEV_1 over 4 hours), average FEV_1 of $AUC_{0\text{-}12h}$ (Average FEV_1 over 12 hours) and (morning) trough FEV_1 on Day 7 (Secondary variables 1, 2 and 3)

Average FEV_1 is defined as the $AUC_{0\text{-}4h}$ FEV_1 collected, divided by the length of the time (in hours). $AUC_{0\text{-}4h}$ FEV_1 is derived using the following formula:

$$AUC = \frac{1}{2}(t_1 - t_0)(y_1 + y_0) + \frac{1}{2}(t_2 - t_1)(y_2 + y_1) + \cdots + \frac{1}{2}(t_i - t_{i-1})(y_i + y_{i+1})$$

where *i* are the number of intervals, t_i are the time values or time intervals (in actual hours) between assessments and y_i the FEV_1 values (highest of the three acceptable readings) at t_i. The AUC result will then be divided by the actual time (the time elapsed since dosing, until the time of assessment) at 4-hour assessment (as this can occur ± 10 minutes) to obtain the average FEV_1. If the assessment at 4-hour is missing, the AUC result will be divided by the actual time of the last collected assessment. For analysis purposes, it will be assumed that the pre-dose value (immediately pre-dose) occurred at time 0 when computing PD parameters. If a patient misses hour 2 and 4 then the $AUC_{0\text{-}4}$ is set to missing.

Descriptive statistics (see Appendix 1 [Programming conventions for outputs]) for $AUC_{0\text{-}4}$ will be presented for all patients assigned to FAS, at each assessment and change from baseline at each assessment as relevant. All summaries will be presented for each treatment group.

Change from baseline FEV_1 to FEV_1 $AUC_{0\text{-}4}$ will be derived to test the hypothesis described in Section 15.2.3 with

baseline defined as the average of the FEV_1 pre-dose assessments (-60 minutes and -5 minutes) collected.

$AUC_{0\text{-}12h}$ FEV_1 is defined and derived similarly to $AUC_{0\text{-}4h}$ above, but over 12-hours post-dose. If patient misses hours 11 and 12 then the $AUC_{0\text{-}12h}$ is set to missing.

Morning trough FEV_1 is the average of the FEV_1 pre-dose assessments (-60 minutes and -5 minutes) on Day 7 and the change from baseline will be analyzed similarly to $AUC_{0\text{-}4h}$ and $AUC_{0\text{-}12h}$.

15.2.1.2. Change in baseline in peak FEV_1 measured after first dose, average FEV_1 of $AUC_{0\text{-}4h}$ on Day 1 and average FEV_1 of $AUC_{0\text{-}12h}$ FEV_1 on Day 1 (Secondary variables 4, 5 and 6)

Peak FEV_1 measured after first dose is defined as the peak FEV_1 (after 4 hours of dosing) on Day 1. It is defined as the change from baseline to peak FEV_1 and derived similarly to primary analysis (see section 15.1.1), but instead at Day 1.

$AUC_{0\text{-}4h}$ FEV_1 and $AUC_{0\text{-}12h}$ FEV_1 on Day 1 are defined and derived similarly to secondary endpoint above (see section 15.2.1.1), but at Day 1. Parameters will be calculated over 4 and 12 hours, respectively (on Day 1 of each treatment period). If patient misses hours 2 and 4 then the $AUC_{0\text{-}4h}$ is set to missing. Similarly, if patient misses hours 11 and 12 then the $AUC_{0\text{-}12h}$ is set to missing. If the assessment at 12-hours is missing, the AUC result will be divided by the actual time of the last collected assessment.

15.2.1.3. Determination of onset of action (>10% increase in FEV_1, from pre-first dose, censored at 120 minutes) on Day 1 (Secondary variable 7)

Onset of action is defined as a >10% increase in FEV_1 from pre-dose on Day 1 over the next 120 minutes (2 hours) after morning dosing on Day 1 (5, 15 and 30 minutes and 1, 1.5, 2 hours). Time to onset will be derived as the time to onset of action is achieved. For analysis purposes, it will be assumed that the pre-dose value occurred at time 0. Patients not experiencing an onset of action will be censored at 120 minutes (2 hours) or at time of premature discontinuation (if withdrawn before 120 minutes). If the number of patient censored regarding onset of action is deemed to be too high (number of patients with onset of action censored >50%), the Kaplan-Meier estimates and

accompanying figure will not be presented. Patients receiving placebo will not be summarized in either tables or figure.

15.2.1.4. RPL554 steady state pharmacokinetics (AUC_{0-12h}, Cmax, time to maximum concentration [tmax]) (Secondary variable 8)

Concentration of RPL554 and computed PK parameters (AUC_{0-12h}, C_{max} [maximum concentration], t_{max} [time to maximum concentration]) on Day 7 of each treatment period (pre-dose, 30 minutes and 1, 1.5, 2, 4, 8 and 12-hours post dose).

15.2.1.5. Change from baseline in rescue medication use during treatment periods (Secondary variable 9)

The average use, in terms of weight (mcg) of rescue medication during the treatment periods will be collected from the Rescue Medication Canister Dispensed and Rescue Medication Canister Weight eCRF pages and will be summarized by treatment group. Rescue medication used will be calculated from the difference in weight at time of dispensing and weight at time of collection. So, change from baseline is the difference in rescue medication from baseline (at pre-dose on Day 1) and the collection visit (12hr post-dose on Day 7).

15.2.2. Missing Data Methods for Secondary Efficacy Variable(s)

No imputation will be applied.

15.2.3. Analysis of Secondary Efficacy Variables

15.2.3.1. Analysis of Secondary Variables 1, 2, 3, 4, 5 and 6

The secondary variables listed above will be analyzed by comparing the RPL554 treatment groups to each other and placebo by rejecting the null hypothesis described below at significance level α=0.05 level (2-sided):

$$H_0: \mu_j = \mu_0 \text{ versus } H_1: \mu_j \neq \mu_0$$

where μ_j and μ_0 are the mean change from Baseline for each parameter for each respective dose of RPL554 and placebo.

ANCOVA analyses will be implemented using the SAS® procedure MIXED as follows:

```
PROC MIXED DATA = …;
      CLASS USUBJID PERIOD TREATMENT;
      MODEL CHG = TREATMENT PERIOD BASELINE;
      LSMEANS TREATMENT / CL DIFF;
      RANDOM USUBJID;
RUN;
```

where CHG = difference in log (parameter – baseline parameter)
TREATMENT = treatment group (Respective dose of RPL554, 150µg, 500µg, 1500µg and 3000µg and placebo)
PERIOD = treatment period (treatment period 1, 2, 3, 4 and 5)
BASELINE = log (baseline parameter)
USUBJID = subject ID

The primary comparison will be the contrast (difference in least squares mean [LSMEAN]) between 3000µg RPL554 and placebo. The parameter value and its baseline covariate will be log-transformed prior to analysis using natural logarithm. The difference between the two log (parameter) – log (baseline parameter). Therefore, the LSMEAN statement between treatments in the above PROC MIXED will provide the log of the contrasts. Prior to presentations, the antilog of these point estimates and associated 95% confidence intervals will be performed, giving ratios of geometric means on the linear scale. The 2-sided p-value for the exponential (exp)least squares mean, exp(LSM), ratio between each of the 2 treatment groups and placebo will be reported.

Summary statistics for each parameter will be presented for baseline, at point of interest (if applicable) and change from baseline by treatment group on patients with both assessments, on the original scale.

15.2.3.2. Analysis of Secondary Variable 7

Onset of action will be summarized by treatment and a Kaplan-Meier plot illustrating time to onset constructed. The SAS® procedure LIFETEST, will be used as follows to calculate the median, 25th and 75th percentile:

```
PROC LIFETEST DATA=...  OUTSURV =... CONFTYPE = LINEAR METHOD =
KM ALPHA = 0.05 ALPHAQT = 0.05 PLOTS = (SURVIVAL (FAILURE NOCENSOR));
       TIME ONSET*STATUS (1);
       STRATA TREATMENT;
RUN;
```

where `ONSET` = time to onset of action

`TREATMENT` = treatment group (Respective dose of RPL554, 150µg, 500µg, 1500µg and 3000µg)

`STATUS (1)` = indicates an event of onset of action

To calculate the mean difference to RPL554 3000µg, the SAS procedure LIFETEST will be carried for each treatment comparison pair individually.

If a patient does not have onset of action from pre-dose on Day 1 over the next 120 minutes (2 hours) the data will be censored at 120 minutes or if a patient prematurely discontinued before 120 minutes, the last available assessment time post-dose (1 indicates censored variables). Median differences to the highest dose (RPL554 3000 µg) will be estimated and the p-value based on the PROC LIFETEST above (Wilcoxon signed rank sum test) between each treatment groups and the highest dose will also be presented.

15.2.3.3. Analysis of Secondary Variable 8

As described in section 4.3, this SAP will not summarise the analyses related to the PK concentrations and parameters and this will be handled by a third-party vendor.

15.2.3.4. Analysis of Secondary Variable 9

Summary statistics of change from baseline will be presented at Days 1 to 7 of each treatment period by treatment group. In addition, all rescue medication used during the serial spirometry assessments(Days 1 and 7) will be listed to assess the accuracy of the FEV_1 recordings.

15.3. EXPLORATORY EFFICACY

15.3.1. EXPLORATORY EFFICACY VARIABLES & DERIVATIONS

15.3.1.1. Evaluation of dose response of RPL554 on peak and average FEV1 AUC_{0-12h} after morning dose on Day 7, and morning trough FEV_1 prior to the last dose on Day 7

The association of dose response for the primary and secondary endpoints listed in this section title will be handled by a third-party vendor.

15.3.1.2. Change from baseline in Likert dyspnea scale measured after morning dose on Day 7

An 11-point Likert scale will be utilized, with patients being asked the following question by a blinded member of staff: "On a scale of zero to ten, please rate your current shortness of breath, with zero indicating no shortness of breath and ten indicating the worst shortness of breath that you can imagine". This scale will be an instantaneous measurement of their dyspnea at that moment, and not reflective. It will be administered on Day 7 pre-dose and 30 minutes, 1, 1.5, 2, 4, 8, 11 and 12 hours post-dose of each treatment period. Baseline will be considered the pre-dose assessment on Day 1 of each treatment period and change from baseline will be assessed at each timepoint on Day 7.

15.3.2. MISSING DATA METHODS FOR EXPLORATORY EFFICACY VARIABLE(S)

No imputation will be applied.

15.3.3. ANALYSIS OF EXPLORATORY EFFICACY VARIABLES

Dyspnea score and the change in dyspnea score will be summarized at each timepoint of interest on Day 7 (pre-dose and 30 minutes, 1, 1.5, 2, 4, 8, 11 and 12 hours post-dose). Treatment comparisons of change from baseline will be performed using an ANCOVA adjusting for treatment, treatment period and patient, and using pre-dose Day 1 baseline value as a covariate, like the hypothesis described in section 15.1.3. The model will be additive; therefore no log-transformation will be applied.

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF.
There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

16.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded by MedDRA dictionary using the version specified in the data management plan.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study medication, based on the investigator assessment of severity. TEAEs will be assigned to treatment groups based on actual treatment received. TEAEs, like medications, may be assigned to multiple treatment groups due to the cross-over design of the study. This will depend on the occurrence date and duration of each TEAE.

See Appendix 2 for handling of partial dates for AEs. 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.
An overall summary of number of patients within each of the categories described in the sub-section below, will be provided as specified in the templates.

Listings will include TEAEs and Non-TEAEs.

16.1.1. ALL TEAES

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and broken down further by maximum severity and relationship to study medication.

16.1.1.1. Severity

Severity is classed as mild/ moderate/ severe (increasing severity). TEAEs starting after the first dose of study

medication with a missing severity will be classified as severe. If a 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.

16.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as "yes" or "no". A related TEAE is defined as a TEAE with a relationship to study medication as "yes". TEAEs with a missing relationship to study medication will be regarded as relationship = "yes" to study medication. If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study medication will be used in the corresponding relationship summaries.

16.1.2. TEAEs Leading to Discontinuation from Study Medication

TEAEs leading to discontinuation from the study will be identified by using the question "Did the AE cause the Patient to discontinue from the study?" from the AE page of the eCRF.

For TEAEs leading to discontinuation from the study medication, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

16.1.3. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the eCRF. A summary of serious TEAEs by SOC and PT will be prepared, similarly to Section 16.1.1 and Section 16.1.2.

16.1.4. Adverse Events Leading to Death

TEAEs leading to Death are those events which are recorded as "Death" on the Adverse Events page of the eCRF. A summary of TEAEs leading to death by SOC and PT will be prepared.

16.2. LABORATORY EVALUATIONS

Results from the local laboratory will be included in the reporting of this study for hematology, blood chemistry, and urinalysis. A list of laboratory assessments to be included in the outputs is included in the protocol, Sections 7.4.3.1, 7.4.3.2, and 7.4.3.3 for hematology, blood chemistry, and urinalysis, respectively. Presentations will use International system (SI) units.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries will be provided for laboratory data:

- Actual and change from baseline (pre-dose at Day 1 for each treatment period) to each pre-dose time point at Day 7 (for quantitative measurements), including overall (where overall is regardless of treatment period, day and timepoint to assess treatment group, as a whole).
- Shift from baseline based on normal range criteria (for quantitative measurements and categorical measurements)
- Incidence of abnormal values according to normal range criteria (in the case of Biochemistry only).
- Listing of all abnormal values occurring after the first dose of study medication.

16.2.1. LABORATORY REFERENCE RANGES AND MARKEDLY ABNORMAL CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

In addition to the high and low quantitative laboratory assignments (as identified by means of the laboratory reference ranges), markedly abnormal quantitative blood chemistry values per the table below will also be identified by the Investigator.

	Blood Chemistry – Markedly Abnormal Definition
Alanine Aminotransferase (ALT)	> 3 x ULN
Alkaline Phosphatase (ALP)	> 3 x ULN
Aspartate Aminotransferase (AST)	> 3 x ULN
Creatinine	> 221 µmol/L
Gamma Glutamyl Transferase (GGT)	> 3 x ULN
Bilirubin (TBL)	> 3 x ULN

ULN: Upper limit of normal.

16.3. ECG EVALUATIONS

Overall results from the local ECG lab will be included in the reporting of this study. The overall assessment of ECG parameters will be reported for this study:

- Normal
- Abnormal not Clinically Significant (ANCS)
- Abnormal Clinically Significant (ACS)
- Incomplete Analysis
- Uninterpretable

The following summaries will be provided for quantitative ECG data, for example heart rate:

- Actual assessments at baseline (pre-dose at Day 1 for each treatment period) and each pre-dose time point at Day 7, including overall (where overall is regardless of treatment period, day and timepoint to assess treatment group as a whole).
  - Shift of overall assessment baseline to post-dose timepoints per Normal, ANCS and ACS overall assessment criteria.
  - Listing of all ECG evaluations and abnormal values occurring after the first dose of study medication.

16.4. 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)

The following summaries will be provided for vital signs data:

- Actual assessments at screening, baseline (pre-dose at each treatment period) and each post-dose time points, including end of study visit and overall (where overall is regardless of treatment period, day and timepoint to assess treatment group as a whole).
- Incidence of markedly abnormal values (number and percent) based on the criteria presented in the table below:

	Low	**High**
Systolic blood pressure (mmHg)	- ≤ 90 mmHg - Decrease from Baseline of ≥ 40 mmHg	- ≥ 180 mmHg - Increase from Baseline of ≥ 40 mmHg
Diastolic blood pressure (mmHg)	- ≤ 50 mmHg - Decrease from Baseline of ≥ 20 mmHg	- ≥ 110 mmHg - Increase from Baseline of ≥ 20 mmHg
Pulse rate (bpm)	- ≤ 50 bpm - Decrease from Baseline of ≥ 30 bpm	- ≥ 110 bpm - Increase from Baseline of ≥ 30 bpm

Peak supine pulse rate after study medication is defined as the maximum value measured in the first 4 hours post-dose. Peak pulse rate and change from baseline to peak on Day 1 and after morning dosing on Day 7 will be summarized similarly to Section 15.1.3, including the figure presentation described in the same section. Treatment comparisons of change from baseline will be performed using an ANCOVA adjusting for treatment, treatment period and patient, and using pre-dose pulse rate as a covariate, like the hypothesis described in Section 15.1.3. The model will be additive; therefore no log-transformation will be applied.

16.5. PHYSICAL EXAMINATION

The following summaries will be provided for the full physical examination data, covering major body systems (nose, throat, skin, thyroid gland, neurological system, respiratory system, cardiovascular system, abdomen [liver and spleen], lymph nodes and extremities):

- Incidence of abnormalities at end of study visit (4-10 days after last treatment period).
- Shifts from baseline at end of study visit.

The following summaries will be provided for a brief physical examination to be also performed, on skin, respiratory system, cardiovascular system, and abdomen (liver and spleen):

- Incidence of abnormalities pre-dose on Day 1 and 7 by treatment period.
- Shifts from baseline by treatment period and timepoint.

16.6. OTHER SAFETY ASSESSMENTS

Inhalation training results on Day 1 pre-dose will be presented in a listing only. In addition, urine pregnancy test results will be listed for women of childbearing potential at Day 1 pre-dose and end of study visits.

17. REFERENCES

Dobson, A. J. (2002). *An introduction to generalized linear models, 2nd ed.* Chapman & Hall/CRC.

Dmitrienko, A., Bretz, F., Westfall, P. H., Troendle, J., Wiens, B. L., Tamhane, A. C., & Hsu, J. C. (2009). *Multiple testing methodology. Multiple Testing Problems in Pharmaceutical Statistics*. Chapman and Hall/CRC Press, New York.

Maurer, W., Hothorn, L. A., & Lehmacher, W. (1995). Multiple Comparisons in Drug Clinical Trials and Preclinical Assays: A-priori ordered Hypotheses. *Testing Principles in Clinical and Preclinical Trials (J. Vollmar, editor) STuttgart, Gustav Fisher Verlag*, 3-18.

SAS Institute, Inc. (1999). *SAS Procedures Guide, version 8.* Cary, NC: SAS Institute.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA OUTPUT CONVENTIONS

Outputs will be presented according to the following:

TABLE AND LISTING OUTPUT CONVENTIONS

General:

- The first row in the body of the table or listing should be blank
- The left-hand column should start in column 1. No indenting or centering of the output should occur.
- Rounding should be done with the SAS function ROUND.
- Numbers in tables should be rounded, not truncated.
- Alphanumeric output should be left aligned.
- Numbers should be decimal point aligned.
- Whole numbers should be right aligned.
- Text values should be left aligned.
- The first letter of a text entry should be capitalized
- Listings of adverse events, concomitant medications, medical histories etc. should be sorted in chronological order, with earliest adverse event, medication or history coming first.
- The study drug should appear first in tables with treatments as columns
- In general, only present totals (across treatment groups) at baseline/randomization, and do not present them post randomization, unless the customer specifically requests it.
- All listing outputs should be sorted (preferably by Treatment, Site Number and Patient Number).
- Exponentiation will be expressed using a superscript with ODS RTF.
- All variables that are output in the CRF (which have data present) should appear in the listings, along with all derived data appearing in the corresponding tables
- The width of the entire output should match the linesize.

Univariate Statistics:

• Statistics should be presented in the same order across tables (i.e., n, Mean, SD, Minimum, Median, Maximum and equivalently, n, GeoMean, CV, Minimum, Median, Maximum)
• Table statistics should line up under the N part of the (N=XXX) in the table header. All decimal points should line up. If the minimum and maximum are output on 1 line as Minimum, Maximum then the comma should line up with the decimal point.
• If the original data has N decimal places, then the summary statistics should have the following decimal places:
Minimum and maximum: N
Mean, median and CV%: N + 1
SD: N + 2

Frequencies and percentages (n and %):
• Percent values should be reported inside parentheses, with 1 space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:
77 (100.0%)
50 (64.9%)
0 (0.0%)
• Percentages will be reported to 1 decimal place, except percentages <100.0% but >99.9% will be presented as '>99.9%' (e.g., 99.99% is presented as >99.9%); and percentages < 0.1% will be presented as '<0.1%' (e.g., 0.08% is presented as <0.1%). Rounding will be applied after the <0.1% and >99.9% rule.
e.g. (<0.1%)
(6.8%)
(>99.9%)
Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).
• Where counts are zero, percentages of 0.0% should appear in the output.

Confidence Intervals:
• As a rule, confidence intervals are output to 1 place more than the raw data, and standard deviations and standard errors to 2 places more than the raw data

• Confidence intervals should be justified so that parentheses displayed on consecutive lines of a table "line up".
• Boundary values of confidence intervals should be separated by a comma.
• Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place.
• An example is given below:
(-0.12, -0.10)
(9.54, 12.91)

P-values:
• P-values should be reported to 4 decimal places, except values <1.000 but >0.999 will be presented as '>0.999' (e.g., 0.9998 is presented as >0.999); and values <0.001 will be presented as '<0.001' (e.g., 0.0009 is presented as <0.001). Rounding will be applied after the <0.001 and >0.999 rule

Ratios:
• Ratios should be reported to 1 more decimal place than the original data.

Spacing:
• There must be a minimum of 1 blank space between columns (preferably 2)

Denominators:
• If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number "n".
• Alternatively, a footnote should be included in each table with percentages to indicate the denominator for percentages.

Missing values
• A "0" should be used to indicate a zero frequency.
• A blank will be used to indicate missing data in an end-of-text table or patient listing.

FIGURE OUTPUT CONVENTIONS

• Figures should be provided in RTF files generated by SAS.
• Should contain the title or footer.
• The image should be clear and of high quality when viewed in the Word document, and when printed.
• In general, boxes around the figures should be used.

DATES & TIMES

Depending on data available, dates and times will take the form DDMMMYYY THH:MM:SS.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

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

Treatment Group	For Tables, Graphs and Listings
RPL554 150 µg double blind	RPL554 150µg
RPL554 500 µg double blind	RPL554 500µg
RPL554 1500 µg double blind	RPL554 1500µg
RPL554 3000 µg double blind	RPL554 3000µg
Placebo	Placebo
Non-randomized (where applicable)	Non-randomized

PRESENTATION OF TREATMENT SEQUENCES

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

Treatment Group	For Tables, Graphs and Listings
RPL554 150 mcg db/RPL554 1500 mcg db/ RPL554 3000 mcg db /RPL554 500 mcg db/Placebo	Seq 1

Treatment Group	For Tables, Graphs and Listings
RPL554 150 mcg db/ RPL554 3000 mcg db /Placebo/RPL554 500 mcg db/RPL554 1500 mcg db	Seq 2
RPL554 500 mcg db/ RPL554 3000 mcg db /RPL554 150 mcg db/Placebo/RPL554 1500 mcg db	Seq 3
RPL554 500 mcg db/RPL554 150 mcg db/RPL554 1500 mcg db/Placebo/ RPL554 3000 mcg db	Seq 4
RPL554 1500 mcg db/RPL554 500 mcg db/Placebo/RPL554 3000 mcg db/RPL554 150 mcg db	Seq 5
RPL554 1500 mcg db/Placebo/RPL554 150 mcg db/ RPL554 3000 mcg db /RPL554 500 mcg db	Seq 6
RPL554 3000 mcg db/RPL554 1500 mcg db/RPL554 500 mcg db/RPL554 150 mcg db/Placebo	Seq 7
RPL554 3000 mcg db/Placebo/RPL554 1500 mcg db/ RPL554 150 mcg db /RPL554 500 mcg db	Seq 8
Placebo/RPL554 150 mcg db/RPL554 500 mcg db/RPL554 1500 mcg db/RPL554 3000 mcg db	Seq 9
Placebo/RPL554 500 mcg db/RPL554 3000 mcg db/RPL554 1500 mcg db/RPL554 150 mcg db	Seq 10
Undefined sequence, not mentioned above	Undefined
Non-randomized (where applicable)	Non-randomized

db = double blind

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order, considering there will be 5 treatment periods (1 to 5):

Long Name (default)	Short Name
Screening	Scr
Day 1	Day 1
Day 7	Day 7
End of Study	EOS
Overall (where applicable)	Overall

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), first by active dose [by ascending dose group] and then placebo.
Center-patient ID,
Date (where applicable),
For listings where non-randomized patients are included, these will appear in a category after the randomized treatment groups labeled 'Non-randomized'.

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, Partial or Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known, Partial or Missing	Not TEAE
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

START DATE	STOP DATE	ACTION
		unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
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 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 stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study
	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 and start date <= end of treatment, assign as concomitant

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