16.1.9 Documentation of Statistical Methods

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STATISTICAL ANALYSIS PLAN – PART A

RPL554-MD-201

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

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STATISTICAL ANALYSIS PLAN – PART A SIGNATURE PAGE

Statistical Analysis Plan V2.0 – Part A (Dated 13JAN2021) for Protocol RPL554-MD-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

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1.0	28AUG2019	Nicholas Roubinis/ Jennifer Allsopp	Not Applicable – First Version
1.1	01APR2020	Jennifer Allsopp	Update approver from Verona on signature page from Brian Maurer to Nancy Herje. Update protocol version SAP is based on in Section 1.
1.2	09DEC2020	Jennifer Allsopp	Update approver from Verona on signature page from Nancy Herje.to Tara Rheault
2.0	13JAN2021	Jennifer Allsopp	Add Thomas Bengtsson as an approver for Verona.

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-MD-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 3.0, dated 24DEC2019. 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 pressurized metered dose inhaler (pMDI), 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 pMDI, including effects on peak pulse and heart rate.
- To investigate the bronchodilator effect of single doses of RPL554 administered by pMDI, 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

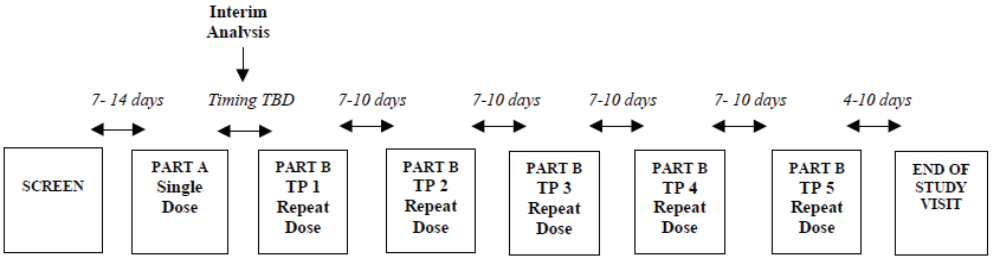
3.1. GENERAL DESCRIPTION

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 pMDI to evaluate the safety and terminal PK profile of a range of doses of RPL554. Five dose levels, 100 µg, 300 µg, 1000 µg, 3000 µg and 6000 µg (single-blind) were selected, covering a 60-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 two study centres in the United Kingdom (UK). At the end of Part A, a data cut-off will be used, selected 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 pMDI to evaluate the steady state efficacy/PD effect of the doses compared to the effect with placebo pMDI. 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



Abbreviations: TBD=to be determined; TP=Treatment Period

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 Part A, a data cut-off will be used, selected data unblinded and analyzed prior to commencing Part B. At the end of Part B, the database will be locked and unblinded, and the full 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

Selected Part A analysis will be performed by IQVIA Biostatistics following the data cut-off. All Part A analyses identified in this SAP will be performed by IQVIA Biostatistics following the Part B 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 data cut-off. 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).

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 planned treatment.

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 100µg
  - RPL554 300µg
  - RPL554 1000µg
  - RPL554 3000µg
  - RPL554 6000µg
  - Placebo

- Baseline value of analyzed variable (covariate).

7.2. MULTICENTER STUDIES

This study will be conducted at 2 study centers, in the UK.

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 (cm)
- Weight (kg)
- 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)
- Pre/Post-bronchodilator FEV_1/FVC
- FEV_1 reversibility test (mL and %)
- Reversibility assessment performed with four puffs of Albuterol
- Met requirements of reversibility test

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 not be coded.
  - Surgical History conditions are defined as those conditions which stop prior to or at Screening.
- 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.

When a rescue medication is used less than 8 or 6 hours (for protocol version 1 or 2 respectively) prior to pre-dose spirometry or between the pre-dose and 12-hour post-dose spirometry a sensitivity analysis will be carried out. For the analysis detailed in Section 15.2.1.2 patients who took rescue medication will be removed. This will only be carried out if at least 1 patient has taken rescue medication less than 8 or 6 hours (for protocol version 1 or 2 respectively) prior to pre-dose spirometry or between the pre-dose and 12-hour post-dose spirometry.

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 RND 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. 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. 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 the assessment at 12-hours is missing, the AUC result will be divided by the actual time of the last collected assessment. If patient misses hours 11 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):

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

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, 100µg, 300µg, 1000µg, 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_{0-4h} and AUC_{0-12h}) 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)	Value ≤ 90 mmHg	Value ≥ 180 mmHg
	Decrease from Baseline of ≥ 40 mmHg	Increase from Baseline of ≥ 40 mmHg
Diastolic blood pressure (mmHg)	Value ≤ 50 mmHg	Value ≥ 110 mmHg
	Decrease from Baseline of ≥ 20 mmHg	Increase from Baseline of ≥ 20 mmHg
Pulse rate (bpm)	Value ≤ 50 bpm	Value ≥ 110 bpm
	Decrease from Baseline of ≥ 30 bpm	Increase from Baseline of ≥ 30 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

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. All PK analysis will be carried out by a third party and will not be detailed in this SAP.

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 4 decimal places, except values <1.000 but >0.9999 will be presented as '>0.9999' (e.g., 0.9999 is presented as >0.9999); and values <0.0001 will be presented as '<0.0001' (e.g., 0.00009 is presented as <0.0001). Rounding will be applied after the <0.0001 and >0.9999 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 100 µg double blind	RPL554 100µg
RPL554 300 µg double blind	RPL554 300µg

Treatment Group	For Tables, Graphs and Listings
RPL554 1000 µg double blind	RPL554 1000µg
RPL554 3000 µg double blind	RPL554 3000µg
RPL554 6000 µg single 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-MD-201

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

AUTHOR: JENNIFER ALLSOPP

VERSION NUMBER AND DATE: V1.0, 13JAN2021

Document: \\ieedc-vnasc01\biosdata\Verona_Pharma\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 SAP v1.0 – Part B

Author: Jennifer Allsopp

Version Number: 1.0

Version Date: 13JAN2021

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

STATISTICAL ANALYSIS PLAN – PART B SIGNATURE PAGE

Statistical Analysis Plan V1.0 – Part B (Dated 13JAN2021) for Protocol RPL554-MD-201.

	Name	Signature	Date
Author:	Jennifer Allsopp	DocuSigned by: Jennifer Allsopp 5E9C02A5CC0A47C...	1/19/2021
Position:	Senior Biostatistician		
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	DocuSigned by: Mark Shaw E2A9CBA2FB8F4B7...	1/19/2021
Position:	Associate Director		
Company:	IQVIA		
Approved By:	Tara Rheault	DocuSigned by: Tara Rheault C1B201F76799452...	1/19/2021
Position:	VP, R&D		
Company:	Verona Pharma		
Approved By:	Thomas Bengtsson	DocuSigned by: Thomas Bengtsson 9570C0A2A259423...	1/19/2021
Position:	Statistical Consultant to Verona		
Company:	StatMind		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	13JAN2021	Jennifer Allsopp	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 B of protocol RPL554-MD-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 3.0, dated 24DEC2019. 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 pMDI (pressurized metered dose 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 pMDI.
- To investigate the bronchodilator effect of RPL554 administered by pMDI, 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 pMDI.
- To evaluate the PK profile of RPL554 administered by pMDI.
- 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 pMDI 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 pMDI to evaluate the safety and terminal PK profile of a range of doses of RPL554. Five dose levels, 100 µg, 300 µg, 1000 µg, 3000 µg and 6000 µg (single-blind) were selected, covering a 60-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 two study centres in the United Kingdom (UK). At the end of Part A, a data cut-off will be used, selected data unblinded and analyzed prior to commencing Part B. Three dose levels, 300 µg, 1000 µg, 3000 µg were selected for Part B, using the same Part A patients. Part B is designed as a complete-block crossover, repeat dose assessment of RPL554 administered by pMDI to evaluate the steady state efficacy/PD effect of the three RPL554 doses compared to the effect with placebo pMDI. The patients in Part B will be expected to complete four treatment periods.

In Part B, the patients from Part A will be randomly assigned in crossover fashion to one of 4 treatment sequences (see Appendix 1; Presentation of Treatment Sequences) each consisting of four 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.

3.2. SCHEDULE OF EVENTS

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

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

The secondary analysis of change from baseline in rescue medication collected via patient diaries will not be carried out as rescue medication data is only collected during the treatment periods. The rescue medication will be summarized by treatment group for the between visit periods.

An initial formal sample size computation was made for Part B. This was a complete block crossover study. Assuming a residual CV of 6% for peak FEV1, it was estimated that 30 evaluable patients would give an 80% power to detect a pairwise difference in peak FEV1 of 4.6%. Assuming a mean baseline FEV1 of 1.5 L this corresponded to a difference of about 70 mL. To account for withdrawals, 36 patients were to be randomized to Part A.

Due to the COVID-19 pandemic, there was a longer than expected period between the completion of Part A and the start of Part B. The long pause made it difficult to re-recruit all patients from Part A and further study conduct with long clinic visits would be more difficult to perform in an ongoing pandemic. It was therefore decided to decrease the patient numbers for Part B to a minimum needed to show efficacy of ensifentrine MDI at doses giving at least 110 mL benefit over placebo on peak FEV1. With 14 fully evaluable patients it was estimated that Part B would have 80% power to fulfill this revised objective.

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 worked with the Part A analysis remained blinded at the time of the Part A data cut-off, an independent unblinded team performed the Part A unblinded analysis. 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). Summary data tables for the Part A dose finding analysis were generated. Individual data listings were not provided to the Verona or IQVIA clinical teams to avoid any potential unblinding.

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 4 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, FVC 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 4 treatment periods per schedule of events (see section 6 of the protocol for schedule details). In the case of dosing errors leading to duplication of treatment period or that treatment during period is undetermined, the patient will be excluded from the completer analysis set. These will be agreed and documented prior to unblinding.

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. 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 (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 4). Baseline for peak FEV_1, FEV_1 $AUC_{0\text{-}4h}$, FEV_1 $AUC_{0\text{-}12h}$ and morning trough is defined as the average of the FEV_1 pre-dose assessment (-60 minutes and -5 minutes) collected on relevant day of each treatment period. 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_{0-12h} 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

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 300µg
  - RPL554 1000µg
  - RPL554 3000µg
  - Placebo
- Treatment period (fixed).
  - Treatment period 1
  - Treatment period 2
  - Treatment period 3
  - Treatment period 4
- Baseline value of analyzed variable (covariate).

7.2. MULTICENTER STUDIES

This study is being conducted at 2 study centers in the UK.

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 and 3 represent increasing dose levels, 0 denoting placebo. Also, let μ_i, i = 0, 1, 2 and 3 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 and 3.

Finally, let p_1, p_2, p_3 denote the marginal p-values obtained from the statistical tests associated with H_1, H_2, H_3 (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 $p_3 \leq \alpha$ reject H_3 and go to Step 2. Otherwise, fail to reject H_3, H_2 and H_1 and stop.
- Step 2: If $p_2 \leq \alpha$ reject H_2 and go to Step 3. Otherwise, fail to reject H_2 and H_1 and stop.
- Step 3: 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 pre-planned 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

Preliminary 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 (cm)
- Weight (kg)
- 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/Rescue Medication Inhaler Dispensed/Rescue Medication Inhaler Weight/Rescue Medication Inhaler Collection/Rescue Medication Diary Dispense/Patient Diary for Rescue Medication 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. Salbutamol/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 6 hours prior to pre-dose spirometry until completion of the 12-hour post-dose 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 in Part B will be primarily provided by patients on paper diaries, which will be transcribed into the eCRF. In the event of missing or incomplete diaries, rescue medication will be determined analytically (by recording the weight of the canister dispensed at the end of Day 1 and start of Day 7 per period). Rescue medication analysis will be described in Section 15.2.1.5.

When a rescue medication is used less than 6 hours prior to study medication a sensitivity analysis will be carried out for the $AUC_{0\text{-}12h}$ FEV_1 analysis detailed in Section 15.2.1.1 and 15.2.1.2 which will remove patients from the treatment periods where rescue medication was taken less than 6 hours prior to study medication or patients who took rescue medication during the 12 hour assessments. This will only be carried out if at least 1 patient has taken rescue medication less than 6-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 pMDIs used per treatment period, as measured on the Drug Exposure eCRF page will be summed to get the total number of pMDIs 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.
- Drug accountability (number of capsules) = Number of pMDIs dispensed – number of pMDIs 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 pMDIs dispensed and returned, as per drug accountability described in Section 13.

15. EFFICACY OUTCOMES

The primary efficacy analyses will be performed for the FAS. Patients withdrawn after only one treatment period will not be included in the analyses of the primary efficacy variable. If the CAS differs from the FAS, the primary efficacy analysis will also be carried out on the CAS.

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 1000µg, RPL554 300µg) 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 1000µg, RPL554 300µg) 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 1000µg, RPL554 300µg, and placebo)

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

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

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_{0-4h} and AUC_{0-12h}.

15.2.1.2. Change in baseline in peak FEV_1 measured after first dose, average FEV_1 of AUC_{0-4h} on Day 1 and average FEV_1 of AUC_{0-12h} 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_{0-4h} FEV_1 and AUC_{0-12h} 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_{0-4h} is set to missing. Similarly, if patient misses hours 11 and 12 then the AUC_{0-12h} 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 patients 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. Rescue medication use during treatment periods (Secondary variable 9)

Use of medication per treatment period is calculated as the mean use daily over the treatment period, (Day 1 to Day 7) calculated only based on the days data was recorded/verified in the patient diary for rescue mediation.
If less than 4 days of data are available for the treatment period, the weekly mean is set to missing, e.g. if data is entered for less than 4 days between Day 1 and Day 7 then no result will be presented for that treatment period. This will be documented in the "Rescue Medication Diary Dispense" page of the eCRF, as well as in the "Patient Diary for Rescue Medication" entry.
The rescue medication use will be confirmed in the diary using the following rules:

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

Rescue medication use, in terms of weight (mcg) of rescue medication during the treatment periods will be collected from the Rescue Medication Inhaler Dispensed, Rescue Medication Inhaler Collected and Rescue Medication

Inhaler Weight eCRF pages and will be summarized by treatment group in a listing.

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, 300µg, 1000µg and 3000µg and placebo)
PERIOD = treatment period (treatment period 1, 2, 3, and 4)
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 using hierarchical testing. 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, 300µg, 1000µg 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 will be presented 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 $AUC_{0\text{-}12h}$ 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 performed by pairwise comparisons of RPL554 doses (ie, 1000µg vs 300µg, and 3000µg vs 1000µg) using ANCOVA models in the same ways as the primary endpoint detailed in Section 15.1.3.

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 1 and 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 in Part B, 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

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, 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)	Value ≤ 90 mmHg	Value ≥ 180 mmHg
	Decrease from Baseline of ≥ 40 mmHg	Increase from Baseline of ≥ 40 mmHg
Diastolic blood pressure (mmHg)	Value ≤ 50 mmHg	Value ≥ 110 mmHg
	Decrease from Baseline of ≥ 20 mmHg	Increase from Baseline of ≥ 20 mmHg
Pulse rate (bpm)	Value ≤ 50 bpm	Value ≥ 110 bpm
	Decrease from Baseline of ≥ 30 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 line size.

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 <1.0000 but >0.9999 will be presented as '>0.9999' (e.g., 0.9998 is presented as >0.9999); and values <0.0001 will be presented as '<0.0001' (e.g., 0.0000 is presented as <0.0001). Rounding will be applied after the <0.0001 and >0.9999 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 300 µg double blind	RPL554 300µg
RPL554 1000 µg double blind	RPL554 1000µg
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 300 mcg db/RPL554 3000 mcg db/Placebo/RPL554 1000 mcg db	Seq 1

Treatment Group	For Tables, Graphs and Listings
RPL554 1000 mcg db/Placebo/RPL554 3000 mcg db/RPL554 300 mcg db	Seq 2
RPL554 3000 mcg db/RPL554 1000 mcg db/RPL554 300 mcg db/Placebo	Seq 3
Placebo/RPL554 300 mcg db/RPL554 1000 mcg db/RPL554 3000 mcg db	Seq 4
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 4 treatment periods (1 to 4):

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 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

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

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
	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

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
	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

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TABLES, LISTINGS AND FIGURES SHELLS – PART A

RPL554-MD-201

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

AUTHOR: NICHOLAS ROUBINIS/JENNIFER ALLSOPP

VERSION NUMBER AND DATE: V2.0, 13JAN2021

TABLES, LISTINGS AND FIGURES SHELLS – PART A SIGNATURE PAGE

Tables, Listings and Figures Shells V2.0 – Part A (Dated 13JAN2021) for Protocol RPL554-MD-201.

	Name	Signature	Date
Author:	Jennifer Allsopp	DocuSigned by: Jennifer Allsopp 5E9C02A5CC0A47C...	1/19/2021
Position:	Senior Biostatistician		
Company:	IQVIA		

Upon review of this document, the undersigned approves this version of the Tables, Listings and Figures Shells – Part A, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved by:	Mark Shaw	DocuSigned by: Mark Shaw E2A9CBA2FB8F4B7...	1/19/2021
Position:	Manager, Biostatistics		
Company:	IQVIA		
Customer Representative			
Approved by:	Tara Rheault	DocuSigned by: Tara Rheault C1B201F76799452...	1/19/2021
Position:	VP, R&D		
Company:	Verona Pharma		
Approved by:	Thomas Bengtsson	DocuSigned by: Thomas Bengtsson 9570C0A2A259423...	1/19/2021
Position:	Statistical Consultant to Verona		
Company:	StatMind		

Modification History

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	27SEP2019	Nicholas Roubinis/ Jennifer Allsopp	Not Applicable – First Draft Version
1.1	04MAY2020	Jennifer Allsopp	1. Update figure numbering from Figure 14.2.5-14.2.8 to 14.3.1-14.3.4. 2. Update listing numbering from Listing 16.2.2.1 to 16.2.3.1. 3. Update lisitng numbering from Listing 16.2.3.1 to 16.2.2.1. 4. Remove DOB from the demographic listing. 5. Update customer representative from Brian Maurer to Nancy Herje. 6. Update footnotes following review of Part A dose finding analysis. 7. Add shell for F14.2.5 – requested as part of the additional dose finding outputs.
1.2	09DEC2020	Jennifer Allsopp	1. Update customer representative from Nancy Herje to Tara Rheault. 2. Aded footnote to table 14.1.5.1 detailing how patients met protocol requirements of the reversibility test. 3. Update title for tables 14.3.5 and 14.3.9 to clarify that the tables are displaying discontinuation of study rather than study medication. 4. Added column for patients who discontinued between Part A and Part B to listing 16.2.1.1.
2.0	13JAN2021	Jennifer Allsopp	Add Thomas Bengtsson as an approver for Verona.

Table of Contents

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Date: 13JAN2021

Document: Z:\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 TLF Shells v2.0 - Part A
Version: 2.0
Author: Nicholas Roubinis/Jennifer Allsopp
Date: 13JAN2021

Tables

14.1 Demographic Data

Table 14.1.1 Patient Disposition (All Patients Enrolled in Part A)

Verona Pharma — Page X of Y

Protocol: RPL554-MD-201 — Part A

RPL554 pressurised Metered Dose Inhaler

Table 14.1.1

Patient Disposition

(All Patients Enrolled in Part A)

Description, n (%)	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)	Overall (N=XX)
Number of patients enrolled							xx
Screen failures							xx
Number of patients randomized	xx (100.0)	xx (100.0)	xx (100.0)	xx (100.0)	xx (100.0)	xx (100.0)	xx (100.0)
Number of patients treated	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of patients who completed Part A	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of patients who discontinued Part A	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of patients who discontinued between Part A and Part B							
Primary reason for early study discontinuation							
Adverse event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pregnancy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol violation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Physician decision	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Study terminated by sponsor	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal by patient	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Document: Z:\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 TLF Shells v2.0 - Part A

Version: 2.0

Author: Nicholas Roubinis/Jennifer Allsopp

Date: 13JAN2021

n = number of patients. N = Number of patients randomized. % = percentage of patients calculated relative to the total number of patients in the All Randomized Analysis Set. Percentage for early discontinuation reasons is calculated based on the number of patients who had early discontinuation data.

Source: Listing 16.2.1.1

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Table 14.1.2

Analysis Sets

(All Patients Enrolled in Part A)

Analysis Set, n (%)	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)	Overall (N=XX)
All Enrolled Analysis Set	xx	xx	xx	xx	xx	xx	xx
All Randomized Analysis Set	xx (100.0)	xx (100.0)	xx (100.0)	xx (100.0)	xx (100.0)	xx (100.0)	xx (100.0)
Safety Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Full Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pharmacokinetics Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	NA	xx (xx.x)

FEV_1: Forced expiratory volume in one second. NA: Not applicable. n = number of patients. N = number of patients randomized. % = percentage of patients calculated relative to the total number of patients in All Randomized Analysis Set. All Enrolled Analysis Set: All patients enrolled. All Randomized Analysis Set: All patients enrolled who are randomized. Safety Analysis Set: Randomized patients who received the single dose of study medication. Full Analysis Set: Patients included in the Safety Analysis Set with sufficient data to compute the pharmacodynamic parameters (FEV_1 measurement pre-dose and at least one post-dose). Pharmacokinetics Analysis Set: Patients included in the All Randomized Analysis Set who have a blood sampling performed after at least one dose of study medication and pharmacokinetic parameter data.

Source: Listing 16.2.2.1

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Table 14.1.3 Critical/Major/Minor Protocol Deviations (ALL Randomised Analysis Set in Part A)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Table 14.1.3

Critical/Major/Minor Protocol Deviations

(All Randomized Analysis Set in Part A)

Severity/ Deviation type	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)	Overall (N=XX)
Patients with at least one critical/major/minor protocol deviation, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Critical	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Type 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Type 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…							
Major							
…							

CTMS: Clinical trial management system. n = number of patients. N = Number of patients in the analysis set. % = percentage of patients calculated relative to the total number of patients in the analysis set. Protocol deviations were obtained from CTMS.

Source: Listing 16.2.3.1

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes:

Deviation types are sorted in descending order of frequency of the Overall column. A patient may have multiple critical/major/minor protocol deviations within and is counted once at each level of summarization.

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Version: 2.0

Author: Nicholas Roubinis/Jennifer Allsopp

Date: 13JAN2021

Table 14.1.4.1 Demographic Characteristics (All Randomized Analysis Set in Part A)
Verona Pharma Page X of Y
Protocol: RPL554-MD-201 Part A
RPL554 pressurised Metered Dose Inhaler

Table 14.1.4.1

Demographic Characteristics

(All Randomized Analysis Set in Part A)

Variable/ Category	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)	Overall (N=XX)
Age (years)							
n	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Sex, n (%)							
Male	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Female	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Childbearing potential, n (%) *							
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Primary race, n (%)							
American Indian or Alaska	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Asian	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black or African American	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Hawaiian or Other Pacific Islander	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
White	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

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Version: 2.0
Author: Nicholas Roubinis/Jennifer Allsopp Date: 13JAN2021

Table 14.1.4.1

Demographic Characteristics

(All Randomized Analysis Set in Part A)

Variable/ Category	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)	Overall (N=XX)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity, n (%)							
Hispanic or Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
African American/African Heritage	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian-Central/South Asian Heritage	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian-East Asian Heritage	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian-Southeast Asian Heritage	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
White-White/Caucasian/European Heritage	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not reported	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Weight (kg)							
n	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Height (cm)							
n	xx	xx	xx	xx	xx	xx	xx

Table 14.1.4.1

Demographic Characteristics

(All Randomized Analysis Set in Part A)

Variable/ Category	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)	Overall (N=XX)
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
BMI (kg/m^2)							
n	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

BMI: Body Mass Index. SD: Standard deviation. n = number of patients. N = Number of patients in the analysis set. % = percentage of patients calculated relative to the total number of patients in the analysis set. * % = Percentage for childbearing potential calculated relative to the total number of female patients in the analysis set. Age (years) = As calculated relative to informed consent date. BMI (kg/m^2) = weight (kg)/ height $(m)^2$.

Source: Listing 16.2.4.1

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes:

Print all statistics and categories even if they are empty, except for the row of missings which will only be shown if present and is not shown in the shell here.

Table 14.1.4.2 Demographic Characteristics (Safety Analysis Set in Part A)

DM002: This output uses shell DM001 [Table 14.1.4.1]

Programming Notes:
Print if the number of patients in the SAF analysis set is different to the RND analysis set.

Table 14.1.4.3 Demographic Characteristics (Full Analysis Set in Part A)

DM003: This output uses shell DM001 [Table 14.1.4.1]

Programming Notes:
Print if the number of patients in the SAF analysis set is different to the RND analysis set.

Table 14.1.4.4 Demographic Characteristics (Pharmacokinetics Analysis Set in Part A)

DM004: This output uses shell DM001 [Table 14.1.4.1]

Programming Notes:
Print if the number of patients in the SAF analysis set is different to the RND analysis set.
Do not present Placebo treatment group as Placebo is not included for Pharmacokinetics analysis set.

Table 14.1.5.1 Screening Disease Characteristics (All Randomized Analysis Set in Part A)
Verona Pharma Page X of Y
Protocol: RPL554-MD-201 Part A
RPL554 pressurised Metered Dose Inhaler

Table 14.1.5.1

Screening Disease Characteristics

(All Randomized Analysis Set in Part A)

Variable/ Statistics	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)	Overall (N=XX)
Pre-bronchodilator FEV_1 (L)							
n	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Pre-bronchodilator FEV_1 (% of predicted normal)							
n	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Post-bronchodilator FEV_1 (L)							
n	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

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Author: Nicholas Roubinis/Jennifer Allsopp Date: 13JAN2021

Table 14.1.5.1

Screening Disease Characteristics

(All Randomized Analysis Set in Part A)

Variable/ Statistics	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)	Overall (N=XX)
Post-bronchodilator FEV_1 (% of predicted normal)							
n	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
FEV_1 reversibility (mL)							
n	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
FEV_1 reversibility (%)							
n	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

Table 14.1.5.1

Screening Disease Characteristics

(All Randomized Analysis Set in Part A)

Variable/ Statistics	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)	Overall (N=XX)
Pre-bronchodilator FVC (L)							
n	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Post-bronchodilator FVC (L)							
n	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Pre-bronchodilator FEV_1/FVC							
n	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Post-bronchodilator FEV_1/FVC							

Table 14.1.5.1

Screening Disease Characteristics

(All Randomized Analysis Set in Part A)

Variable/ Statistics	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)	Overall (N=XX)
n	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Reversibility assessment performed with four puffs of albuterol, n (%)							
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Met protocol requirements of reversibility test [a], n (%)							
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

FEV_1: Forced expired volume in 1 second. FVC: Forced vital capacity. SD: Standard deviation. n = number of patients. N = Number of patients in the analysis set. % = percentage of patients calculated relative to the total number of patients in the analysis set. Pre-, post-bronchodilator and reversibility values are the results of the screening reversibility test.
[a] Patients meet the protocol requirements of the reversibility test by demonstatating >=150 mL increase from pre-bronchodilator FEV_1.

Source: Listing 16.2.4.2

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Version: 2.0
Author: Nicholas Roubinis/Jennifer Allsopp
Date: 13JAN2021

Table 14.1.5.1
Screening Disease Characteristics
(All Randomized Analysis Set in Part A)

Variable/ Statistics	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)	Overall (N=XX)

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Table 14.1.5.2 Screening Disease Characteristics (Safety Analysis Set in Part A)

DM006: This output uses shell DM005 [Table 14.1.5.1]

Programming Notes:
Print if the number of patients in the SAF analysis set is different to the RND analysis set.

Table 14.1.5.3 Screening Disease Characteristics (Full Analysis Set in Part A)

DM007: This output uses shell DM005 [Table 14.1.5.1]

Programming Notes:
Print if the number of patients in the SAF analysis set is different to the RND analysis set.

Table 14.1.5.4 Screening Disease Characteristics (Pharmacokinetics Analysis Set in Part A)

DM008: This output uses shell DM005 [Table 14.1.5.1]

Programming Notes:
Print if the number of patients in the SAF analysis set is different to the RND analysis set.
Do not present Placebo treatment group as Placebo is not included for Pharmacokinetics analysis set.

Table 14.1.6 COPD and Smoking History (All Randomized Analysis Set in Part A)
Verona Pharma Page X of Y
Protocol: RPL554-MD-201 Part A
RPL554 pressurised Metered Dose Inhaler

Table 14.1.6

COPD and Smoking History

(All Randomized Analysis Set in Part A)

Variable/ Category	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)	Overall (N=XX)
Duration of COPD (years) (time since diagnosis)							
n	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Patient known to have Chronic Bronchitis, n (%)							
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Patient known to have Emphysema, n (%)*							
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Smoking status, n (%)							
Current Smokers	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ex-smokers	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of packs per day							

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Author: Nicholas Roubinis/Jennifer Allsopp Date: 13JAN2021

Table 14.1.6

COPD and Smoking History

(All Randomized Analysis Set in Part A)

Variable/ Category	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)	Overall (N=XX)
n	xx	xx	xx	xx	xx	xx	xx
Mean	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
SD	xx.xxxx	xx.xxxx	xx.xxxx	xx.xxxx	xx.xxxx	xx.xxxx	xx.xxxx
Median	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Min, Max	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx	xx.xx, xx.xx
Number of years smoking							
n	xx	xx	xx	xx	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Smoking exposure (pack-years)							
n	xx	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

COPD: Chronic obstructive pulmonary disease. SD: Standard deviation. n = number of patients. N = Number of patients in the analysis set. % = percentage of patients calculated relative to the total number of patients in the analysis set. Number of packs per day = average consumption during their smoking duration. Smoking exposure (pack-years) = number of packs per day x number of years smoking, for patients with a smoking history or a current smoker. Duration of COPD (years) (time since diagnosis) = Randomization date - first

Table 14.1.6

COPD and Smoking History

(All Randomized Analysis Set in Part A)

Variable/ Category	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)	Overall (N=XX)

COPD diagnosis date. * Patients known to have emphysema will potentially overlap with patients known to have chronic bronchitis.

Source: Listing 16.2.4.3

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

14.2 Efficacy

Secondary Efficacy

Table 14.2.1 FEV1 by Treatment and Timepoint Pre- and Post- Single Dose (Full Analysis Set in Part A)

Table 14.2.1

FEV1 by Treatment and Timepoint Pre- and Post- Single Dose

(Full Analysis Set in Part A)

			Statistics					
Timepoint	Treatment group	Category	n	Mean	SD	Minimum	Median	Maximum
1-hour pre-dose	RPL554 100µg (N=xx)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
	RPL554 300µg (N=xx)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
	RPL554 1000µg (N=xx)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
	RPL554 3000µg (N=xx)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
	RPL554 6000µg (N=xx)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
	Placebo (N=xx)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
Immediately pre-dose	RPL554 100µg (N=xx)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
…	…	…	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
5 minutes post-dose	RPL554 100µg (N=xx)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
		Pre-dose	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
		Change from Pre-dose	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
…	…	…	…	…	…	…	…	…

SD: Standard deviation. FEV_1: Forced expired volume in 1 second. n = Number of patients who have an assessment available pre-dose and the relevant post-dose assessment timepoint (Pre-dose and Change from Pre-dose). N = Number of patients in the analysis set. Pre-dose FEV_1 is defined as the average of the FEV_1 pre-dose assessments collected on Day 1 (within 60 and 5 minutes). Change from Pre-dose: Post-dose assessment - Pre-dose.

Source: Listing 16.2.6.1

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Nicholas Roubinis/Jennifer Allsopp Date: 13JAN2021

Table 14.2.1

FEV1 by Treatment and Timepoint Pre- and Post- Single Dose

(Full Analysis Set in Part A)

			Statistics					
Timepoint	Treatment group	Category	n	Mean	SD	Minimum	Median	Maximum

Programming Notes:

Display for the following days and timepoints, relative to dosing: 1 hour pre-dose and immediately pre-dose, 5 (± 2), 15 (± 5) and 30 minutes (± 10) and 1, 1.5, 2, 4, 8, 11 and 12 hours (the latter assessments all ± 15 minutes).

Table 14.2.2 Change from Baseline FEV_1 to Average FEV_1 (over 4 hours) After Single Dose (Full Analysis Set in Part A)

EFF006: This output uses shell EFF004 [Table 14.2.4]

ANCOVA: Analysis of covariance. CFB: Change from Baseline. CI: Confidence interval. FEV_1: Forced expiratory volume in 1 second. GeoMean: Geometric mean. GeoMean Ratio: Geometric mean ratio to baseline. SD: Standard deviation. N = Number of patients in the analysis set. Baseline: average of the FEV_1 pre-dose assessments collected on Day 1 (within 60 and 5 minutes). Change from Baseline: Ratio of (Post-dose assessment - Pre-dose), as each assessment will be log-transformed prior to analysis. [a] number of patients with valid values at baseline and timepoints. [b] ANCOVA model is used to model the change from baseline using baseline FEV_1 as a continuous fixed effect and planned treatment as categorical fixed effects. [c] number of patients with at least one on treatment value who contributed to the model estimation. * Indicates a significant p-value (<0.05).

Source: Listing 16.2.6.2

Programming Notes

Replace footnotes in original shell with those listed above

Table 14.2.3 Change from Baseline FEV_1 to Average FEV_1 (over 12 hours) After Single Dose (Full Analysis Set in Part A)

EFF007: This output uses shell EFF004 [Table 14.2.4]

ANCOVA: Analysis of covariance. CFB: Change from Baseline. CI: Confidence interval. FEV_1: Forced expiratory volume in 1 second. GeoMean: Geometric mean. GeoMean Ratio: Geometric mean ratio to baseline. SD: Standard deviation. N = Number of patients in the analysis set. Baseline: average of the FEV_1 pre-dose assessments collected on Day 1 (within 60 and 5 minutes). Change from Baseline: Ratio of (Post-dose assessment - Pre-dose), as each assessment will be log-transformed prior to analysis. [a] number of patients with valid values at baseline and timepoints. [b] ANCOVA model is used to model the change from baseline using baseline FEV_1 as a continuous fixed effect and planned treatment as categorical fixed effects. [c] number of patients with at least one on treatment value who contributed to the model estimation. * Indicates a significant p-value (<0.05).

Source: Listing 16.2.6.2

Programming Notes

Replace footnotes in original shell with those listed above

Table 14.2.3a Change from Baseline FEV_1 to Average FEV_1 (over 12 hours) After Single Dose - Sensitivity Analysis (Full Analysis Set in Part A)

EFF007: This output uses shell EFF004 [Table 14.2.4]

ANCOVA: Analysis of covariance. CFB: Change from Baseline. CI: Confidence interval. FEV_1: Forced expiratory volume in 1 second. GeoMean: Geometric mean. GeoMean Ratio: Geometric mean ratio to baseline. SD: Standard deviation. N = Number of patients in the analysis set. Baseline: average of the FEV_1 pre-dose assessments collected on Day 1 (within 60 and 5 minutes). Change from Baseline: Ratio of (Post-dose assessment - Pre-dose), as each assessment will be log-transformed prior to analysis. [a] number of patients with valid values at baseline and timepoints. [b] ANCOVA model is used to model the change from baseline using baseline FEV_1 as a continuous fixed effect and planned treatment as categorical fixed effects. [c] number of patients with at least one on treatment value who contributed to the model estimation. * Indicates a significant p-value (<0.05).

Source: Listing 16.2.6.2

Programming Notes

Replace footnotes in original shell with those listed above
Only include if at least 1 subject has taken rescue medication less than 6 hours prior to spirometry (ANL02FL="Y")

Table 14.2.4 Change from Baseline FEV_1 to Peak FEV_1 (over 4 hours) After Single Dose (Full Analysis Set in Part A)
Verona Pharma Page X of Y
Protocol: RPL554-MD-201 Part A
RPL554 pressurised Metered Dose Inhaler

Table 14.2.4

Change from Baseline FEV1 to Peak FEV1 (over 4 hours) After Single Dose

(Full Analysis Set in Part A)

	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)
Baseline FEV_1 (L)						
n [a]	xx	xx	Xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Peak FEV_1 (L)						
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
CFB FEV_1						
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Estimates from ANCOVA [b]						
n [c]	Xx	xx	xx	xx	xx	xx
GeoMean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
95% CI for GeoMean	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
Comparisons Against Placebo						

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Author: Nicholas Roubinis/Jennifer Allsopp Date: 13JAN2021

Table 14.2.4

Change from Baseline FEV1 to Peak FEV1 (over 4 hours) After Single Dose

(Full Analysis Set in Part A)

	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)
Treatment Effect - ANCOVA						
GeoMean Ratio	xx.x	xx.x	xx.x	xx.x	xx.x	
95% CI for GeoMean Ratio	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	
p-value	x.xxxx	x.xxxx	x.xxxx	x.xxxx	x.xxxx	
Comparisons Against RPL554 doses						
Treatment Effect - ANCOVA		Comparison Against RPL554 100µg	Comparison Against RPL554 300µg	Comparison Against RPL554 1000µg	Comparison Against RPL554 3000µg	
GeoMean Ratio		xx.x	xx.x	xx.x	xx.x	
95% CI for GeoMean Ratio		(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	
p-value		x.xxxx	x.xxxx	x.xxxx	x.xxxx	

ANCOVA: Analysis of covariance. CFB: Change from Baseline. CI: Confidence interval. FEV_1: Forced expiratory volume in 1 second. GeoMean: Geometric mean. GeoMean Ratio: Geometric mean ratio to baseline. SD: Standard deviation. N = Number of patients in the analysis set. Baseline: average of the FEV_1 pre-dose assessments collected on Day 1 (within 60 and 5 minutes). Change from Baseline: Ratio of (Post-dose assessment – Pre-dose), as each assessment will be log-transformed prior to analysis. [a] number of patients with valid values at baseline and timepoints. [b] ANCOVA model is used to model the change from baseline using baseline FEV_1 as a continuous fixed effect and planned treatment as categorical fixed effects. [c] number of patients with at least one on treatment value who contributed to the model estimation. * Indicates a significant p-value (<0.05).

Source: Listing 16.2.6.2

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

14.3 Safety
Adverse Event

Table 14.3.1 Treatment-emergent Adverse Events Summary (Safety Analysis Set in Part A)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Table 14.3.1
Treatment-emergent Adverse Events Summary
(Safety Analysis Set in Part A)

Variable/ Category	RPL554 100µg N=xx n (%) E	RPL554 300µg N=xx n (%) E	RPL554 1000µg N=xx n (%) E	RPL554 3000µg N=xx n (%) E	RPL554 6000µg N=xx n (%) E	Placebo N=xx n (%) E	Overall N=xx n (%) E
Any TEAE	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Any TEAE related to study medication	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Any TEAE leading to studydiscontinuation	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Any TEAEs classified by maximum severity							
Severe	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Moderate	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Mild	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Any serious TEAE	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Any serious TEAE related to study medication	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Any serious TEAE leading to studydiscontinuation	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Any serious TEAEs classified by maximum severity							
Severe	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Moderate	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Mild	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx

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Author: Nicholas Roubinis/Jennifer Allsopp
Date: 13JAN2021

Table 14.3.1

Treatment-emergent Adverse Events Summary

(Safety Analysis Set in Part A)

Variable/ Category	RPL554 100µg N=xx n (%) E	RPL554 300µg N=xx n (%) E	RPL554 1000µg N=xx n (%) E	RPL554 3000µg N=xx n (%) E	RPL554 6000µg N=xx n (%) E	Placebo N=xx n (%) E	Overall N=xx n (%) E
Any TEAE leading to death	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx

TEAE: Treatment-emergent adverse event. n = Number of patients with at least one TEAE in each category. E = Number of mentions (events) in each category. N = Number of patients in the analysis set. % = percentage of patients calculated relative to the total number of patients in the analysis set. TEAE = All AEs that started or worsened in severity on or after the single dose of study medication, based on the investigator assessment of severity. TEAEs with a missing relationship to study medication were regarded as related to study medication. TEAEs starting after the single dose of study medication with a missing severity were classified as severe.

Source: Listing 16.2.7.1

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Table 14.3.2 Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set in Part A)
Verona Pharma Page X of Y
Protocol: RPL554-MD-201 Part A
RPL554 pressurised Metered Dose Inhaler

Table 14.3.2

Treatment-emergent Adverse Events by System Organ Class and Preferred Term

(Safety Analysis Set in Part A)

System Organ Class Preferred Term [a]	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)
Patients with at least one TEAE	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
System Organ Class #1	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Preferred Term #1	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Preferred Term #2	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
System Organ Class #2	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Preferred Term #1	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Preferred Term #2	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
…						

PT: Preferred term. SOC: System organ class. TEAE: Treatment-emergent adverse event. n = number of patients with at least one TEAE in each category. E = Number of mentions (events) in each category. N = Number of patients in the analysis set. % = percentage of patients calculated relative to the total number of patients in the analysis set. TEAE = All AEs that started or worsened in severity on or after the first dose of study medication, based on the investigator assessment of severity. Each patient is counted once for each applicable specific AE, and a patient with multiple AEs within a SOC is counted once for that SOC. [a] SOCs and PTs are coded using the MedDRA (Version 21.0).

Source: Listing 16.2.7.1

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes:
SOCs and PTs within each SOC are sorted in descending order of percentage in the highest dose-level group.

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Table 14.3.3 Treatment-emergent Adverse Events Related to Study Medication by System Organ Class and Preferred Term (Safety Analysis Set in Part A)

AE003: This output uses shell AE002 [Table 14.3.2]

PT: Preferred term. SOC: System organ class. TEAE: Treatment-emergent adverse event related to study medication. n = number of patients with at least one related TEAE in each category. E = Number of mentions (events) in each category. N = Number of patients in the analysis set. % = percentage of patients calculated relative to the total number of patients in the analysis set. TEAE = All AEs that started or worsened in severity on or after the first dose of study medication, based on the investigator assessment of related or not. Each patient is counted once for each applicable specific AE, and a patient with multiple AEs within a SOC is counted once for that SOC. [a] SOCs and PTs are coded using the MedDRA (Version 21.0).

Source: Listing 16.2.7.1

Programming Notes:

Replace footnotes in original shell with those listed above

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Date: 13JAN2021

Table 14.3.4 Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Analysis Set in Part A)

Table 14.3.4

Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity

(Safety Analysis Set in Part A)

System Organ Class (%) Preferred Term, n (%) [a]	Maximum Severity	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)
Patients with at least one TEAE, n (%)	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class #1	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #1	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #2	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class #1	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	…	…	…	…	…	…	…

PT: Preferred term. SOC: System organ class. TEAE: Treatment-emergent adverse event. n = number of patients with at least one TEAE in each category. N = Number of patients in the analysis set. % = percentage of patients calculated relative to the total number of patients in the analysis set. TEAE = All AEs that started or worsened in severity on or after the first dose of study medication, based on the investigator assessment of severity. Each patient is counted once for each applicable specific TEAE at the maximum severity and a patient with multiple TEAEs within a SOC is counted once for that SOC at the maximum severity. [a] SOCs and PTs are coded using MedDRA (Version 21.0). SOCs and PTs within each SOC are sorted in descending order of percentage of severe AEs (then

Table 14.3.4

Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity

(Safety Analysis Set in Part A)

System Organ Class (%) Preferred Term, n (%) [a]	Maximum Severity	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)

moderate and mild AEs). TEAEs starting after the first dose of study medication with a missing severity will be classified as severe.

Source: Listing 16.2.7.1

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Table 14.3.5 Treatment-emergent Adverse Events Leading to Discontinuation of Study by System Organ Class and Preferred Term (Safety Analysis Set in Part A)

AE005: This output uses shell AE004 [Table 14.3.2]

Programming Notes
Use the same template of table 14.3.2, selecting only the TEAEs leading to discontinuation of study and update "Any TEAE" to "Any TEAE leading to discontinuation of study".
Update source footnote to "Source: Listing 16.2.7.2".

Table 14.3.6 Serious treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set in Part A)

AE006: This output uses shell AE002 [Table 14.3.2]

Programming Notes

Replace footnotes in original shell updating "Patients with at least one TEAE" to "Patients with at least one serious TEAE".
Update source footnote to "Source: Listing 16.2.7.4".

Table 14.3.7 Serious treatment-emergent Adverse Events Related to Study Medication by System Organ Class and Preferred Term (Safety Analysis Set in Part A)

AE007: This output uses shell AE003 [Table 14.3.3]

Programming Notes

Use the same template of Table 14.3.3, selecting only the serious TEAEs and update "Patients with at least one TEAE" to "Patients with at least one serious TEAE".
Update source footnote to "Source: Listing 16.2.7.4".

Table 14.3.8 Serious treatment-emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity (Safety Analysis Set in Part A)

AE008: This output uses shell AE004 [Table 14.3.4]

Programming Notes

Use the same template of Table 14.3.4, selecting only the serious TEAEs and update "Patients with at least one TEAE" to "Patients with at least one serious TEAE".
Update source footnote to "Source: Listing 16.2.7.4".

Table 14.3.9 Serious treatment-emergent Adverse Events Leading to Discontinuation of Sutdy by System Organ Class and Preferred Term (Safety Analysis Set in Part A)

AE009: This output uses shell AE005 [Table 14.3.5]

Programming Notes

Use the same template of Table 14.3.5, selecting only the serious TEAEs and update "Any TEAE leading to discontinuation of study" to "Any serious TEAE leading to discontinuation of study".
Update source footnote to "Source: Listing 16.2.7.4".

Table 14.3.10 Treatment-emergent Adverse Events with Outcome of Death by System Organ Class and Preferred Term (Safety Analysis Set in Part A)

AE010: This output uses shell AE002 [Table 14.3.2]

Programming Notes

Replace footnotes in original shell updating "Patients with at least one TEAE" to "Patients with a TEAE with outcome of death".
Update source footnote to "Source: Listing 16.2.7.3".

Laboratory

Table 14.3.11 Hematology Laboratroy Data at Screening (Safety Analysis Set in Part A)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Table 14.3.11

Hematology Laboratory Data at Screening

(Safety Analysis Set in Part A)

Laboratory Test (unit) Statistics	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)
Test #1 (unit)						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Test #2 (unit)	…	…	…	…	…	…

SD: Standard deviation. n = Number of patients with a screening value. N = Number of patients in the analysis set.

Source: Listing 16.2.8.1

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes:
At Screening, blood samples will be taken and tested at the laboratory for the following hematology laboratory tests: Hemoglobin, hematocrit, total white cell count, leukocyte differential count and platelet count. Present in alphabetical order.

Document: Z:\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 TLF Shells v2.0 - Part A
Version: 2.0

Author: Nicholas Roubinis/Jennifer Allsopp
Date: 13JAN2021

Table 14.3.12 Biochemistry Laboratroy Data at Screening (Safety Analysis Set in Part A)

LB002: This output uses shell LB001 [Table 14.3.11]

Programming Notes

Repeat 14.3.11 for Biochemistry (includes creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine transaminase, gamma-glutamyl transferase, lactate dehydrogenase, creatine kinase, thyroid stimulating hormone, triiodothyronine and thyroxine, glucose, potassium, sodium, and calcium. Present in alphabetical order.
Update source footnote to "Source: Listing 16.2.8.2".

Table 14.3.13 Urinalysis Laboratroy Data at Screening (Safety Analysis Set in Part A)
Verona Pharma Page X of Y
Protocol: RPL554-MD-201 Part A
RPL554 pressurised Metered Dose Inhaler

Table 14.3.13

Urinalysis Laboratory Data at Screening

(Safety Analysis Set in Part A)

Laboratory Test (unit) Category	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)
Test #1 (unit)						
Negative	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Trace	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1+	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2+	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3+	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
4+	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Test #2 (unit)	…	…	…	…	…	…

n = Number of patients with a Screening value. N = Number of patients in the analysis set. % = Percentage of patients in each category relative to the total number of patients in the analysis set, with assessments at Screening.

Source: Listing 16.2.8.3

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes:
At Screening, samples will be taken and tested at the laboratory for the following Urinalyis laboratory tests: Leukocytes esterase, blood, ketones, bilirubin, urobilinogen, protein and glucose. If urinalysis on Dipstick is positive for leucocytes and/or blood/hemoglobin, a microscopic examination including erythrocytes, leucocytes, bacteria, casts, epithelial cells and crystals). Present in alphabetical order.

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Version: 2.0
Author: Nicholas Roubinis/Jennifer Allsopp Date: 13JAN2021

Table 14.3.14 Viral Serology Laboratroy Data at Screening (Safety Analysis Set in Part A)

LB008: This output uses shell LB001 [Table 14.3.11]

Programming Notes

Repeat 14.3.13 for Viral Serology (includes [to confirm post-menopausal status where appropriate] follicle-stimulating hormone [FSH]).. Present in alphabetical order.

Update source footnote to "Source: Listing 16.2.8.4".

Document: Z:\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 TLF Shells v2.0 - Part A
Version: 2.0
Author: Nicholas Roubinis/Jennifer Allsopp
Date: 13JAN2021

Table 14.3.15 Hematology Laboratroy Data at Screening - Normal Reference Ranges (Safety Analysis Set in Part A)
Verona Pharma Page X of Y
Protocol: RPL554-MD-201 Part A
RPL554 pressurised Metered Dose Inhaler

Table 14.3.15

Hematology Laboratory Data at Screening - Normal Reference Ranges

(Safety Analysis Set in Part A)

Laboratory Test/ Reference Range	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)
Test #1 (unit)						
Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Test #2 (unit)	…	…	…	…	…	…

LLN: Lower limit of normal. ULN: Upper limit of normal reference range. n = Number of patients with a Screening value. N = Number of patients in the analysis set. % = Percentage of patients in each category relative to the total number of patients in the analysis set, with assessments at Screening. Reference range classification: Low: < LLN. Normal: >= LLN to <= ULN. High: > ULN.

Source: Listing 16.2.8.1

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes:
At Screening, blood samples will be taken and tested at the laboratory for the following laboratory tests: Hemoglobin, hematocrit, total white cell count, leukocyte differential count and platelet count. Present in alphabetical order.

Document: Z:\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 TLF Shells v2.0 - Part A
Version: 2.0
Author: Nicholas Roubinis/Jennifer Allsopp Date: 13JAN2021

Table 14.3.16 Biochemistry Laboratroy Data at Screening - Normal Reference Ranges (Safety Analysis Set in Part A)

LB004: This output uses shell LB003 [Table 14.3.15]

Programming Notes

Repeat Table 14.3.15 for Biochemistry. Table should present these parameters only: Creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine transaminase, gamma-glutamyl transferase, lactate dehydrogenase, creatine kinase, thyroid stimulating hormone, triiodothyronine and thyroxine, glucose, potassium, sodium, and. Present in alphabetical order.
Update source footnote to "Source: Listing 16.2.8.2".

Table 14.3.17 Urinalysis Laboratroy Data at Screening - Normal Reference Ranges (Safety Analysis Set in Part A)

LB005: This output uses shell LB003 [Table 14.3.15]

Programming Notes

Repeat Table 14.3.15 for Urinalysis, and update category to 'Negative' if the results are 'Normal' or 'Negative', to 'Trace' if the results are 'Trace' and 'Positive' if the results are equal to '1+', '2+', '3+',' or '4+'.
Table should present these parameters only: Leukocytes esterase, occult blood, ketones, bilirubin, urobilinogen, protein and glucose. If urinalysis on Dipstick is positive for leucocytes and/or blood/hemoglobin, a microscopic examination including erythrocytes, leucocytes, bacteria, casts, epithelial cells and crystals. Present in alphabetical order.
Update source footnote to "Source: Listing 16.2.8.3".

Table 14.3.18 Viral Serology Laboratroy Data at Screening (Safety Analysis Set in Part A)

LB009: This output uses shell LB003 [Table 14.3.15]

Programming Notes

Repeat 14.3.13 for Viral Serology (includes human immunodeficiency virus, hepatitis B and hepatitis C serology). Present in alphabetical order. Note: Patients who received a hepatitis B vaccination and are positive for hepatitis B surface antibody, but are negative for both hepatitis B surface antigen and hepatitis B core antibody, do not need to be excluded from the study.
Update source footnote to "Source: Listing 16.2.8.4".

Table 14.3.19 Hematology Laboratroy Data at Screening - Markedly Abnormal Values (Safety Analysis Set in Part A)
Verona Pharma Page X of Y
Protocol: RPL554-MD-201 Part A
RPL554 pressurised Metered Dose Inhaler

Table 14.3.19

Biochemistry Laboratory Data - Markedly Abnormal Values

(Safety Analysis Set in Part A)

Laboratory Test, n (%)	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)
Alanine Aminotransferase (ALT)						
> 3 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Alkaline Phosphatase (ALP)						
> 3 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Aspartate Aminotransferase (AST)						
> 3 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Creatinine						
> 221 µmol/L	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Gamma Glutamyl Transferase (GGT)						
> 3 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Bilirubin (TBL)						
> 3 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

ULN: Upper limit of normal reference range. n = Number of patients with at least one markedly abnormal value. N = Number of patients in the analysis set. % = percentage of patients with at least one markedly abnormal value relative to the total number of patients in the analysis set.

Source: Listing 16.2.8.2

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0
Author: Nicholas Roubinis/Jennifer Allsopp Date: 13JAN2021

ECG

Table 14.3.20 12-Lead Electrocardiogram Data by Timepoint (Safety Analysis Set in Part A)

Verona Pharma

Protocol: RPL554-MD-201 Part A

RPL554 pressurised Metered Dose Inhaler

Table 14.3.20

12-Lead Electrocardiogram Data by Timepoint

(Safety Analysis Set in Part A)

Parameter (Unit) Timepoint Statistics	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)
Parameter #1 (unit)						
Pre-dose						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
1-hour post-dose						
Observed						
n [a]	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Change from Pre-dose						
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

Document: Z:\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 TLF Shells v2.0 - Part A Version: 2.0

Author: Nicholas Roubinis/Jennifer Allsopp Date: 13JAN2021

Table 14.3.20

12-Lead Electrocardiogram Data by Timepoint

(Safety Analysis Set in Part A)

Parameter (Unit) Timepoint / Statistics	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Parameter #2 (unit)						
…						

SD: Standard deviation. n = Number of patients who have an assessment available. N = Number of patients in the analysis set. Change from Pre-dose: (Post-dose assessment – Pre-dose assessment).

Source: Listing 16.2.9.2

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes:
ECG quantitative assessments include: QTcF Interval (msec), QRS Interval (msec), PR Interval (msec), RR (msec), Heart rate (bpm).
Present in alphabetical order. Display for the following timepoints: Pre-dose, 1, 1.5, 2, 4 and 8 hours (all ± 10 minutes)

Table 14.3.21 12-Lead Electrocardiogram - Shifts from Pre-Dose ECG Assessment by Timepoint (Safety Analysis Set in Part A)
Verona Pharma Page X of Y
Protocol: RPL554-MD-201 Part A
RPL554 pressurised Metered Dose Inhaler

Table 14.3.21

12-Lead Electrocardiograms - Shifts from Pre-Dose ECG Assessment by Timepoint

Safety Analysis Set

			Category at Timepoint			
Timepoint Treatment group	N	Pre-dose Category	Normal n (%)	Abnormal NCS n (%)	Abnormal CS n (%)	Total n (%)
1-hour post-dose						
RPL554 100µg	xxx	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal NCS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal CS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
RPL554 300µg	xxx	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal NCS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal CS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	…	…	…	…	…	…

NCS: Not clinically significant; CS: Clinically significant. n = Number of patients in each category with a pre-dose and post-dose assessment. N = Number of patients in the analysis set. % = Percentage of patients in each category relative to the total number of patients in the analysis set, with assessments pre-dose and at the relevant timepoint.

Source: Listing 16.2.9.1

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes:
ECG quantitative assessments include: QTcF Interval (msec), QRS Interval (msec), PR Interval (msec), RR (msec), Heart rate (bpm).
Display for timepoints: 1, 1.5, 2, 4 and 8 hours (all ± 10 minutes).

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Version: 2.0
Author: Nicholas Roubinis/Jennifer Allsopp Date: 13JAN2021

Table 14.3.22 Change from Baseline Heart Rate to peak Heart Rate (over 4 hours) After Single Dose (Safety Analysis Set in Part A)

This output uses shell Table 14.2.4

ANCOVA: Analysis of covariance. CFB: Change from Baseline. CI: Confidence interval. LSMean: Least square mean. LSMean Diff: Least square mean difference. SD: Standard deviation. N = number of patients in the analysis set. Baseline: Pre-dose heart rate. Change from Baseline: Post-dose assessment - Pre-dose. [a] number of patients with valid values at baseline and timepoints. [b] ANCOVA model is used to model the change from baseline heart rate using baseline heart rate as a continuous fixed effect and actual treatment as categorical fixed effects. [c] number of patients with at least one on treatment value who contributed to the model estimation. * Indicates a significant p-value (<0.05).

Source: Listing 16.2.9.4

Programming Notes

Replace footnotes in original shell with those listed above

Document: Z:\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 TLF Shells v2.0 - Part A
Version: 2.0
Author: Nicholas Roubinis/Jennifer Allsopp
Date: 13JAN2021

Vital Signs

Table 14.3.23 Vital Sign Data - Change from Pre- to Post- dose by Timepoint (Safety Analysis Set in Part A)

RPL554 pressurised Metered Dose Inhaler

Table 14.3.23

Vital Sign Data - Change from Pre- to Post- dose by Timepoint

(Safety Analysis Set in Part A)

Parameter (Unit) Timepoint Statistics	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)
Systolic Blood Pressure (mmHg)						
Pre-dose						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
1-hour post-dose						
Observed						
n	xx	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Change from Pre-dose						
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

Table 14.3.23

Vital Sign Data - Change from Pre- to Post- dose by Timepoint

(Safety Analysis Set in Part A)

Parameter (Unit) Timepoint / Statistics	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
2-hours post-dose						
…						

SD: Standard deviation. n = Number of patients who have an assessment available. N = Number of patients in the analysis set. Change from Pre-dose: (Post-dose assessment – Pre-dose assessment).

Source: Listing 16.2.9.3

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes:
Vital signs assessments include: Systolic blood pressure, diastolic blood pressure and pulse rate. Present in alphabetical order.
Display for the following timepoints: Pre-dose, 1, 1.5, 2, 4, 8, 12 and 24 hours (all ± 10 minutes).

Table 14.3.24 Vital Sign Data - Markedly Abnormal Values (Safety Analysis Set in Part A)
Verona Pharma Page X of Y
Protocol: RPL554-MD-201 Part A
RPL554 pressurised Metered Dose Inhaler

Table 14.3.24
Vital Sign Data - Markedly Abnormal Values
Safety Analysis Set

Vital Sign Parameter	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)
Systolic Blood Pressure (mmHg), n (%)						
n [a]	xx	xx	xx	xx	xx	xx
Value <=90	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
A decrease from baseline of >=40	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Value >=180	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
An increase from baseline of >=40	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Diastolic Blood Pressure (mmHg), n (%)						
n [a]	xx	xx	xx	xx	xx	xx
Value <=50	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
A decrease from baseline of >=20	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Value >=105	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
An increase from baseline of >=20	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pulse Rate (bpm), n (%)						
n [a]	xx	xx	xx	xx	xx	xx
Value <=50	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
A decrease from baseline of >=30	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Value >=110	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
An increase from baseline of >=30	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Document: Z:\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 TLF Shells v2.0 - Part A
Version: 2.0
Author: Nicholas Roubinis/Jennifer Allsopp Date: 13JAN2021

Table 14.3.24

Vital Sign Data - Markedly Abnormal Values

Safety Analysis Set

Vital Sign Parameter	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)

bpm: beats per minute. mmHg: millimeters mercury. [a] n = Number of patients with a baseline value and post-baseline value. Baseline and post-baseline value would be needed for criteria relating to an increase/decrease from baeline. N = Number of patients in the analysis set. % = percentages are based on n.

Source: Listing 16.2.9.3

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Table 14.3.25 Change from Baseline Pulse Rate to Peak Pulse Rate (over 4 hours) After Single Dose (Safety Analysis Set in Part A)

This output uses shell Table 14.2.4

ANCOVA: Analysis of covariance. CFB: Change from Baseline. CI: Confidence interval. LSMean: Least square mean. LSMean Difference: Leat square mean difference. SD: Standard deviation. N = number of patients in the analysis set. Baseline: Pre-dose pulse rate. Change from Baseline: Post-dose assessment - Pre-dose. [a] number of patients with valid values at baseline and timepoints. [b] ANCOVA model is used to model the change from baseline pulse rate using baseline pulse rate as a continuous fixed effect and actual treatment as categorical fixed effects. [c] number of patients with at least one on treatment value who contributed to the model estimation. * Indicates a significant p-value (<0.05).

Source: Listing 16.2.9.4

Programming Notes:
Replace footnotes in original shell with those listed above

Document: Z:\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 TLF Shells v2.0 - Part A
Version: 2.0
Author: Nicholas Roubinis/Jennifer Allsopp
Date: 13JAN2021

Physical Examination

Table 14.3.26 Physical Examination Data by Timepoint (Safety Analysis Set in Part A)

RPL554 pressurised Metered Dose Inhaler

Table 14.3.26

Physical Examination Data by Timepoint

(Safety Analysis Set in Part A)

Physical Examination: <Full/Brief>

Assessment Timepoint Category	RPL554 100µg (N=XX)	RPL554 300µg (N=XX)	RPL554 1000µg (N=XX)	RPL554 3000µg (N=XX)	RPL554 6000µg (N=XX)	Placebo (N=XX)
Abdomen (liver and spleen)						
Pre-dose						
Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Abnormal NCS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Abnormal CS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Cardiovascular system						
Pre-dose						
…						

CS = Clinically significant. NCS = Not clinically significant. n = Number of patients who have an assessment available at the relevant timepoint. N = Total number of patients in the analysis set.

Source: Listing 16.2.9.5 and 16.2.9.6

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes:
• Full Physical Examination assessments include: Abdomen [liver and spleen], Cardiovascular system, Extremities, Lymph nodes, Neurological system, Nose, Throat, Respiratory system, Skin, Thyroid gland. Present in alphabetical order.
• Brief Physical Examination assessments include: Abdomen (liver and spleen), Cardiovascular system, Respiratory system, Skin. Present in alphabetical order.
• Display for the following timepoints: Full Physical Examination: Screening and Brief Physical Examination: Pre-dose.

Document: Z:\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 TLF Shells v2.0 - Part A
Version: 2.0
Author: Nicholas Roubinis/Jennifer Allsopp Date: 13JAN2021

Figures

Figure 14.2.1 Geometric Mean of ratios of Average FEV_1 (over 4 hours)to pre-dose FEV_1 by Treatment (Full Analysis Set in Part A)

EFF09: This output uses shell EFF008 [Figure 14.2.3]

Programming Notes

Use template of figure 14.2.3, adjusting for Average FEV_1 (over 4 hours).

Figure 14.2.2 Geometric Mean of ratios of Average FEV_1 (over 12 hours) to pre-dose FEV_1 by Treatment (Full Analysis Set in Part A)

EFF10: This output uses shell EFF008 [Figure 14.2.3]

Programming Notes

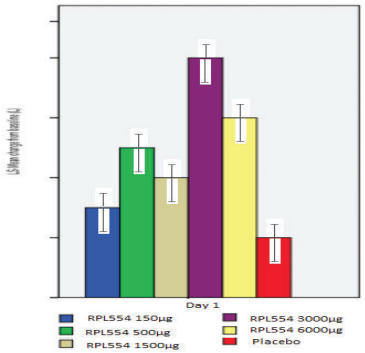
Use template of figure 14.2.3, adjusting for Average FEV_1 (over 12 hours).

Figure 14.2.3 Geometric Mean of ratios to Peak FEV_1 (over 4 hours) to pre-dose FEV_1 by Treatment (Full Analysis Set in Part A)

Figure 14.2.3

Geometric Mean of ratios of Peak FEV_1 (over 4 hours) to pre-dose FEV_1 by Treatment

(Full Analysis Set in Part A)



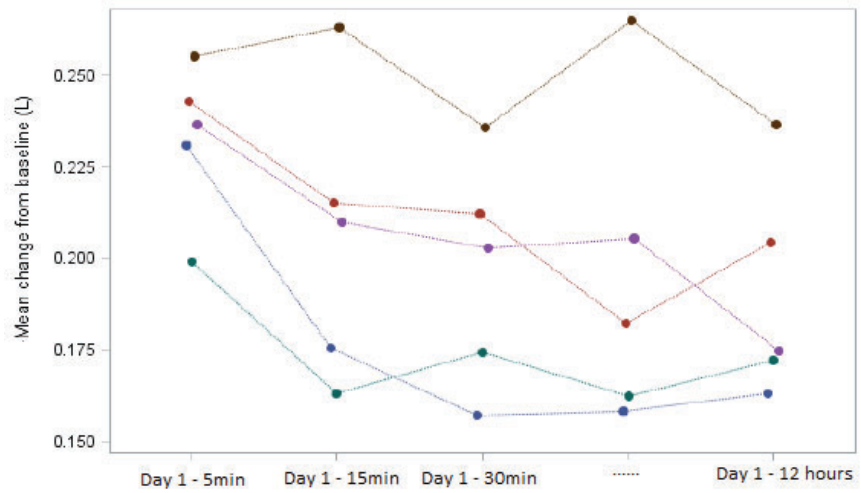
FEV1: Forced expiratory volumn in 1 second. Pre-dose FEV1: Average of pre-dose FEV1 assessed immediately pre-dose (within 5 minutes) and 1 hour pre-dose (within 5 minutes). Bottom and top whiskers: 95% lower confidence limit and 95% upper confidence limit. Bar: Geometric means of the ratio to pre-dose. ANCOVA model is used to model the change from pre-dose FEV1 using pre-dose FEV1 as a continuous fixed effect and planned treatment as categorical fixed effects.
Source: Listing 16.2.6.2

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes:

Above is an example. Display for all treatment groups in Part A in ascending order (RPL554 100µg, RPL554 300µg, RPL554 1000µg, RPL554 3000µg and RPL554 6000µg) and then placebo. For each treatment group present the LSMean and SEM (standard error of the mean).

Figure 14.2.4
Mean Change from pre-dose FEV_1 during spirometry over Time by Treatment
(Full Analysis Set in Part A)



Means are calculated on the observed data.

Pre-dose: the highest FEV1 result collected immediately pre-dose (within 5 minutes).

Source: Listing 16.2.6.1

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes:

Above is an example. Display for all treatment groups and placebo. For each treatment group present the Mean change from baseline. Display for the following time points on Day 1: 5 minutes, 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 4 hours, 8 hours, 11 hours and 12 hours. On the x-axis present actual time scale (in spacing of timepoints).

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Date: 13JAN2021

Figure 14.2.5 Change from Pre-dose FEV_1 over Time by Treatment by Subject (Full Analysis Set in Part A)

EFF09: This output uses shell EFF009 [Figure 14.2.4]

Programming Notes

Use template of figure 14.2.4.
Update to have 1 page per treatment group with "Planned Treatment:" displayed above the figure on the left.
Present each patient for that treatment. Do no include a legend so that unblinding does not occur on a subject-level.
Update y-axis title to "Change from pre-dose FEV1 (L)".
Include the following footnote: "Pre-dose: the average of the FEV1 pre-dose assessments collected on Day 1 (within 60 and 5 minutes)."

Document: Z:\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 TLF Shells v2.0 - Part A
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Author: Nicholas Roubinis/Jennifer Allsopp
Date: 13JAN2021

Figure 14.3.1 Mean Change from Pre-dose Heart Rate to Peak Heart Rate (over 4 hours) by Treatment (Safety Analysis Set in Part A)

This output uses shell Figure 14.2.1

Pre-dose heart rate: The heart rate value assessed immediately before administration. Bottom and top whiskers: 95% lower confidence and 95% upper confidence limit. Bar: Results on orginal scale. ANCOVA model is used to model the change from pre-dose heart rate using pre-dose heart rate as a continuous fixed effect, and actual treatment as categorical fixed effects.

Programming Notes

Use template of figure 14.2.1, adjusting for ECG assessment = heart rate.
Update source footnote to "Source: Listing 16.2.9.4".
Replace footnotes in original shell with those listed above

Figure 14.3.2 Mean Change from Pre-dose in Heart Rate over Time by Treatment (Safety Analysis Set in Part A)

This output uses shell Figure 14.2.4

Means are calculated on the observed data.
Pre-dose: the pre-dose assessment collected of day 1.

Programming Notes

Display for all treatment groups and placebo. For each treatment group present the Mean change from baseline.
Display for the following time points on Day 1: 1 hour, 2 hours, 4 hours and 8 hours.
Update source footnote to "Source: Listing 16.2.9.2".
Replace footnotes in original shell with those listed above

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Figure 14.3.3 Mean Change from Pre-dose Pulse Rate to Peak Pulse Rate (over 4 hours) by Treatment (Safety Analysis Set in Part A)

This output uses shell Figure 14.2.1

Pre-dose pulse rate: The pulse rate value assessed immediately before administration. Bottom and top whiskers: 95% lower confidence and 95% upper confidence limit. Bar: Results on orginal scale. ANCOVA model is used to model the change from pre-dose pulse rate using pre-dose pulse rate as a continuous fixed effect, and actual treatment as categorical fixed effects.

Programming Notes:

Use template of figure 14.2.1, adjusting for vital sign assessment = pulse rate.
Update source footnote to "Source: Listing 16.2.9.4".
Replace footnotes in original shell with those listed above

Figure 14.3.4 Mean Change from Pre-dose in Pulse Rate over Time by Treatment (Safety Analysis Set in Part A)

This output uses shell Figure 14.2.4

Means are calculated on the observed data.
Pre-dose: the pre-dose assessment collected on day 1.

Programming Notes:

Display for all treatment groups and placebo. For each treatment group present the Mean change from baseline.
Display for the following time points on Day 1: 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, Day 2: 24 hours.
Update source footnote to "Source: Listing 16.2.9.3".
Replace footnotes in original shell with those listed above

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Listings

Listing 16.2.1.1 Completed/Discontinued Patients (All Randomized Analysis Set in Part A)

Listing 16.2.1.1

Completed/Discontinued Patients

(All Randomized Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Informed consent date/Study day	Randomization date/Study day	Completed Part A/Primary reason if not completed	Part A Treatment discontinued	Discontinued between Part A and Part B	Date of completion/discontinuation/ Study day
XXXXXXX	DDMMMYYYY/xx	DDMMMYYYY/xx	No/XXXXXX	xx	xx	DDMMMYYYY/xx

Study day: Day relative to day of the single dose of study medication.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes
Order by treatment group (as per shell) and within group by patient ID.

Listing 16.2.2.1

Protocol Deviations

(All Randomized Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Age/Sex/Race	Deviation date/Study Day	Protocol deviation	Type of deviation	Severity
XXXXXXXXXXXXX	XX/X/XXXXXXX	DDMMMYYYY/xx	XXXXXXXXXX	XXXXXXXXXX	XXXXXXXXXX

As: Native Asian. Bl: Black or African American. F: Female. Ia: American Indian or Alaskan. M: Male. Ot: Other. PI: Native Hawaiian or Pacific Islanders. Un: Unknown. W: White. Age (years): As calculated relative to informed consent date. Study day: Day relative to day of the single dose of study medication.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes

Order by treatment group (as per shell) and within group by patient ID and then the deviation date.

Listing 16.2.3.1

Patient Excluded from Analysis Sets

(All Randomized Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Age/Sex/Race	Affected analysis set
XXXXXXX	47/M/W	PK
XXXXXXX	67/M/Bl	SAF
…		

As: Native Asian. Bl: Black or African American. eCRF: Electronic case report form. F: Female. Ia: American Indian or Alaskan. M: Male. Ot: Other. PI: Native Hawaiian or Pacific Islanders. Un: Unknown. W: White. Age (years): As calculated relative to informed consent date. All measurements listed above are measured at Screening on the Demography eCRF.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes
Order by treatment group (as per shell) and within group by patient ID.
Print "No patient excluded from any analysis set" if the listing has no observations.

Listing 16.2.4.1

Demographic Characteristics

(All Randomized Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Country	Age/Sex/Race	Ethnicity	Weight (kg)	Height (cm)	BMI (kg/m^2)	Re-screened patient	Childbearing potential
XXXXXXXXX	USA	62/F/W	White-White/Caucasian/European Heritage	XX	XXX	XX.X	X	X
XXXXXXXXX	USA	67/M/W	White-White/Caucasian/European Heritage	XX	XXX	XX.X	X	NA

As: Native Asian. Bl: Black or African American. BMI: Body mass index. eCRF: Electronic case report form. F: Female. Ia: American Indian or Alaska. M: Male. NA: Not applicable. Ot: Other. Pi: Native Hawaiian or Pacific Islanders. Un: Unknown. W: White. Age (years): As calculated relative to informed consent date. BMI (kg/m^2) = Weight (kg) / Height $(m)^2$. All measurements listed above are measured at Screening on the Demography eCRF.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes:
Order by treatment group (as per shell) and within group by patient ID.

Listing 16.2.4.2 Screening Disease Characteristics (All Randomized Analysis Set in Part A)
Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.4.2

Screening Disease Characteristics

(All Randomized Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

		Bronchodilator FEV_1				Bronchodilator FVC (L)		Bronchodilator FEV_1/FVC		Reversibility FEV_1			
Patient ID	Age/Sex/Race	Pre (L)	Post (L)	Pre (%)	Post (%)	Pre	Post	Pre	Post	mL	%	Assessment performed with four puffs of albuterol	Met reversibility test criteria?
XXXX	XX/X/XXX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XXX	XXX

As: Native Asian. Bl: Black or African American. eCRF: Electronic case report form. F: Female. FEV_1: Forced expired volume in 1 second. FVC: Forced vital capacity. Ia: American Indian or Alaskan. Ot: Other. PI: Native Hawaiian or Pacific Islanders. Un: Unknown. W: White. Age (years): As calculated relative to informed consent date. Pre-, post-bronchodilator and reversibility values are the results of the screening reversibility test.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes
Order by treatment group (as per shell) and within group by patient ID.

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Author: Nicholas Roubinis/Jennifer Allsopp
Date: 13JAN2021

Listing 16.2.4.3

COPD and Smoking History

(All Randomized Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

						Smoking History		
Patient ID	Date of COPD first diagnosed	Duration of COPD (years) (time since diagnosis)	Date of most recent exacerbation/Study day	Bronchitis?/ Emphysema?	Smoking category	Number of packs per day	Number of years smoking	Smoking exposure (pack-years)
XXXXXXX	DDMMMYYYY	xx.x	DDMMMYYYY/xx	Yes/Yes	Current	XX	XX	XX

COPD: Chronic Obstructive Pulmonary Disease. Smoking exposure (pack-years) = Number of packs per day * Number of years smoking, for patients with a smoking history or a current smoker. Study day: Day relative to day of the first dose of study medication. Duration of COPD (years) (time since diagnosis) = Randomization date - date COPD first diagnosed.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes:

Order by treatment group (as per shell) and within group by patient ID.

Listing 16.2.4.4

Medical History

(All Randomized Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Medical history diagnosis	SOC/PT	Start date/ Study day	End date/ Study day
XXXXXXXXX	XXXXXXXXXXXXXXXX	XXXXXXXXXXX/ XXXXXXXXXXXXX	DDMMMYYYY/xx	DDMMMYYYY/xx

MedDRA: Medical Dictionary for Regulatory Activities. PT: Preferred Term. SOC: System Organ Class. Medical history: Coded using MedDRA (Version 21.0). Study day: Day relative to day of the single dose of study medication.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes:

Order by treatment group (as per shell) and within group by patient ID.

Listing 16.2.4.5

Surgical Procedure History

(All Randomized Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Reported name of procedure	Purpose of procedure	Start date of procedure/ Study day	End date of procedure/ Study day
XXXXXXXXX	XXXXXXXXXXXXXXXX	XXXXXXXXXXXXX	DDMMMYYYY/xx	DDMMMYYYY/xx

Surgical procedure history: Coded using MedDRA (Version 21.0). Study day: Day relative to day of the single dose of study medication.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes:
Order by treatment group (as per shell) and within group by patient ID.

Listing 16.2.4.6 Prior and Concomitant Medications (All Randomized Analysis Set in Part A)
Verona Pharma Page X of Y
Protocol: RPL554-MD-201 Part A
RPL554 pressurised Metered Dose Inhaler

Listing 16.2.4.6

Prior and Concomitant Medications

(All Randomized Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Start date (Study day)/ End date (Study day)	Prior?[a]/ Concomitant?[b]	System organ class/ Preferred term/ Reported term	Indication	Dose (Unit)	Frequency	Route
XXXXX	DDMMMYYYY (xx)/ DDMMMYYYY (xx)	Prior	xxxxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxxx	xxxxxxx	xxxx (xx)	xx	xxx
	DDMMMYYYY (xx)/ ongoing	Prior/Concomitant	xxxxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxxx	xxxxxxx	xxxx (xx)	xx	xxx
	DDMMMYYYY (xx)/ ongoing	Concomitant	xxxxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxxx	xxxxxxx	xxxx (xx)	xx	xxx

[a] Medications which started and stopped in the 3 months prior to the single dose of study medication [b] Medication with onset date on or after the single dose of study medication and ended on or after the single dose of study medication or were ongoing at the end of Part A. A patient can report more than one concomitant medication with the same preferred term. Study day: Day relative to day of the single dose of study medication.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes
Order by treatment group (as per shell) and within group by patient ID.

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Version: 2.0
Author: Nicholas Roubinis/Jennifer Allsopp Date: 13JAN2021

Listing 16.2.5.1

Drug Exposure and Accountability

(All Randomized Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Dosing date/ Study day	Start time of inhalations	Date of Part A completion/ discontinuation/Study day
XXXXXXXXX	DDMMMYYYY/xx	HH:MM	DDMMMYYYY/xx

Study day: Day relative to day of the single dose of study medication.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes
Order by treatment group (as per shell) and within group by patient ID.

Listing 16.2.6.1

Spirometry: FEV1 Results

(Full Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Timepoint	Assessment performed/ Date and time/ Study day	Refrained from smoking	Capable of withdrawing from long acting bronchodilators	FEV_1 measurement (L)	Predicted FEV_1 (%)
XXXXX	XXXXXX	XX/DDMMYYY HH:MM/xx	XX	XX	X.XXX	XX.X
	XXXXXX					
	…					

FEV_1: Forced expiratory volume in 1 second. FEV_1 pre-dose assessment (-5 minutes) collected at visit of interest. Study day: Day relative to day of the first dose of study medication.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes
The assessment timepoints can be Pre PFT, Post PFT, Pre PFT -60 min, Immediately Predose, Post PFT 5min, 15min, 30min, 1h, 1.5h, 2h, 4h, 8h, 11h, 12h and EOS. The minutes from dosing is the difference between the Date/Time of assessments (from dataset CDM.T_SSM/CDM.R_SSM) and the Date/Time of Dosing (from dataset CDM.EX). Order by treatment group (as per shell) and within group by patient ID.

Listing 16.2.6.2

Spirometry: FEV1 Derived Measurements

(Full Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Assessment performed/ Date/ Study day	Peak FEV_1 (over 4 hours)	Average FEV_1 (over 4 hours)	Average FEV_1 (over 12 hours)
XXXXX	XX/DDMMYYY/xx	X.XXX	X.XXX	X.XXX
…	…	…	…	…

AUC: Area under the curve. FEV_1: Forced expiratory volume in 1 second. FEV1 pre-dose assessment (-5 minutes) collected at visit of interest. Peak FEV_1 = Maximum post-dose value among the values collected up to timepoint of interest hours. Average FEV_1 AUC: AUC of the FEV1 values divided by the length of the time (in hours) interval of interest (per visit). Study day: Day relative to day of the single dose of study medication. * when a subject has taken rescue medication less than 8 or 6 hours (for protocol version 1 or 2 respectively) prior to study medication.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes
The assessment timepoints can be Pre PFT, Post PFT, Pre PFT -60 min, Immediately Pre-dose, Post PFT 5min, 15min, 30min, 1h, 1.5h, 2h, 4h, 8h, 11h, 12h and EOS. The minutes from dosing is the difference between the Date/Time of assessments (from dataset CDM.SPIRO) and the Date/Time of Dosing (from dataset CDM.EX) Order by treatment group (as per shell) and within group by patient ID.
*In the "Average FEV1 (over 12 hours)" * any results where a subject has taken rescue medication less than 8 or 6 hours (for protocol version 1 or 2 respectively) prior to study medication.*

Listing 16.2.6.3

Rescue Medications Taken at Site

(All Randomized Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Medication name	Date/time of administration/ Study day	Number of Albuterol or Salbuterol puffs taken/ Number of Ipratropium puffs taken
XXXX/XXXX	XXXXXXXXX	DDMMMYYYY/ HH:MM/xx	XX/YY

Rescue medications = Short acting bronchodilators used to relieve i.e., rescue symptoms immediately. Study day: Day relative to day of the single dose of study medication.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes

Order by treatment group (as per shell) and within group by patient ID and visit.

Listing 16.2.6.4

Rescue Medications Taken between Visits

(All Randomized Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Inhaler number	Rescue medication canister dispensed?/ collected? (Y/N)	Date and time canister dispensed/collected	Reason canister not dispensed/collected	Dispensed rescue medication weight (g) / Collected weight (g)
	xx	X/X	DDMMMYYYY/HH:MM/ DDMMMYYYY/HH:MM	XXXXXXX/ XXXXXXX	XX.X/ XX.X

Rescue medications = Short acting bronchodilators used to relieve i.e., rescue symptoms immediately.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes
Order by treatment group (as per shell) and within group by patient ID and visit.

Listing 16.2.7.1

All Adverse Events

(Safety Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Study day of first treatment	SOC/PT/Reported term [a]	Start/End date or ongoing (Study day) [b]	Sev [c]	Rel [d]	Act [e]	Ser [f]	Out [g]	Chronicity [h]	Treatment given	Discontinued from study	Blind broken
XXXXX	XX	XXXXXX/XXXXX/XXXXX	DDMMMYYYYY	MI	Y	NC	N	Rslv	XX/X/X	Yes	Yes	Yes

PT: Preferred term. SOC: System organ class.

[a] An asterisk "*" indicates a non-treatment-emergent adverse event.

[b] Study day: Day relative to day of the single dose of study medication.

[c] Severity: MI=Mild, MO=Moderate, SE=Severe.

[d] Related to study drug.

[e] Action taken with respect to study drug: NC = Dose not changed, DI = Drug Interrupted DW = Drug withdrawn, OT = Other, NA = Not Applicable.

[f] Serious AE.

[g] Outcome: Fatal = Fatal, NRslv = Not recovered/not resolved, Rslv = Recovered/Resolved, RslvS = Recovered/Resolved with sequelae, Recovering/Resolving = RslvG, Unk = Unknown.

[h] S = Single Occasion, I = Intermittent, P = Persistent.
SOCs and PTs are coded using the MedDRA (Version 21.0).

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes
Order by treatment group (as per shell) and within treatment by patient ID, adverse event start date and adverse event end date (in that order).

Listing 16.2.7.2 Treatment-emergent Adverse Events Leading to Study Discontinuation (Safety Analysis Set in Part A)

L017: This output uses shell L016 [Listing 16.2.7.1]

Listing 16.2.7.3 Treatment-emergent Adverce Events Leading to Death (Safety Analysis Set in Part A)

L018: This output uses shell L016 [Listing 16.2.7.1]

Listing 16.2.7.4 Serious Treatment-emergent Adverse Events (Safety Analysis Set in Part A)

L019: This output uses shell L016 [Listing 16.2.7.1]

Listing 16.2.7.5

Serious Treatment-emergent Adverse Events - Details

(Safety Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	SOC/PT/ Reported Term	SAE details	Answer
XXXXXXXXXXX	XXXXXXX/XXXXXXX/XXXXXX	Date Investigator became aware of SAE	DDMMMYYYY
		Death	XXXXX
		Life-threatening	XXXXX
		Initial or prolonged hospitalization	XXXXX
		Date of admission (DD MMM YYYY)	DDMMMYYYY
		Date of discharge (DD MMM YYYY)	DDMMMYYYY
		Persistent or significant disability/incapacity	XXXXX
		Congenital anomaly/birth defect	XXXXX
		Occurred with overdose	XXXXX
		Other medically important event	XXXXX
		Was the SAE caused by other medication? (e.g. Concomitant medication, background medication, rescue medication)	XXXXX
		If Yes, Please Specify	XXXXX
		Was the SAE caused by study procedure(s)?	XXXXX
		If Yes, Please Specify	XXXXX
		Describe treatment for event including medications (1)	XXXXX
		Describe treatment for event including medications (2)	XXXXX
		Describe treatment for event including medications (3)	XXXXX
		List all diagnostic tests that were done to confirm event (1)	XXXXX
		List all diagnostic tests that were done to confirm event (2)	XXXXX
		List all diagnostic tests that were done to confirm event (3)	XXXXX
		Description of SAE/narrative	XXXXX
		Additional information	XXXXX

Listing 16.2.7.5

Serious Treatment-emergent Adverse Events - Details

(Safety Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	SOC/PT/ Reported Term	SAE details	Answer

PT: Preferred Term. SAE: Serious Adverse Event. SOC: System Organ Class. SOCs and PTs are coded using the MedDRA (Version 21.0).

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes
Order by treatment group (as per shell) and within group by patient ID.

Listing 16.2.8.1 Hematology (Safety Analysis Set in Part A)
Verona Pharma Page X of Y
Protocol: RPL554-MD-201 Part A
RPL554 pressurised Metered Dose Inhaler

Listing 16.2.8.1

Hematology

(Safety Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Parameter	Reference Range (Lower-Upper)	Timepoint	Date/Time of assessment/ Study day	Value (unit) L/H [a]	Change from Baseline
XXXXXXXXXX	Hemoglobin	XX.X - XX.X	Scr	DDMMMYYYY/HH:MM/ xx	XX (unit)	XX.X

Scr: Screening. [a] L = Below low normal range. H = Above high normal range. * = Markedly abnormal values. Study day: Day relative to day of the single dose of study medication.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes
Add a symbol '' next to the value to identify markedly abnormal values.*
Order by treatment group (as per shell), hematology parameter (in alphabetical order) and by patient ID.

Listing 16.2.8.2 Biochemistry (Safety Analysis Set in Part A)

L022: This output uses shell L021 [Listing 16.2.8.1]

Scr: Screening. [a] L = Below lower limit of reference range. H = Above upper limit of reference range. Study day: Day relative to day of the single dose of study medication.
* = Markedly abnormal value (refer to section 16.2.1 of the statistical analysis plan for the markedly abnormal criteria).

Programming Notes

Replace footnotes with those above.

Document: Z:\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 TLF Shells v2.0 - Part A
Version: 2.0
Author: Nicholas Roubinis/Jennifer Allsopp Date: 13JAN2021

Listing 16.2.8.3 Urinalysis (Safety Analysis Set in Part A)
Verona Pharma Page X of Y
Protocol: RPL554-MD-201 Part A
RPL554 pressurised Metered Dose Inhaler

Listing 16.2.8.3
Urinalysis
(Safety Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Parameter	Timepoint	Date/Time of assessment/ Study day	Result [a]
XXXXXXXXXX	Bilirubin	Screening	DDMMMYYYY/HH:MM/xx	NEGATIVE (N)
		…	DDMMMYYYY/HH:MM/xx	TRACE (T)
		…	DDMMMYYYY/HH:MM/xx	1+ (P)

Scr: Screening. [a] Category assigned and used in the shift table: N = Normal or 'Negative'; T = 'Trace' P = '1+','2+','3+',' or '4+'. The flag appears only for the following parameters: Leucocyte Esterase, Bilirubin, Glucose, Ketones, Occult blood, Protein and Urobilinogen. Study day: Day relative to day of the single dose of study medication.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes
Order by treatment group (as per shell), urinalysis parameter (in alphabetical order) and by patient ID.

Listing 16.2.8.4 Viral Serology (Safety Analysis Set in Part A)

L022: This output uses shell L021 [Listing 16.2.8.3]

Programming Notes
Replace footnotes with those related to Viral Serology

Document: Z:\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 TLF Shells v2.0 - Part A
Version: 2.0
Author: Nicholas Roubinis/Jennifer Allsopp Date: 13JAN2021

Listing 16.2.9.1

Electrocardiogram Local Reading Overall Evaluation

(Safety Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Day/Timepoint	Date/Time of assessment/Study day	Overall ECG Evaluation	Abnormal Significant
XXXXXXXXXXXX	XXXX/XXXX	DDMMMYYYY/HH:MM/xx	Normal	Y

ECG: Electrocardiogram. Study day: Day relative to day of the single dose of study medication.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes
Order by treatment group (as per shell), within group by patient ID and then by timepoint.

Listing 16.2.9.2

12-lead ECG

(Safety Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Day/Timepoint	Date/Time of assessment/Study day	ECG parameter (unit)	Result	Baseline	CFB
XXXXXXXXXXXXX	XXXXX	DDMMMYYY/HH:MM/xx	HR (bpm)	XX.X	XX.X	XX.X
			RR interval (msec)	XX.X	XX.X	XX.X
			PR interval (msec)	XX.X	XX.X	XX.X
			QRS duration (msec)	XX.X	XX.X	XX.X
			QT interval (msec)	XX.X	XX.X	XX.X
			Bazett's QTc (msec)	XX.X	XX.X	XX.X
			Fridericia's QTc (msec)	XX.X	XX.X	XX.X
	XXXXX	DDMMMYYY/HH:MM/xx	…	…	…	…

bpm: beats per minute. CFB: Change from baseline. ECG: Electrocardiogram. HR: Heart rate. QTcB: QT interval using Bazett's correction formula. msec: milliseconds. QTcF: QT interval using Fridericia's correction formula. Study day: Day relative to day of the single dose of study medication.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes

Order by treatment group (as per shell), within group by patient ID and then by timepoint.

Listing 16.2.9.3

Vital Signs

(Safety Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Day/Timepoint	Date/Time of assessment/Study day	Vital sign parameter (unit)	Result	Baseline	CFB	Markedly abnormal
XXXXXXXXXXX	XXXXX	DDMMMYYYY/HH:MM/xx	SBP (mmHg)	XX.X L	XX.X	XX.X	Y
			DBP (mmHg)	XX.X	XX.X	XX.X	
			Pulse (beats/min)	XX.X	XX.X	XX.X H	Y
	XXXXX	DDMMMYYYY/HH:MM/xx	…	…	…	…	…

CFB: Change from baseline. Study day: Day relative to day of the single dose of study medication. Baseline: Defined as the assessment performed pre-dose. L and H represents marked decrease or increase from baseline.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes
Order by treatment group (as per shell), within group by patient ID, and then timepoint.

Listing 16.2.9.4

Derived Safety Measurements

(Safety Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Date/ Study day	Peak Heart Rate (bpm) (over 4 hours)	Peak Pulse Rate (bpm) (over 4 hours)
XXXXX	DDMMMYYYY/xx	X.XXX	X.XXX
…	…	…	…

Peak = Maximum post-dose value among the values collected up to timepoint of interest hours. Study day: Day relative to day of the single dose of study medication.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes
Order by treatment group (as per shell), within group by patient ID, and then date/time.

Listing 16.2.9.5

Brief Physical Examination

(Safety Analysis Set in Part A)

Treatment group: <RPL554 150µg/RPL554 500µg/RPL554 1500µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Date/Time of examination/Study day	Body system	Result If Abnormal, clinical significant, Specify
XXXXXXXXXX	DDMMMYYYY/HH:MM/xx	XXXXXXXXXXXXX	XXXXXXXXXXXXX

Study day: Day relative to day of the single dose of study medication.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes
Order by treatment group (as per shell), within group by patient ID and then alphabetically by body system.
Only include patients with at least one markedly abnormal clinically significant finding.

Listing 16.2.9.6

Full Physical Examination

(Safety Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Date/Time of examination/Study day	Body system	Result If Abnormal, clinical significant, Specify
XXXXXXXXXX	DDMMMYYYY/HH:MM/xx	XXXXXXXXXXXXX	XXXXXXXXXXXXX

CFB: Change from baseline. Study day: Day relative to day of the single dose of study medication.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes
Order by treatment group (as per shell), within group by patient ID and then alphabetically by body system.
Only include patients with at least one markedly abnormal clinically significant finding.

Listing 16.2.9.7

Chest X-ray

(All Randomized Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Chest X-ray performed	Date of X-ray/ Study day	Result of X-ray/ Specification (eCRF)
XXXXXXXXX	New	DDMMMYYYY/xx	Abnormal clinically significant/please specify
XXXXXXXXX	Historical	DDMMMYYYY/xx	Consistent with COPD

eCRF: Electronic case report form. Study day: Day relative to day of the single dose of study medication. Chest X-ray is assessed at Screening. Patient performs either a new X-ray ("New") or if an X-ray was performed in the last 12 months, this is acceptable ("Historical").

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes
Order by treatment group (as per shell) and within group by patient ID. Specification (eCRF) refers to result "Abnormal clinically significant" where free text could be required to be concatenated.

Listing 16.2.9.8

Inhalation Training

(All Randomized Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Timepoint	Inhalation training given?	Date of inhalation training/ Study day
XXXXXXX	XXXX/XXXX	XXXXXXX	DDMMMYYYY/xx

Study day: Day relative to day of the single dose of study medication.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes
Order by treatment group (as per shell) and within group by patient ID.

Listing 16.2.9.9

Pregnancy Serum and Urine Test at Screening

(All Randomized Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Serum pregnancy test performed/Date of test/Study day	Serum pregnancy test result	Urine pregnancy test performed/Date of test/Study day	Urine pregnancy test result
XXXXXXX	XX/DDMMMYYYY/xx	XXXXXXX	XX/DDMMMYYYY/xx	XXXXXXX

Study day: Day relative to day of the single dose of study medication.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes
Order by treatment group (as per shell) and within group by patient ID.
Consider only female patients.
Multiple pregnancy risk factors and multiple relevant family history will be presented as one result per row, as these are not presented separately in Pregnancy report eCRF.

Listing 16.2.9.10

Pregnancy Report at Screening

(All Randomized Analysis Set in Part A)

Treatment group: <RPL554 100µg/RPL554 300µg/RPL554 1000µg/RPL554 3000µg/RPL554 6000µg/Placebo>

Patient ID	Pregnancy report item	Results
XXXXXXXXXXXX	Date of last menstrual period/Study day	DDMMMYYYY/xx
	Date of expected delivery/Study day	DDMMMYYYY/xx
	Overall number of previous pregnancies	XX
	Number of normal deliveries	XX
	Number of spontaneous miscarriages	XX
	Number of other previous pregnancies	XX
	Relevant pregnancy risk factors	XXXXXXXXX
	Relevant family history	XXXXXXXXX

Study day: Day relative to day of the single dose of study medication.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Programming Notes
Order by treatment group (as per shell) and within group by patient ID.
Consider only female patients.
Multiple pregnancy risk factors and multiple relevant family history will be presented as one result per row, as these are not presented separately in Pregnancy report eCRF.

TABLES, LISTINGS AND FIGURES SHELLS – PART B

RPL554-MD-201

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

AUTHOR: JENNIFER ALLSOPP
VERSION NUMBER AND DATE: V2.0, 22JAN2021

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Version: 2.0
Author: Jennifer Allsopp
Date: 22JAN2021

TABLES, LISTINGS AND FIGURES SHELLS – PART B SIGNATURE PAGE

Tables, Listings and Figures Shells V2.0 – Part B (Dated 22JAN2021) for Protocol RPL554-MD-201.

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

Upon review of this document, the undersigned approves this version of the Tables, Listings and Figures Shells – 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:	Tara Rheault		
Position:	VP, R&D Operations and Project Management		
Company:	Verona Pharma		
Approved by:	Thomas Bengtsson		
Position:	Statistical Consultant to Verona		
Company:	StatMind		

Document: \\ieedc-vnasc01\biosdata\Verona_Pharma\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 TLF Shells v2.0 - Part B
Version: 2.0
Author: Jennifer Allsopp
Date: 22JAN2021

Modification History

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	13JAN2021	Jennifer Allsopp	Not Applicable – First Draft Version
2.0	22JAN2021	Jennifer Allsopp	Update treatment sequences from blinded sequences to unblinded sequences in output footnotes.

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Version: 2.0

Author: Jennifer Allsopp

Date: 22JAN2021

Tables

14.1 Demographic Data

Table 14.1.7 Patient Disposition by Treatment Sequence (Part A Completers)

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Protocol: RPL554-MD-201 Part B

RPL554 pressurised Metered Dose Inhaler

Table 14.1.7

Patient Disposition by Treatment Sequence

(Part A Completers)

Description, n (%)	Seq 1 N=XX	Seq 2 N=XX	Seq 3 N=XX	Seq 4 N=XX	Overall N=XX
Number of patients conmpleted Part A					xx
Number of patients to withdrew between Part A and Part B					xx
Number of patients randomized (n)	xx	xx	xx	xx	xx
Number of patients treated in:					
Treatment Period 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treatment Period 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treatment Period 3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treatment Period 4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of patients who completed the study	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of patients who discontinued the study in:					
Treatment Period 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treatment Period 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treatment Period 3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Treatment Period 4	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Overall	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Primary reason for early study discontinuation

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Author: Jennifer Allsopp Date: 22JAN2021

Table 14.1.7

Patient Disposition by Treatment Sequence

(Part A Completers)

Description, n (%)	Seq 1 N=XX	Seq 2 N=XX	Seq 3 N=XX	Seq 4 N=XX	Overall N=XX
Adverse event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pregnancy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol violation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Physician decision	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Study terminated by sponsor	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal by patient	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

n = Number of patients. N = Number of patients randomized in Part B. % = Percentage of patients calculated relative to the total number of patients in the analysis Set.
Patients who completed the study excludes patients who withdrew from the study and patients who did not complete all treatment periods i.e. a patient who receives a first and last dose intake plus 1 day for all 4 treatment periods per schedule of events.
Percentages for early discontinuation reasons is calculated based on the number of patients who had early discontinuation data.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Source: Listing 16.2.1.2

Output ID: DS001

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0
Author: Jennifer Allsopp Date: 22JAN2021

Table 14.1.8 Patient Disposition by Treatment Group (All Randomized Analysis Set in Part B)
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Protocol: RPL554-MD-201 Part B
RPL554 pressurised Metered Dose Inhaler

Table 14.1.8

Patient Disposition by Treatment Group

(All Randomized Analysis Set in Part B)

Description, n (%)	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX	Overall N=XX
Number of patients treated	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of patients who completed the study	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of patients who discontinued the study	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Primary reason for early study discontinuation					
Adverse event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to follow-up	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pregnancy	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol violation	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Physician decision	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Study terminated by sponsor	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal by patient	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

N = Number of patients in the analysis set. % = Percentage of patients calculated relative to the total number of patients in the analysis Set.
Patients who completed the study excludes patients who withdrew from the study and patients who did not complete all treatment periods i.e. a patient who receives a first and last dose intake plus 1 day for all 4 treatment periods per schedule of events.
Percentages for early discontinuation reasons is calculated based on the number of patients who had early discontinuation data.

Source: Listing 16.2.1.2

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Author: Jennifer Allsopp Date: 22JAN2021

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Protocol: RPL554-MD-201 Part B

RPL554 pressurised Metered Dose Inhaler

Table 14.1.8

Patient Disposition by Treatment Group

(All Randomized Analysis Set in Part B)

Description, n (%)	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX	Overall N=XX

Output ID: DS002

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Table 14.1.9 Analysis Set by Treatment Sequence (All Randomized Analysis Sets in Part B)
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Protocol: RPL554-MD-201 Part B
RPL554 pressurised Metered Dose Inhaler

Table 14.1.9

Analysis Sets by Treatment Sequence

(All Randomized Analysis Set in Part B)

Analysis set, n (%)	Seq 1 N=XX	Seq 2 N=XX	Seq 3 N=XX	Seq 4 N=XX	Overall N=XX
Randomized Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Safety Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Full Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completers Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pharmacokinetics Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

n = Number of patients. N = Number of patients in the analysis set. % = Percentage of patients calculated relative to the total number of patients in All Randomized Analysis Set in Part B.
All Randomized Analysis Set: Randomized patients.
Safety Analysis Set: Randomized patients who received at least one dose of study medication.
Full Analysis Set: Patients included in the Safety Analysis Set with sufficient data to compute the pharmacodynamic parameters on at least two treatment periods.
Completers Analysis Set: Patients included in the Safety Analysis Set who complete all treatment periods i.e. a patient who receives a first and last dose intake plus 1 day for all 4 treatment periods per schedule of events.
Pharmacokinetics Analysis Set: Patients included in the All Randomized Analysis Set who have a blood sampling performed after at least one dose of study medication and pharmacokinetic parameter data.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Source: Listing 16.2.3.2

Output ID: DS003

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Document: \\ieedc-vnasc01\biosdata\Verona_Pharma\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 TLF Shells v2.0 - Part B
Version: 2.0
Author: Jennifer Allsopp Date: 22JAN2021

Table 14.1.10 Analysis Set by Treatment Group (All Randomized Analysis Sets in Part B)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Table 14.1.10

Analysis Sets by Treatment Group

(All Randomized Analysis Set in Part B)

Analysis set, n (%)	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX	Overall N=XX
Randomized Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Safety Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Full Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completers Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pharmacokinetics Analysis Set	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

n = Number of patients. N = Number of patients randomized. % = Percentage of patients calculated relative to the total number of patients in All Randomized Analysis Set in Part B.
All Randomized Analysis Set: Randomized patients.
Safety Analysis Set: Randomized patients who received at least one dose of study medication.
Full Analysis Set: Patients included in the Safety Analysis Set with sufficient data to compute the pharmacodynamic parameters on at least two treatment periods.
Completers Analysis Set: Patients included in the Safety Analysis Set who complete all treatment periods i.e. a patient who receives a first and last dose intake plus 1 day for all 4 treatment periods per schedule of events.
Pharmacokinetics Analysis Set: Patients included in the All Randomized Analysis Set who have a blood sampling performed after at least one dose of study medication and pharmacokinetic parameter data.

Source: Listing 16.2.3.2

Output ID: DS004

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Table 14.1.11 Major/Critical Protocol Deviations (All Randomized Analysis Sets in Part B)

Verona Pharma

Protocol: RPL554-MD-201 Part B

RPL554 pressurised Metered Dose Inhaler

Table 14.1.11

Major/Critical Protocol Deviations

(All Randomized Analysis Set in Part B)

Severity/ Deviation type	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX	Overall N=XX
Patients with at least one critical/major protocol deviation, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Critical	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Type 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Type 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…					
Major					
…					

CTMS: Clinical trial management system. n = Number of patients. N = Number of patients in the analysis set. % = Percentage of patients calculated relative to the total number of patients in the analysis set. Protocol deviations were obtained from CTMS.

Source: Listing 16.2.2.2

Programming Notes

Deviation types are sorted in descending order of frequency of the Overall column. A patient may have multiple critical/major protocol deviations within and is counted once at each level of summarization.

Output ID: DV001

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Table 14.1.12 Demographic Characteristics (All Randomized Analysis Sets in Part B)
Verona Pharma
Protocol: RPL554-MD-201
RPL554 pressurised Metered Dose Inhaler

Table 14.1.12

Demographic Characteristics

(All Randomized Analysis Set in Part B)

Characteristic / Statistics	RND N=XX	SAF N=XX	FAS N=XX	CAS N=XX	PK N=XX
Age (years)					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Sex, n (%)					
Male	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Female	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Childbearing potential, n (%) *					
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Primary race, n (%)					
American Indian or Alaska	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Asian	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black or African American	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Hawaiian or Other Pacific Islander	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
White	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

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Author: Jennifer Allsopp
Date: 22JAN2021

Table 14.1.12

Demographic Characteristics

(All Randomized Analysis Set in Part B)

Characteristic / Statistics	RND N=XX	SAF N=XX	FAS N=XX	CAS N=XX	PK N=XX
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity, n (%)					
Hispanic or Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
African American/African Heritage	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian-Central/South Asian Heritage	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian-East Asian Heritage	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian-Southeast Asian Heritage	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
White/Caucasian/European Heritage	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not reported	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Weight (kg)					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Height (cm)					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

Table 14.1.12

Demographic Characteristics

(All Randomized Analysis Set in Part B)

Characteristic / Statistics	RND N=XX	SAF N=XX	FAS N=XX	CAS N=XX	PK N=XX
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
BMI (kg/m^2)					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

BMI: Body Mass Index. SD: Standard deviation.
n = Number of patients. N = Number of patients in the analysis set. % = Percentage of patients calculated relative to the total number of patients in the analysis set. * % = Percentage for childbearing potential calculated relative to the total number of female patients in the analysis set.
All Randomised Analysis Set in Part B (RND): Randomized patients in Part B.
Safety Analysis Set (SAF): Randomized patients who received at least one dose of study medication.
Full Analysis Set (FAS): Patients included in the Safety Analysis Set with sufficient data to compute the pharmacodynamic parameters on at least two treatment periods.
Completers Analysis Set (CAS): Patients included in the Safety Analysis Set who complete all treatment periods i.e. a patient who receives a first and last dose intake plus 1 day for all 4 treatment periods per schedule of events.
Pharmacokinetics Analysis Set (PK): Patients included in the All Randomized Analysis Set who have a blood sampling performed after at least one dose of study medication and pharmacokinetic parameter data.

Source: Listing 16.2.4.7

Programming Notes

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Version: 2.0

Author: Jennifer Allsopp

Date: 22JAN2021

Table 14.1.12

Demographic Characteristics

(All Randomized Analysis Set in Part B)

Characteristic / Statistics	RND N=XX	SAF N=XX	FAS N=XX	CAS N=XX	PK N=XX

Print all statistics and categories even if they are empty, except for the row of missings which will only be shown if present and is not shown in the shell here. This will not be relevant for ethnicity as there is a category noted as not reported. Therefore, no reason why missing should occur.

Output ID: DM001

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Table 14.1.13 Screening Disease Characteristics (All Randomized Analysis Sets in Part B)
Verona Pharma
Protocol: RPL554-MD-201
RPL554 pressurised Metered Dose Inhaler

Table 14.1.13
Screening Disease Characteristics
(All Randomized Analysis Set in Part B)

Characteristic / Statistics	RND N=XX	SAF N=XX	FAS N=XX	CAS N=XX	PK N=XX
Pre-bronchodilator FEV_1 (L)					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Post-bronchodilator FEV_1 (L)					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
FEV_1 reversibility (mL)					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

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Version: 2.0
Author: Jennifer Allsopp
Date: 22JAN2021

Table 14.1.13
Screening Disease Characteristics
(All Randomized Analysis Set in Part B)

Characteristic / Statistics	RND N=XX	SAF N=XX	FAS N=XX	CAS N=XX	PK N=XX
FEV_1 reversibility (%)					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Pre-bronchodilator FVC (L)					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Post-bronchodilator FVC (L)					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Pre-bronchodilator FEV_1/FVC					

Table 14.1.13
Screening Disease Characteristics
(All Randomized Analysis Set in Part B)

Characteristic / Statistics	RND N=XX	SAF N=XX	FAS N=XX	CAS N=XX	PK N=XX
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Post-bronchodilator FEV_1/FVC					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Post-bronchodilator FEV_1 (% of predicted normal)					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

Table 14.1.13

Screening Disease Characteristics

(All Randomized Analysis Set in Part B)

Characteristic / Statistics	RND N=XX	SAF N=XX	FAS N=XX	CAS N=XX	PK N=XX
Reversibility assessment performed with four puffs of albuterol, n (%)					
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Met protocol requirements of reversibility test [a], n (%)					
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

FEV_1: Forced expired volume in 1 second. FVC: Forced vital capacity. SD: Standard deviation.
n = Number of patients. N = Number of patients in the analysis set. % = Percentage of patients calculated relative to the total number of patients in the analysis set.
Pre-, post-bronchodilator and reversibility values are the results of the screening reversibility test.
[a] Patients meet the protocol requirements of the reversibility test by demonstrating >=150 mL increase from pre-bronchodilator FEV_1.
All Randomised Analysis Set in Part B (RND): Randomized patients in Part B.
Safety Analysis Set (SAF): Randomized patients who received at least one dose of study medication.
Full Analysis Set (FAS): Patients included in the Safety Analysis Set with sufficient data to compute the pharmacodynamic parameters on at least two treatment periods.
Completers Analysis Set (CAS): Patients included in the Safety Analysis Set who complete all treatment periods i.e. a patient who receives a first and last dose intake plus 1 day for all 4 treatment periods per schedule of events.
Pharmacokinetics Analysis Set (PK): Patients included in the All Randomized Analysis Set who have a blood sampling performed after at least one dose of study medication and pharmacokinetic parameter data.

Source: Listing 16.2.4.8

Output ID: DM005

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp

Date: 22JAN2021

Table 14.1.14 COPD and Smoking History (All Randomized Analysis Sets in Part B)
Verona Pharma
Page X of Y
Protocol: RPL554-MD-201
Part B
RPL554 pressurised Metered Dose Inhaler

Table 14.1.14

COPD and Smoking History

(All Randomized Analysis Set in Part B)

Variable/ Category	RND N=XX	SAF N=XX	FAS N=XX	CAS N=XX	PK N=XX
Duration of COPD (years) (time since diagnosis)					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Patient known to have Chronic Bronchitis, n (%)					
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Patient known to have Emphysema, n (%)					
Yes	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Smoking status, n (%)					
Current Smokers	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ex-smokers	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Smoking exposure (pack-years)					
n	xx	xx	xx	xx	xx

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Author: Jennifer Allsopp
Date: 22JAN2021

Table 14.1.14

COPD and Smoking History

(All Randomized Analysis Set in Part B)

Variable/ Category	RND N=XX	SAF N=XX	FAS N=XX	CAS N=XX	PK N=XX
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

COPD: Chronic obstructive pulmonary disease. SD: Standard deviation.
n = Number of patients. N = Number of patients in the analysis set. % = Percentage of patients calculated relative to the total number of patients in the analysis set.
Smoking exposure (pack-years) = Number of packs per day x Number of years smoking, for patients with a smoking history or a current smoker.
Duration of COPD (years) (time since diagnosis) = (Randomization date - first COPD diagnosis date) / 365.25.
All Randomised Analysis Set in Part B (RND): Randomized patients in Part B.
Safety Analysis Set (SAF): Randomized patients who received at least one dose of study medication.
Full Analysis Set (FAS): Patients included in the Safety Analysis Set with sufficient data to compute the pharmacodynamic parameters on at least two treatment periods.
Completers Analysis Set (CAS): Patients included in the Safety Analysis Set who complete all treatment periods i.e. a patient who receives a first and last dose intake plus 1 day for all 4 treatment periods per schedule of events.
Pharmacokinetics Analysis Set (PK): Patients included in the All Randomized Analysis Set who have a blood sampling performed after at least one dose of study medication and pharmacokinetic parameter data.

Source: Listing 16.2.4.9

Output ID: MH001

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp

Date: 22JAN2021

Table 14.1.15 Drug Exposure and Accountability (Safety Analysis Sets in Part B)

Verona Pharma

Protocol: RPL554-MD-201 Part B

RPL554 pressurised Metered Dose Inhaler

Table 14.1.15
Drug Exposure and Accountability
(Safety Analysis Set in Part B)

Variable/ Category	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX	Overall N=XX
Duration of exposure (days) [a]					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx
Drug accountability (weight of pMDI used (g)) [b]					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx	xx, xx

SD: Standard deviation.
Study medication administration and accountability data are from the Drug Accountability eCRF page.
[a] Duration of exposure per period (days) = (Date of last study medication administration - date of first study medication administration + 1).
[b] Drug accountability (weight of pMDI used (g)) = Weight of pMDI dispensed - weight of pMDI returned, including those dispensed and taken on site.

Source: Listing 16.2.5.2

Output ID: DA001

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

14.2 Efficacy

Primary Efficacy

Table 14.2.5 FEV_1 by Treatment and Timepoint (Full Analyis Set in Part B)

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Protocol: RPL554-MD-201 — Part B

RPL554 pressurised Metered Dose Inhaler

Table 14.2.5

FEV_1 by Treatment and Timepoint

(Full Analysis Set in Part B)

				Statistics					
Day	Timepoint	Treatment group	Category	n	Mean	SD	Minimum	Median	Maximum
Day 1	1-hour pre-dose	RPL554 300µg (N=XX)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
		RPL554 1000µg (N=XX)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
		RPL554 3000µg (N=XX)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
		Placebo (N=XX)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
	Immediately pre-dose	RPL554 300µg (N=XX)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
	…	…	…	…	…	…	…	…	…
	5 mins post-dose	RPL554 300µg (N=XX)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
			Pre-dose	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
			Change from Pre-dose	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
	…	…	…	…	…	…	…	…	…

SD: Standard deviation. FEV_1: Forced expiratory volume in 1 second.
n = Number of patients who have an assessment available at the relevant post-dose assessment timepoint (Result). n = Number of patients who have an assessment available at Pre-dose and the relevant post-dose assessment timepoint (Pre-dose and Change from Pre-dose). N = Number of patients in the analysis set.
Pre-dose: highest FEV_1 result collected immediately pre-dose (within 5 minutes). Change from Pre-dose: Post-dose assessment – Baseline.

Source: Listing 16.2.6.5

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Version: 2.0

Author: Jennifer Allsopp — Date: 22JAN2021

Programming Notes

Display for the following days and timepoints, relative to dosing:
Day 1 - 1 hour pre-dose and immediately pre-dose, 5 (± 2), 15 (± 5) and 30 minutes (± 10) and 1, 1.5, 2, 4, 8 and 12 hours (the latter assessments all ± 15 minutes).
Day 7 - 1 hour pre-dose and immediately pre-dose, 30 minutes (± 10) and 1, 1.5, 2, 4, 8, 11 and 12 hours (the latter assessments all ± 15 minutes).

Output ID: EFF003

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp

Date: 22JAN2021

Table 14.2.6 Change from Baseline FEV_1 to Peak FEV_1 (over 4 hours) on Day 7 (Full Analysis Set in Part B)

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Protocol: RPL554-MD-201 Part B

RPL554 pressurised Metered Dose Inhaler

Table 14.2.6

Change from Baseline FEV_1 to Peak FEV_1 (over 4 hours) on Day 7

(Full Analysis Set in Part B)

Day 7	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX
Baseline FEV_1 (L)				
n [a]	xx	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Peak FEV_1 (L)				
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Change from Baseline FEV_1				
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Estimates from ANCOVA [b]				
n [c]	xx	xx	xx	xx
GeoMean	xx.x	xx.x	xx.x	xx.x
95% CI for GeoMean	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Table 14.2.6

Change from Baseline FEV_1 to Peak FEV_1 (over 4 hours) on Day 7

(Full Analysis Set in Part B)

Day 7	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX
Comparisons Against Placebo				
Treatment Effect - ANCOVA [c]				
GeoMean Ratio	xx.x	xx.x	xx.x	
95% CI for GeoMean Ratio	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	
p-value	x.xxxx	x.xxxx	x.xxxx	
Comparisons Against RPL554 doses				
Treatment Effect - ANCOVA [c]		Comparison Against RPL554 300µg	Comparison Against RPL554 1000µg	
GeoMean Ratio		xx.x	xx.x	
95% CI for GeoMean Ratio		(xx.x, xx.x)	(xx.x, xx.x)	
p-value		x.xxxx	x.xxxx	

ANCOVA: Analysis of covariance. CI: Confidence interval. FEV_1: Forced expiratory volume in 1 second. GeoMean: Geometric mean. GeoMean Ratio: Geometric mean ratio. SD: Standard deviation.
N = Number of patients in the analysis set.
Baseline: average of the FEV_1 pre-dose assessments collected on Day 1 (within 60 and 5 minutes).
[a] number of patients with valid values at baseline and peak.
[b] ANCOVA model is used to model the change from baseline using baseline FEV_1 as a continuous fixed effect and planned treatment and treatment period as categorical fixed effects.
[c] number of patients with at least one on treatment value who contributed to the model estimation.
* Indicates a significant adjusted p-value (<0.05).

Source: Listing 16.2.6.6

Output ID: EFF004

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Table 14.2.6a Change from Baseline FEV_1 to Peak FEV_1 (over 4 hours) on Day 7 – Sensitivity Analysis (Completers Analysis Set in Part B)

EFF005: This output uses shell EFF004 [Table 14.2.6]

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Version: 2.0
Author: Jennifer Allsopp
Date: 22JAN2021

Secondary Efficacy

Table 14.2.7 Average FEV_1 by Day and Treatment Group (Full Analysis Set in Part B)

EFF006: This output uses shell EFF003 [Table 14.2.5]

AUC: Area under the curve. SD: Standard deviation.
n = Number of patients who have an assessment available at the relevant post-dose assessment timepoint (Result). n = Number of patients who have an assessment available pre-dose and the relevant post-dose assessment timepoint (Pre-dose and Change from Pre-dose). N = Number of patients in the analysis set.
Pre-dose: average of the FEV_1 pre-dose assessments (-60 minutes and -5 minutes). Change from Pre-dose: Post-dose assessment – Pre-dose. AUC: If a patient misses' the last two assessments in the time interval measured, or does not have any pre-dose assessments then the AUC is set to missing.

Source: Listing 16.2.6.6

Programming Notes

Replace footnotes in original shell with tha listed above.
Amend the presentation to AUC.
To be presented for both AUC_{0-4h} and AUC_{0-12h} on Day 1 and Day 7, respectively.

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Version: 2.0
Author: Jennifer Allsopp
Date: 22JAN2021

Table 14.2.8 Change from Baseline FEV_1 to Average FEV_1 (over 4 hours) on Day 7 (Full Analysis Set in Part B)

EFF007: This output uses shell EFF004 [Table 14.2.6]

ANCOVA: Analysis of covariance. AUC: Area under the curve. CI: Confidence interval. FEV_1: Forced expiratory volume in 1 second. GeoMean: Geometric mean. GeoMean Ratio: Geometric mean ratio. SD: Standard deviation.
N = Number of patients in the analysis set.
Baseline: average of the FEV_1 pre-dose assessments collected on Day 1 (within 60 and 5 minutes).
[a] number of patients with valid values at baseline and average.
[b] ANCOVA model is used to model the change from baseline AUC_{0-t} using baseline FEV_1 as a continuous fixed effect and actual treatment and treatment period as categorical fixed effects.
[c] number of patients with at least one on treatment value who contributed to the model estimation.
* Indicates a significant adjusted p-value (<0.05).

Source: Listing 16.2.6.6

Programming Notes

Replace footnotes in original shell with those listed above.

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Author: Jennifer Allsopp
Date: 22JAN2021

Table 14.2.9 Change from Baseline FEV_1 to Average FEV_1 (over 12 hours) on Day 7 (Full Analysis Set in Part B)

EFF008: This output uses shell EFF004 [Table 14.2.6]

ANCOVA: Analysis of covariance. AUC: Area under the curve. CI: Confidence interval. FEV_1: Forced expiratory volume in 1 second. GeoMean: Geometric mean. GeoMean Ratio: Geometric mean ratio. SD: Standard deviation.
N = Number of patients in the analysis set.
Baseline: average of the FEV_1 pre-dose assessments collected on Day 1 (within 60 and 5 minutes).
[a] number of patients with valid values at baseline and average.
[b] ANCOVA model is used to model the change from baseline AUC_{0-t} using baseline FEV_1 as a continuous fixed effect and actual treatment and treatment period as categorical fixed effects.
[c] number of patients with at least one on treatment value who contributed to the model estimation.
* Indicates a significant adjusted p-value (<0.05).

Source: Listing 16.2.6.6

Programming Notes

Replace footnotes in original shell with those listed above

Table 14.2.9a Change from Baseline FEV_1 to Average FEV_1 (over 12 hours) on Day 7 - Sensitivity Analysis (Full Analysis Set in Part B)

EFF009: This output uses shell EFF004 [Table 14.2.6]

ANCOVA: Analysis of covariance. AUC: Area under the curve. CI: Confidence interval. FEV_1: Forced expiratory volume in 1 second. GeoMean: Geometric mean. GeoMean Ratio: Geometric mean ratio. SD: Standard deviation.
N = Number of patients in the analysis set.
Baseline: average of the FEV_1 pre-dose assessments collected on Day 1 (within 60 and 5 minutes).
Includes subjects who took rescue medication less than 6 hours prior to spirometry.
[a] number of patients with valid values at baseline and average.
[b] ANCOVA model is used to model the change from baseline AUC_{0-t} using baseline FEV_1 as a continuous fixed effect and actual treatment and treatment period as categorical fixed effects.
[c] number of patients with at least one on treatment value who contributed to the model estimation.
* Indicates a significant adjusted p-value (<0.05).

Source: Listing 16.2.6.6

Programming Notes

Replace footnotes in original shell with those listed above
Only include if at least 1 subject has taken rescue medication less than 6 hours prior to spirometry (ANL02FL="Y")

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Date: 22JAN2021

Table 14.2.10 Change from Baseline FEV_1 to Morning Trough FEV_1 on Day 7 (Full Analysis Set in Part B)

EFF0010: This output uses shell EFF004 [Table 14.2.6]

ANCOVA: Analysis of covariance. CI: Confidence interval. FEV_1: Forced expiratory volume in 1 second. GeoMean: Geometric mean. GeoMean Ratio: Geometric mean ratio. SD: Standard deviation.
N = Number of patients in the analysis set.
Baseline: average of the FEV_1 pre-dose assessments collected on Day 1 (within 60 and 5 minutes).
Morning trough FEV_1 is the average of the FEV_1 pre-dose assessments (-60 minutes and -5 minutes) on Day 7.
[a] number of patients with valid values at baseline and morning trough.
[b] ANCOVA model is used to model the change from baseline in morning trough FEV_1 using baseline FEV_1 as a continuous fixed effect, actual treatment and treatment period as categorical fixed effects.
[c] number of patients with at least one on treatment value who contributed to the model estimation.
* Indicates a significant p-value (<0.05).

Source: Listing 16.2.6.6

Programming Notes

Replace footnotes in original shell with those listed above

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Author: Jennifer Allsopp
Date: 22JAN2021

Table 14.2.11 Change from Baseline FEV_1 to Peak FEV_1 (over 4 hours) on Day 1 (Full Analysis Set in Part B)

EFF11: This output uses shell EFF004 [Table 14.2.6]

Programming Notes

Footnotes should be the same as Table 14.2.6

Table 14.2.12 Change from Baseline FEV_1 to Average FEV_1 (over 4 hours) on Day 1 (Full Analysis Set in Part B)

EFF12: This output uses shell EFF006 [Table 14.2.8]

Programming Notes

Footnotes should be the same as Table 14.2.8

Table 14.2.13 Change from Baseline FEV_1 to Average FEV_1 (over 12 hours) on Day 1 (Full Analysis Set in Part B)

EFF13: This output uses shell EFF007 [Table 14.2.9]

Programming Notes

Footnotes should be the same as Table 14.2.9

Table 14.2.14 Time to Onset of Action (>10% Increase in FEV_1) on Day 1 (Full Analysis Set in Part B)

Table 14.2.14

Time to Onset of Action (>10% Increase in FEV_1) on Day 1

(Full Analysis Set in Part B)

Parameter	Statistics	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX
Number of patients with onset of action	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of patients censored	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Time to onset of action (mins)	P25	x.x	x.x	x.x
	Median (Min, Max)	x.x (x.x, x.x)	x.x (x.x, x.x)	x.x (x.x, x.x)
	P75	x.x	x.x	x.x
	Hodges-Lehmann Median difference to RPL554 3000µg	x.x	x.x	
	p-value	x.xxxx	x.xxxx	

n = Number of patients with onset of action. % = Percentage of patients calculated relative to the total number of patients in the analysis set.
Time to onset of action (mins): Time of onset of action (defined as >10% increase in FEV_1 from pre-first dose) = Time of onset of action (or censoring time) - time of end of inhalation (mins).
P25, Median and P75: Patients not experiencing onset of action are censored at 120 mins or at time of premature discontinuation (if withdrawn before 120 minutes).
p-value is based on a Gehan-Wilcoxon test between treatment groups and highest dose (RPL554 3000µg).

Source: Listing 16.2.6.7

Programming Notes

Only present if the number of onset of action cases are sufficient to calculate the statistics presented (≥ 10% of patients with onset of action).
The pre-dose value is inserted at time 0.

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Author: Jennifer Allsopp
Date: 22JAN2021

Table 14.2.14

Time to Onset of Action (>10% Increase in FEV_1) on Day 1

(Full Analysis Set in Part B)

Parameter	Statistics	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX

Output ID: EFF14

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Table 14.2.15 Rescue Medication Use (Full Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201 Part B

RPL554 pressurised Metered Dose Inhaler

Table 14.2.15

Rescue Medication Use

(Full Analysis Set in Part B)

		Statistics					
Treatment group	Category	n	Mean	SD	Minimum	Median	Maximum
RPL554 300µg (N=XX)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
RPL554 1000µg (N=XX)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
RPL554 3000µg (N=XX)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
Placebo (N=XX)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x

SD: Standard deviation. n = Number of patients who have an assessment available at the relevant post-dose assessment timepoint (Result). N = Number of patients in the analysis set. The average number of puffs of rescue medication taken per day between days 1 and 7 (inclusive) for each treatment period was collected in the patient diaries.

Source: Listing 16.2.6.9

Programming Notes

Use information from the patient diarys (number of puffs).
For each treatment period calculate the average of the 7 days.
If less than 4 days have results between days 1 and 7 then no result will be presented for that treatment period.

Output ID: EFF15

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Author: Jennifer Allsopp Date: 22JAN2021

Exploratory Efficacy

Table 14.2.16 Dyspnea Scale by Day and Timepoint (Full Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Table 14.2.16

Dyspnea Scale by Day and Timepoint

(Full Analysis Set in Part B)

				Statistics					
Day	Timepoint	Treatment group	Category	n	Mean	SD	Minimum	Median	Maximum
Day 1	Pre-dose	RPL554 300µg (N=XX)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
		RPL554 1000µg (N=XX)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
		RPL554 3000µg (N=XX)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
		Placebo (N=XX)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
	30 mins post-dose	RPL554 300µg (N=XX)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
			Baseline	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
			CFB	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
		RPL554 1000µg (N=XX)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
		…	…	…	…	…	…	…	…
	1 hour post-dose	RPL554 300µg (N=XX)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x
		…	…	…	…	…	…	…	…

CFB: Change from Baseline. SD: Standard deviation.
n = Number of patients who have an assessment available at the relevant post-dose assessment timepoint (Result). n = Number of patients who have an assessment available at Baseline and the relevant post-dose assessment timepoint (Baseline and Change from Baseline). N = Number of patients in the analysis set.
Baseline dyspnea score is defined as the value of dyspnea assessed prior to dosing on day 1 of treatment period 1.
Change from Baseline: Post-dose assessment – Baseline.

Source: Listing 16.2.6.8

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Author: Jennifer Allsopp

Date: 22JAN2021

Table 14.2.16

Dyspnea Scale by Day and Timepoint

(Full Analysis Set in Part B)

				Statistics					
Day	Timepoint	Treatment group	Category	n	Mean	SD	Minimum	Median	Maximum
Day 1	Pre-dose	RPL554 300µg (N=XX)	Result	xx	xx.x	xx.xx	xx.xx	xx.x	xx.x

Programming Notes

Display for the following day and timepoints, relative to dosing:
Day 1 - 30 minutes and 1, 1.5, 2, 4, 8 and 12 hours post-dose
Day 7 - 30 minutes and 1, 1.5, 2, 4, 8, 11 and 12 hours post-dose

Output ID: EFF16

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Table 14.2.17 Comparison of Change from Baseline Dyspnea Score by Day and Timepoint (Full Analysis Set in Part B)
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Protocol: RPL554-MD-201 Part B
RPL554 pressurised Metered Dose Inhaler

Table 14.2.17

Comparisons of Change from Baseline Dyspnea Score by Day and Timepoint

(Full Analysis Set in Part B)

Day	Timepoint	Statistic	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX
Day 1	Pre-dose	Baseline Dyspnea Score				
		n [a]	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Day 7	Pre-dose	Dyspnea Score				
		n	xx	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
		CFB Dyspnea Score				
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
		Estimates from ANCOVA [b]				
		n [c]	xx	xx	xx	xx
		LSMean	xx.x	xx.x	xx.x	xx.x
		95% CI for LSMean	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)

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Table 14.2.17

Comparisons of Change from Baseline Dyspnea Score by Day and Timepoint

(Full Analysis Set in Part B)

Day	Timepoint	Statistic	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX
		Comparisons Against Placebo				
		Treatment Effect - ANCOVA [c]				
		LSMean Diff	xx.x	xx.x	xx.x	
		95% CI for LSMean Diff	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	
		p-value	x.xxxx	x.xxxx	x.xxxx	
		Comparisons Against RPL554 doses				
		Treatment Effect - ANCOVA [c]		Comparison Against RPL554 300µg	Comparison Against RPL554 1000µg	
		LSMean Diff		xx.x	xx.x	
		95% CI for LSMean Diff		(xx.x, xx.x)	(xx.x, xx.x)	
		p-value		x.xxxx	x.xxxx	
	30 mins post-dose	…	…	…	..	…

ANCOVA: Analysis of covariance. CFB: Change from Baseline. CI: Confidence interval. LSMean: Least square mean. LSMean Diff: Least squares mean difference. SD: Standard deviation.
N = Number of patients in the analysis set. n = Number of patients who have an assessment available pre-dose and the relevant post-baseline timepoint. Baseline: Day 1 pre-dose Dyspnea Score.
[a] number of patients with valid values at baseline and post-baseline.
[b] ANCOVA model is used to model the change from baseline using baseline Dyspnea Score as a continuous fixed effect and planned treatment and treatment period as categorical fixed effects.
[c] number of patients with at least one on treatment value who contributed to the model estimation.
* Indicates a significant adjusted p-value (<0.05).

Source: Listing 16.2.6.8

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Table 14.2.17

Comparisons of Change from Baseline Dyspnea Score by Day and Timepoint

(Full Analysis Set in Part B)

Day	Timepoint	Statistic	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX
Programming Notes						
Display for the following day and timepoints, relative to dosing: *Day 1 – Pre-dose (Baseline), 30 minutes and 1, 1.5, 2, 4, 8 and 12 hours post-dose* *Day 7 – Pre-dose, 30 minutes and 1, 1.5, 2, 4, 8, 11 and 12 hours post-dose*						

Output ID: EFF17

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

14.3 Safety
Adverse Event
Table 14.3.27 Treatment-emergent Adverse Events Summary (Safety Analysis Set in Part B)
Verona Pharma Page X of Y
Protocol: RPL554-MD-201 Part B
RPL554 pressurised Metered Dose Inhaler

Table 14.3.27
Treatment-emergent Adverse Events Summary
(Safety Analysis Set in Part B)

Variable/ Category	RPL554 300µg N=XX n (%) E	RPL554 1000µg N=XX n (%) E	RPL554 3000µg N=XX n (%) E	Placebo N=XX n (%) E	Overall N=XX n (%) E
Any TEAE	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Any TEAE related to study medication	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Any TEAE leading to study discontinuation	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Any TEAEs classified by maximum severity, n (%)					
Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Any TEAE leading to death	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Any serious TEAE	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Any serious TEAE related to study medication	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Any serious TEAE leading to study discontinuation	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Any serious TEAEs classified by maximum severity, n (%)					
Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

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Author: Jennifer Allsopp Date: 22JAN2021

Table 14.3.27

Treatment-emergent Adverse Events Summary

(Safety Analysis Set in Part B)

Variable/ Category	RPL554 300µg N=XX n (%) E	RPL554 1000µg N=XX n (%) E	RPL554 3000µg N=XX n (%) E	Placebo N=XX n (%) E	Overall N=XX n (%) E

TEAE: Treatment-emergent adverse event.
n = Number of patients with at least one TEAE in each category. E = Number of mentions (events) in each category. N = Number of patients in the analysis set. % = Percentage of patients calculated relative to the total number of patients in the analysis set.
TEAE = All AEs that started or worsened in severity on or after the first dose of study medication, based on the investigator assessment of severity.
TEAEs with a missing relationship to study medication will be regarded as related to study medication.
TEAEs starting after the first dose of study medication with a missing severity will be classified as severe.
Overall group TEAEs are independent of treatment group. Overall = Presented for all patients in the Safety Analysis Set.

Source: Listing 16.2.7.6

Output ID: AE001

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Table 14.3.28 Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set in Part B)
Verona Pharma Page X of Y
Protocol: RPL554-MD-201 Part B
RPL554 pressurised Metered Dose Inhaler

Table 14.3.28

Treatment-emergent Adverse Events by System Organ Class and Preferred Term

(Safety Analysis Set in Part B)

System Organ Class (%) Preferred Term (%) [a]	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX	Overall N=XX
Patients with at least one TEAE, n (%) E	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
System Organ Class #1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class #2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…					

PT: Preferred term. SOC: System organ class. TEAE: Treatment-emergent adverse event.
n = Number of patients with at least one TEAE in each category. E = Number of mentions (events) in each category. N = Number of patients in the analysis set. % = Percentage of patients calculated relative to the total number of patients in the analysis set.
TEAE = All AEs that started or worsened in severity on or after the first dose of study medication, based on the investigator assessment of severity.
Each patient is counted once for each applicable specific AE, and a patient with multiple AEs within an SOC is counted once for that SOC.
[a] SOCs and PTs are coded using the MedDRA (Version 21.0).

Source: Listing 16.2.7.6

Programming Notes

SOCs and PTs within each SOC are sorted in descending order of percentage in the Overall group.

Output ID: AE002

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Table 14.3.28

Treatment-emergent Adverse Events by System Organ Class and Preferred Term

(Safety Analysis Set in Part B)

System Organ Class (%)	RPL554 300µg	RPL554 1000µg	RPL554 3000µg	Placebo	Overall
Preferred Term (%) [a]	N=XX	N=XX	N=XX	N=XX	N=XX

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Table 14.3.29 Treatment-emergent Adverse Events Related to Study Medication by System Organ Class and Preferred Term (Safety Analysis Set in Part B)

AE003: This output uses shell AE002 [Table 14.3.28]

PT: Preferred term. SOC: System organ class. TEAE: Treatment-emergent adverse event.
n = Number of patients with at least one related TEAE in each category. E = Number of mentions (events) in each category. N = Number of patients in the analysis set. % = Percentage of patients calculated relative to the total number of patients in the analysis set.
TEAE = All AEs that started or worsened in severity on or after the first dose of study medication, based on the investigator assessment of related or not.
Each patient is counted once for each applicable specific AE, and a patient with multiple AEs within an SOC is counted once for that SOC.
[a] SOCs and PTs are coded using the MedDRA (Version 21.0).

Source: Listing 16.2.7.6

Programming Notes:

Replace footnotes in original shell with those listed above

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Table 14.3.30 Treatment-emergent Adverse Events by System Organ Class and Preferred Term and Maximum Severity (Safety Analysis Set in Part B)

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Protocol: RPL554-MD-201 — Part B

RPL554 pressurised Metered Dose Inhaler

Table 14.3.30

Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity

(Safety Analysis Set in Part B)

System Organ Class (%) Preferred Term, n (%) [a]	Maximum Severity	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX	Overall N=XX
Patients with at least one TEAE, n (%)	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class #1	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #1	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #2	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class #2	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	…	…	…	…	…	…

PT: Preferred term. SOC: System organ class. TEAE: Treatment-emergent adverse event.
n = Number of patients with at least one TEAE in each category. N = Number of patients in the analysis set. % = Percentage of patients calculated relative to the total number of patients in the analysis set.

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Version: 2.0

Author: Jennifer Allsopp — Date: 22JAN2021

Table 14.3.30

Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity

(Safety Analysis Set in Part B)

System Organ Class (%) Preferred Term, n (%) [a]	Maximum Severity	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX	Overall N=XX

TEAE = All AEs that started or worsened in severity on or after the first dose of study medication, based on the investigator assessment of severity.
Each patient is counted once for each applicable specific TEAE at the maximum severity and a patient with multiple TEAEs within an SOC is counted once for that SOC at the maximum severity.
[a] SOCs and PTs are coded using MedDRA (Version 21.0).
TEAEs starting after the first dose of study medication with a missing severity will be classified as missing.
Overall = Presented for all patients in the Safety Analysis Set.

Source: Listing 16.2.7.6

Programming Note
SOCs and PTs within each SOC are sorted in descending order of percentage in the Overall group.>

Output ID: AE004

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Table 14.3.31 Treatment-emergent Adverse Events Leading to Discontinuation of Study by System Organ Class and Preferred Term (Safety Analysis Set in Part B)

AE005: This output uses shell AE004 [Table 14.3.28]

Programming Notes

Use the same template of table 14.3.28, selecting only the TEAEs leading to discontinuation of study medications and update "Any TEAE" to "Any TEAE leading to discontinuation of study".
Update source footnote to "Source: Listing 16.2.7.7".

Table 14.3.32 Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set in Part B)

AE006: This output uses shell AE002 [Table 14.3.28]

Programming Notes

Replace footnotes in original shell updating "Patients with at least one TEAE" to "Patients with at least one serious TEAE".
Update source footnote from to "Source: Listing 16.2.7.9".

Table 14.3.33 Serious Treatment-emergent Adverse Events Related to Study Medication by System Organ Class and Preferred Term (Safety Analysis Set in Part B)

AE007: This output uses shell AE003 [Table 14.3.28]

Programming Notes

Use the same template of Table 14.3.28, selecting only the serious TEAEs and update "Patients with at least one TEAE" to "Patients with at least one serious TEAE".
Update source footnote from to "Source: Listing 16.2.7.9".

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Table 14.3.34 Serious Treatment-emergent Adverse Events by System Organ Class, and Preferred Term and Maximum Severity (Safety Analysis Set in Part B)

AE008: This output uses shell AE004 [Table 14.3.30]

Programming Notes

Use the same template of Table 14.3.28, selecting only the serious TEAEs and update "Patients with at least one TEAE" to "Patients with at least one serious TEAE".
Update source footnote to "Source: Listing 16.2.7.9".

Table 14.3.35 Serious Treatment-emergent Adverse Events Leading to Discontinaution of Study by System Organ Class and Preferred Term (Safety Analysis Set in Part B)

AE009: This output uses shell AE005 [Table 14.3.28]

Programming Notes

Use the same template of Table 14.3.29, selecting only the serious TEAEs and update "Any TEAE leading to discontinuation of study" to "Any serious TEAE leading to discontinuation of study". Also update "n = Number of patients with at least one related TEAE in each category." to "n = Number of patients with at least one serious TEAE leading to discontinuation of study.".
Update source footnote to "Source: Listing 16.2.7.9".

Table 14.3.36 Treatment-emergent Adverse Events with Outcome of Death by System Organ Class and Preferred Term (Safety Analysis Set in Part B)

AE010: This output uses shell AE002 [Table 14.3.28]

Programming Notes

Replace footnotes in original shell updating "Patients with at least one TEAE" to "Patients with a TEAE with outcome of death".
Update source footnote to "Source: Listing 16.2.7.8".

Laboratory

Table 14.3.37 Hematology Laboratory Data by Day (Safety Analysis Set in Part B)

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RPL554 pressurised Metered Dose Inhaler

Table 14.3.37

Hematology Laboratory Data by Day

(Safety Analysis Set in Part B)

Laboratory Test Time Point Statistics	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX	Overall N=XX
Test #1 (unit)					
Baseline					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Day 7					
Observed					
n	xx	xx	xx	xx	
Mean	xx.x	xx.x	xx.x	xx.x	
SD	xx.xx	xx.xx	xx.xx	xx.xx	
Median	xx.x	xx.x	xx.x	xx.x	
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	
Change from Baseline					
Mean	xx.x	xx.x	xx.x	xx.x	
SD	xx.xx	xx.xx	xx.xx	xx.xx	

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Author: Jennifer Allsopp

Date: 22JAN2021

Table 14.3.37

Hematology Laboratory Data by Day

(Safety Analysis Set in Part B)

Laboratory Test Time Point Statistics	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX	Overall N=XX
Median	xx.x	xx.x	xx.x	xx.x	
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	
Test #2 (unit)	…	…	…	…	

SD: Standard deviation.
n = Number of patients with a Baseline value and a post-baseline value. N = Number of patients in the analysis set.
Change from Baseline: (Post-baseline assessment – Baseline).
Baseline: Defined as the pre-dose assessment for each treatment period.
Overall: Presented for all patients in the first treatment period in the Safety Analysis Set. Overall n = Number of Baseline values with an assessment available at Baseline and at least one post-dose assessment for treatment period 1.

Source: Listing 16.2.8.5

Programming Notes

Blood samples will be taken and tested at the laboratory for the following hematology laboratory tests: Hemoglobin, hematocrit, total white cell count, leukocyte differential count and platelet count. Present in alphabetical order.

Output ID: LB001

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Table 14.3.38 Biochemistry Laboratory Data by Day (Safety Analysis Set in Part B)

LB002: This output uses shell LB001 [Table 14.3.37]

Programming Notes

Repeat 14.3.37 for Biochemistry (includes creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine transaminase, gamma-glutamyl transferase, lactate dehydrogenase, creatine kinase, thyroid stimulating hormone, triiodothyronine and thyroxine, glucose, potassium, sodium, calcium. Present in alphabetical order.
Update source footnote to "Source: Listing 16.2.8.6".
Add footnote "A number of missing chemistry labs are due to a processing issues such as hemolyzed samples.".

Table 14.3.39 Urinalysis Laboratory Data by Day (Safety Analysis Set in Part B)

LB007: This output uses shell LB001 [Table 14.3.37]

Programming Notes

Repeat 14.3.37 for Urinalysis (includes Leukocytes esterase, occult blood, ketones, bilirubin, urobilinogen, protein and glucose. If urinalysis on Dipstick is positive for leucocytes and/or blood/hemoglobin, a microscopic examination including erythrocytes, leucocytes, bacteria, casts, epithelial cells and crystals). Present in alphabetical order.
Update source footnote to "Source: Listing 16.2.8.7".

Table 14.3.40 Hematology Laboratory Data - Shifts from Baseline in Normal Reference Ranges by Day (Safety Analysis Set in Part B)
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RPL554 pressurised Metered Dose Inhaler

Table 14.3.40

Hematology Laboratory Data - Shifts from Baseline in Normal Reference Ranges by Day

(Safety Analysis Set in Part B)

			Category at Time Point			
Laboratory Test Day Treatment	N [a]	Baseline Category	Low n (%)	Normal n (%)	High n (%)	Total n (%)
Test #1						
Day 7						
RPL554 300µg	xx	Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	
RPL554 1000µg	xx	Low	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		High	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	
RPL554 3000µg	xx	…	…	…	…	…
…		…	…	…	…	…
		…	…	…	…	…
		…	…	…	…	…
End of Study						
Overall	xx	…	…	…	…	…

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Table 14.3.40

Hematology Laboratory Data - Shifts from Baseline in Normal Reference Ranges by Day

(Safety Analysis Set in Part B)

			Category at Time Point			
Laboratory Test						
Day		Baseline	Low	Normal	High	Total
Treatment	N [a]	Category	n (%)	n (%)	n (%)	n (%)
		…	…	…	…	…
		…	…	…	…	…
Test #2						
…						

LLN: Lower limit of normal reference range. ULN: Upper limit of normal reference range.
n = Number of patients. [a] N = Number of patients with a baseline value and a post-baseline value at the time point. Percentages are based on N.
Reference range classification: Low: < LLN. Normal: >= LLN to <= ULN. High: > ULN.
Baseline: Defined as the pre-dose assessment for each treatment period.
End of Study: Defined as the last available assessment assigned to study.

Source: Listing 16.2.8.5

Programming Notes

Blood samples will be taken and tested at the laboratory for the following laboratory tests: Hemoglobin, hematocrit, total white cell count, leukocyte differential count and platelet count. Present in alphabetical order.

Output ID: LB003

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Date: 22JAN2021

Table 14.3.41 Biochemistry Laboratory Data – Shifts from Baseline in Normal Reference Ranges by Day (Safety Analysis Set in Part B)

LB004: This output uses shell LB003 [Table 14.3.40]

Programming Notes

Repeat Table 14.3.40 for Biochemistry. Table should present these parameters only: Creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine transaminase, gamma-glutamyl transferase, lactate dehydrogenase, creatine kinase, thyroid stimulating hormone, triiodothyronine and thyroxine, glucose, potassium, sodium, and calcium. Present in alphabetical order.
Update source footnote to "Source: Listing 16.2.8.6".
Add footnote "A number of missing chemistry labs are due to a processing issues such as hemolyzed samples.".

Table 14.3.42 Urinalysis Laboratory Data – Shifts from Baseline in Normal Reference Ranges by Day (Safety Analysis Set in Part B)

LB005: This output uses shell LB003 [Table 14.3.40]

Programming Notes

Repeat Table 14.3.40 for Urinalysis, and update category to "Negative' if the results are 'Normal' or 'Negative', to 'Trace' if the results are 'Trace' and 'Positive' if the results are equal to '1+','2+','3+',' or '4+'.
Table should present these parameters only: Leukocytes esterase, occult blood, ketones, bilirubin, urobilinogen, protein and glucose. If urinalysis on Dipstick is positive for leucocytes and/or blood/hemoglobin, a microscopic examination including erythrocytes, leucocytes, bacteria, casts, epithelial cells and crystals. Present in alphabetical order.
Update source footnote to "Source: Listing 16.2.8.7".

Table 14.3.43 Biochemistry Laboratory Data - Markedly Abnormal Values (Safety Analysis Set in Part B)
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RPL554 pressurised Metered Dose Inhaler

Table 14.3.43
Biochemistry Laboratory Data - Markedly Abnormal Values
(Safety Analysis Set in Part B)

Laboratory Test, n (%)	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX
Alanine Aminotransferase (ALT)				
> 3 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Alkaline Phosphatase (ALP)				
> 3 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Aspartate Aminotransferase (AST)				
> 3 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Creatinine				
> 2.5 mg/dL	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Gamma Glutamyl Transferase (GGT)				
> 3 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Bilirubin (TBL)				
> 3 x ULN	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

ULN: Upper limit of normal reference range. n = Number of patients in each category with at least one markedly abnormal value. N = Number of patients in the analysis set. % = Percentage of patients with at least one markedly abnormal value relative to the total number of patients in each treatment group.

Source: Listing 16.2.8.6

Output ID: LB006

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Author: Jennifer Allsopp Date: 22JAN2021

ECG
Table 14.3.44 12-Lead Electrocardiogram Data by Day and Timepoint (Safety Analysis Set in Part B)
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Protocol: RPL554-MD-201 Part B
RPL554 pressurised Metered Dose Inhaler

Table 14.3.44
12-Lead Electrocardiogram Data by Day and Timepoint
(Safety Analysis Set in Part B)

Parameter (Unit) Day Time Point Statistics	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX	Overall N=XX
ECG Parameter #1 (unit)					
Baseline					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Day 7					
Pre-dose					
Observed					
n	xx	xx	xx	xx	
Mean	xx.x	xx.x	xx.x	xx.x	
SD	xx.xx	xx.xx	xx.xx	xx.xx	
Median	xx.x	xx.x	xx.x	xx.x	
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	
Change from Baseline					

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Table 14.3.44

12-Lead Electrocardiogram Data by Day and Timepoint

(Safety Analysis Set in Part B)

Parameter (Unit) / Day / Time Point / Statistics	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX	Overall N=XX
Mean	xx.x	xx.x	xx.x	xx.x	
SD	xx.xx	xx.xx	xx.xx	xx.xx	
Median	xx.x	xx.x	xx.x	xx.x	
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	
ECG Parameter #2 (unit)					
…					

SD: Standard deviation.
n = Number of patients with baseline value and a post-baseline value at the time point. N = Number of patients in the analysis set.
Change from baseline: (Pre-dose assessment – baseline assessment).
Baseline: Defined as the pre-dose assessment for each treatment period.
Overall n = Number of patients with a Baseline value at treatment period 1, Day 1.

Source: Listing 16.2.9.12

Programming Notes

ECG quantitative assessments include: QTcF Interval (msec), QRS Interval (msec), PR Interval (msec), RR (msec), Heart rate (bpm). Present in alphabetical order. Display for Pre-dose on Day 7.

Output ID: EG001

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Table 14.3.45 12-Lead Electrocardiogram – Shifts from Baseline by Day and Timepoint (Safety Analysis Set in Part B)
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Protocol: RPL554-MD-201 Part B
RPL554 pressurised Metered Dose Inhaler

Table 14.3.45
12-Lead Electrocardiograms – Shifts from Baseline by Day and Timepoint
(Safety Analysis Set in Part B)

Day / Time Point / Treatment	N	Baseline Category	Category at Timepoint: Normal n (%)	Abnormal NCS n (%)	Abnormal CS n (%)	Total n (%)
Day 7						
Pre-dose						
RPL554 300µg	xxx	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal NCS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal CS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
RPL554 1000µg	xxx	…	…	…	…	…
…						

NCS = Not clinically significant; CS = Clinically significant.
N = Number of patients with a baseline value and a post-baseline value at the time point. Percentages are based on N.
Baseline: Defined as the pre-dose assessment for each treatment period.

Source: Listing 16.2.9.11

Programming Notes

ECG quantitative assessment is Interpretation of results. Display for Pre-dose on Day 7.

Output ID: EG002

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Vital Signs

Table 14.3.46 Vital Sign Data - Change from Baseline to Post-dose by Day and Timepoint (Safety Analysis Set in Part B)

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RPL554 pressurised Metered Dose Inhaler

Table 14.3.46

Vital Sign Data - Change from Baseline to Post-dose by Day and Timepoint

(Safety Analysis Set in Part B)

Parameter (Unit) Day Time Point Statistics	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX	Overall N=XX
Systolic Blood Pressure (mmHg)					
Baseline					
n	xx	xx	xx	xx	xx
Mean	xx.x	xx.x	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Day 1					
1-hour post-dose					
Observed					
n [a]	xx	xx	xx	xx	
Mean	xx.x	xx.x	xx.x	xx.x	
SD	xx.xx	xx.xx	xx.xx	xx.xx	
Median	xx.x	xx.x	xx.x	xx.x	
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	
Change from Baseline					

Document: \\ieedc-vnasc01\biosdata\Verona_Pharma\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 TLF Shells v2.0 - Part B Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Table 14.3.46

Vital Sign Data - Change from Baseline to Post-dose by Day and Timepoint

(Safety Analysis Set in Part B)

Parameter (Unit) Day Time Point Statistics	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX	Overall N=XX
Mean	xx.x	xx.x	xx.x	xx.x	
SD	xx.xx	xx.xx	xx.xx	xx.xx	
Median	xx.x	xx.x	xx.x	xx.x	
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	
2-hour post-dose					
…					

SD: Standard deviation.
[a] n = Number of patients who have an assessment available at the relevant post-dose assessment timepoint (Observed).
n = Number of patients who have an assessment available at Baseline and the relevant post-dose assessment timepoint (Baseline).
N = Number of patients in the analysis set.
Change from baseline: (Pre-dose assessment - baseline assessment).
Baseline: Defined as the pre-dose assessment for each parameter.
Overall: Presented for all patients in the first treatment period in the Safety Analysis Set. Overall n = Number of Baseline values with an assessment available at Baseline and at least one post-dose assessment for treatment period 1, Day 1.

Source: Listing 16.2.9.13

Programming Notes

Vital signs assessments include: Systolic blood pressure, diastolic blood pressure and pulse rate. Present in alphabetical order.
Display for the following timepoints: Day 1 and Day 7: Pre-dose, 1, 2, 4, 8 and 12 hours (all ± 10 minutes).

Output ID: VS001

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Author: Jennifer Allsopp
Date: 22JAN2021

Table 14.3.47 Vital Sign Data - Number and Percentage of Markedly Abnormal Values (Safety Analysis Set in Part B)
Verona Pharma Page X of Y
Protocol: RPL554-MD-201 Part B
RPL554 pressurised Metered Dose Inhaler

Table 14.3.47

Vital Sign Data - Number and Percent of Markedly Abnormal Values

(Safety Analysis Set in Part B)

Vital Sign Parameter	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX
Systolic Blood Pressure (mmHg), n (%)				
n [a]	xx	xx	xx	xx
Value <= 90	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
A decrease from baseline of >=40	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Value >= 180	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
An increase from baseline of >=40	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Diastolic Blood Pressure (mmHg), n (%)				
n [a]	xx	xx	xx	xx
Value <= 50	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
A decrease from baseline of >=20	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Value >= 110	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
An increase from baseline of >=20	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pulse Rate (bpm), n (%)				
n [a]	xx	xx	xx	xx
Value <= 50	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
A decrease from baseline of >=30	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Value >= 110	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
An increase from baseline of >=30	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Document: \\ieedc-vnasc01\biosdata\Verona_Pharma\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 TLF Shells v2.0 - Part B
Version: 2.0
Author: Jennifer Allsopp Date: 22JAN2021

Table 14.3.47

Vital Sign Data - Number and Percent of Markedly Abnormal Values

(Safety Analysis Set in Part B)

Vital Sign Parameter	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX

bpm: beats per minute. mmHg: millimeters mercury.
[a] n = Number of patients with a baseline value and a post-baseline value.
Baseline and post-baseline value would be needed for criteria relating to an increase/decrease from baseline.
N = Number of patients in the analysis set. % = Percentages are based on n.

Source: Listing 16.2.9.14

Output ID: VS002

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Table 14.3.48 Change from Baseline Pulse Rate to Peak Pulse Rate (over 4 hours) (Safety Analysis Set in Part B)

VS005: This output uses shell EFF004 [Table 14.2.6]

Programming Notes

Replace footnotes with:
ANCOVA: Analysis of covariance. CI: Confidence interval. LSMean: Least square mean. LSMean Diff: Least squares mean difference. SD: Standard deviation.
N = number of patients in the analysis set.
Baseline: Pre-dose pulse rate on Day 1 of each treatment period.
Change from Baseline: Post-dose assessment - Pre-dose.
[a] Number of patients with valid values at baseline and timepoint.
[b] ANCOVA model is used to model the change from baseline in pulse rate using baseline assessment as a continuous fixed effect, actual treatment and treatment period as categorical fixed effects.
[c] Number of patients with at least one on treatment value who contributed to the model estimation.
* Indicates a significant p-value (<0.05).

Source: Listing 16.2.9.15

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Version: 2.0
Author: Jennifer Allsopp
Date: 22JAN2021

Physical Examination

Table 14.3.49 Physical Examination Data by Treatment Period and Timepoint (Safety Analysis Set in Part B)

Table 14.3.49

Physical Examination Data by Treatment Period and Timepoint

(Safety Analysis Set in Part B)

Physical Examination: Brief Assessment Treatment Period Time Point Category	RPL554 300µg N=XX	RPL554 1000µg N=XX	RPL554 3000µg N=XX	Placebo N=XX
Physical Examination Test #1				
Treatment Period X - Day Y				
Pre-dose				
Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Abnormal NCS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Abnormal CS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…				
Physical Examination Test #2				
Treatment Period X - Day Y				
Pre-dose				
Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Abnormal NCS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Abnormal CS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…				

CS = Clinically significant. NCS = Not clinically significant. EOS: End of Study.
n = Number of patients who have an assessment available at the relevant timepoint. N = Number of patients in the analysis set. % = Percentage of patients calculated relative to the total number of patients in the analysis set.
Pre-dose: Defined as the assessment taken immediately prior to study medication.
End of Study: Defined as the last available assessment assigned to study.

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Author: Jennifer Allsopp
Date: 22JAN2021

Table 14.3.49

Physical Examination Data by Treatment Period and Timepoint

(Safety Analysis Set in Part B)

Physical Examination: Brief

Assessment / Treatment Period / Time Point / Category	RPL554 300µg	RPL554 1000µg	RPL554 3000µg	Placebo
	N=XX	N=XX	N=XX	N=XX

Source: Listing 16.2.9.16 and 16.2.9.17

Programming Notes

Full/Brief Physical Examination assessments include: For Full: Abdomen [liver and spleen], Cardiovascular system, Extremities, Lymph nodes, Neurological system, Nose, Throat, Respiratory system, Skin, Thyroid gland. For Brief: Abdomen (liver and spleen), Cardiovascular system, Respiratory system, Skin. Present in alphabetical order.

For Full, display for treatment period/timepoints: EOS.
For Brief, display for treatment period/timepoints: Treatment period 1 to 4 - Day 1/7 - pre-dose.

Output ID: PE001

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Table 14.3.50 Physical Examinations - Shifts from Baseline by Treatment Period and Timepoint (Safety Analysis Set in Part B)
Verona Pharma Page X of Y
Protocol: RPL554-MD-201 Part B
RPL554 pressurised Metered Dose Inhaler

Table 14.3.50

Physical Examinations - Shifts from Baseline by Treatment Period and Timepoint

(Safety Analysis Set in Part B)

Physical Examination: Brief

Assessment / Treatment Period / Time Point / Treatment	N	Baseline Category	Category at Timepoint: Normal n (%)	Abnormal NCS n (%)	Abnormal CS n (%)	Total n (%)
Physical Examination Parameter #1						
Treatment Period X - Day Y						
Pre-dose						
RPL554 300µg	xx	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal NCS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal CS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	
RPL554 1000µg	xx	Normal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal NCS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal CS	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	
…						

CS = Clinically significant. NCS = Not clinically significant. EOS: End of Study.
n = Number of patients. N = Number of patients with a baseline value and a post-baseline value at the time point. Percentages are based on N.
Baseline: Defined as the assessment taken immediately prior to study medication.
End of Study: Defined as the last available assessment assigned to study.
For full physical examination baseline is defined as the screening assessment. Baseline for brief physical examinations is Day 1 of each treatment period. Baseline for full physical examination is screening collected in Part A which is compared to the EOS visit from Part B.

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Author: Jennifer Allsopp Date: 22JAN2021

Table 14.3.50

Physical Examinations - Shifts from Baseline by Treatment Period and Timepoint

(Safety Analysis Set in Part B)

Physical Examination: Brief

Assessment / Treatment Period / Time Point / Treatment	N	Baseline Category	Category at Timepoint: Normal n (%)	Abnormal NCS n (%)	Abnormal CS n (%)	Total n (%)

Source: Listing 16.2.9.16 and 16.2.9.17

Full/Brief Physical Examination assessments include: For Full: Abdomen [liver and spleen], Cardiovascular system, Extremities, Lymph nodes, Neurological system, Nose, Throat, Respiratory system, Skin, Thyroid gland. For Brief: Abdomen (liver and spleen), Cardiovascular system, Respiratory system, Skin. Present in alphabetical order.

For Full, display for treatment period/timepoints: EOS.
For Brief, display for treatment period/timepoints: Treatment period 1 to 4 - Day 1/7 - pre-dose.

Output ID: PE002

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Figures

Figure 14.2.6 Geometric Mean of ratios of Peak FEV_1 (over 4 hours) to pre-dose FEV_1 by Treatment (Full Analysis Set in Part B)

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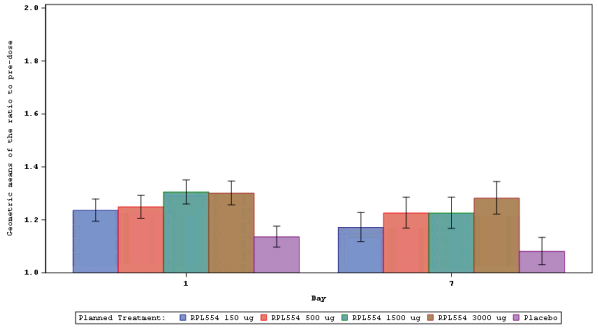
Protocol: RPL554-MD-201 Part B

RPL554 pressurised Metered Dose Inhaler

Figure 14.2.6

Geometric Mean of ratios of Peak FEV_1 (over 4 hours) to pre-dose FEV_1 by Treatment

(Full Analysis Set in Part B)



FEV_1: Forced expiratory volume in 1 second. Pre-dose FEV_1: The value of FEV_1 assessed immediately before first administration on each Day 1.
Bottom and top whiskers: 95% lower confidence limit and 95% upper confidence limit.
Bar: Geometric means on the ratio to pre-dose. ANCOVA model is used to model the change from pre-dose FEV_1 using pre-dose FEV_1 as a continuous fixed effect, planned treatment and treatment period as categorical fixed effects.

Source: Listing 16.2.6.6

Programming Notes

Above is an example. Display for all treatment groups in Part B in ascending order (RPL554 300µg, RPL554 1000µg and RPL554 3000µg) and then placebo. For each treatment group present the GeoMean and SEM (standard error of the mean).

Output ID: EFF11

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Author: Jennifer Allsopp Date: 22JAN2021

Figure 14.2.7 Mean Change from pre-dose FEV_1 to Peak FEV_1 (over 4 hours) by Treatment (Full Analysis Set in Part B)

Verona Pharma

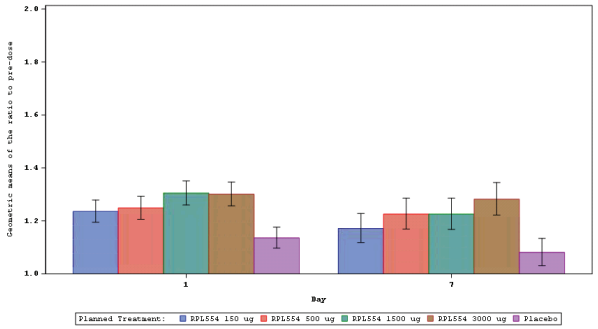
Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Figure 14.2.7

Mean Change from pre-dose FEV_1 to Peak FEV_1 (over 4 hours) Treatment

(Full Analysis Set in Part B)



FEV_1: Forced expiratory volume in 1 second. Pre-dose FEV_1: The value of FEV_1 assessed immediately before first administration on each Day 1.
Bottom and top whiskers: 95% lower confidence limit and 95% upper confidence limit.
Bar: LS Means change from pre-dose. ANCOVA model is used to model the change from pre-dose FEV_1 using pre-dose FEV_1 as a continuous fixed effect, planned treatment and treatment period as categorical fixed effects.

Source: Listing 16.2.6.6

Programming Notes

Above is an example. Display for all treatment groups in Part B in ascending order (RPL554 300µg, RPL554 1000µg and RPL554 3000µg) and then placebo. For each treatment group present the LSMean and SEM (standard error of the mean).
Update y-axis label to "LS Means change from pre-dose (mL)".

Output ID: EFF12

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Figure 14.2.8 Mean Change from Pre-dose FEV_1 during spirometry over Time by Treatment and Day (Full Analysis Set in Part B)

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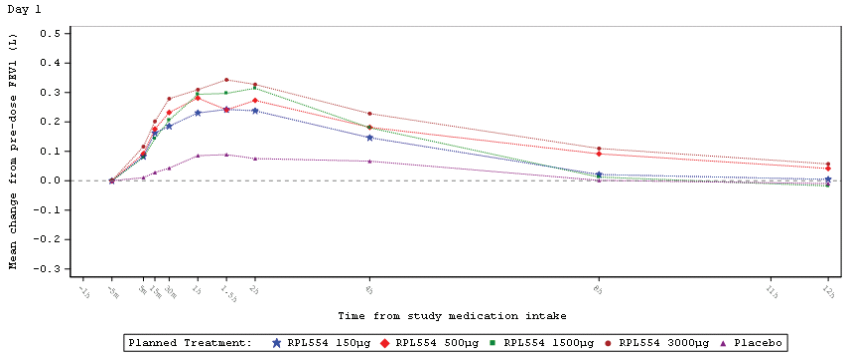
Protocol: RPL554-MD-201 Part B

RPL554 pressurised Metered Dose Inhaler

Figure 14.2.8

Mean Change from Pre-dose FEV_1 during Spirometry over Time by Treatment and Day

(Full Analysis Set in Part B)



Means are calculated on the observed data.
Pre-dose: the highest FEV_1 result collected immediately pre-dose (within 5 minutes) on day 1 for each treatment period.

Source: Listing 16.2.6.5

Programming Notes

Insert a label below the figure for each of the treatment groups, each with a different colour and symbol. Display for all treatment groups in Part B in ascending order (RPL554 300µg, RPL554 1000µg and RPL554 3000µg) and then placebo. Also adjust x-axis for the correct timepoints.
Repeat figure for Day 7.

Output ID: EFF09

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Author: Jennifer Allsopp Date: 22JAN2021

Figure 14.2.9 Kaplan-Meier plot of Time to Onset of Action (>10% Increase in FEV_1) on Day 1 (Full Analysis Set in Part B)

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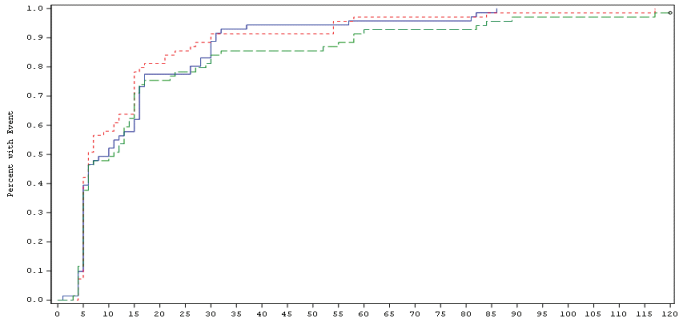
Protocol: RPL554-MD-201 Part B

RPL554 pressurised Metered Dose Inhaler

Figure 14.2.9

Kaplan-Meier plot of Time to Onset of Action (>10% Increase in FEV_1) on Day 1

(Full Analysis Set in Part B)



Time to first onset of action (mins): Time of first onset of action (defined as >10% increase in FEV_1 from pre-first dose) = Time of onset of action (or censoring time) - time of end of inhalation (mins).
P25, Median and P75 time to onset of action: Estimated using Kaplan-Meier statistics.
Censored: Patients not experiencing onset of action are censored at 120 mins or at time of premature discontinuation (if withdrawn before 120 minutes).

Source: Listing 16.2.6.7

Programming Notes

Insert a label below the figure for each of the treatment groups, each with a different colour and symbols.

Output ID: EFF10

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Figure 14.3.5 Mean Change from Pre-dose Pulse Rate to Peak Pulse Rate (over 4 hours) by Treatment (Safety Analysis Set in Part B)

VS003: This output uses shell EFF11 [Figure 14.2.6]

Pre-dose pulse rate: The pulse rate value assessed immediately before administration on each Day 1. Bottom and top whiskers: 95% lower confidence and 95% upper confidence limit. Bar: Results on orginal scale. ANCOVA model is used to model the change from pre-dose pulse rate using pre-dose pulse rate as a continuous fixed effect, and actual treatment as categorical fixed effects.

Programming Notes
Update source footnote to "Source: Listing 16.2.9.15".
Replace footnotes in original shell with those listed above

Figure 14.3.6 Mean Change from Pre-dose in Pulse Rate over Time by Treatment and Day (Safety Analysis Set in Part B)

VS004: This output uses shell EFF09 [Figure 14.2.6]

Means are calculated on the observed data.
Pre-dose: the pre-dose assessment collected on day 1 for each treatment period.

Programming Notes
Update source footnote to "Source: Listing 16.2.9.15".
Replace footnotes in original shell with those listed above

Listings

Listing 16.2.1.2 Completed/Discontinued Patients (All Randomized Analysis Set in Part B)

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Protocol: RPL554-MD-201 — Part B

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.1.2

Completed/Discontinued Patients

(All Randomized Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

			First date of treatment/Study day						
Patient ID	Randomiz-ation date/ Study day	Was treatment unblinded by the site? If yes, provide date and reason	TP 1	TP 2	TP 3	TP 4	Treatment period discontinued	Completed study/ Date of completion/ discontinuation/ Study Day/Primary reason if not completed	Reason not completed, Other (specify)/If AE, specification/If death, date of death
XXXXXXX	DDMMMYYYY/ xx	XXX/DDMMMYYYY/XXXX	DDMMMYYYY/ xx	DDMMMYYYY/ xx	DDMMMYYYY/ xx	DDMMMYYYY/ xx	XXXXXXXXX	No/DDMMMYYYY/xx/ XXXXXX	XXXXXXXXX/XXXXXXXX /DDMMMYYYY

TP: Treatment Period. Study day: Relative to first dose of study medication (i.e., Treatment period 1, Day 1).
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell) and within group by patient ID.

Output ID: L001

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Document: \\ieedc-vnasc01\biosdata\Verona_Pharma\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 TLF Shells v2.0 - Part B

Version: 2.0

Author: Jennifer Allsopp — Date: 22JAN2021

Listing 16.2.2.2 Protocol Deviations (All Randomized Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.2.2

Protocol Deviations

(All Randomized Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Age/Sex/Race	Treatment group	Deviation date/ Relative Day	Protocol deviation	Type of deviation	Severity
XXXXXXXXXXXXXX	XX/X/XXXXXXX	XXXXXXXXX	DDMMMYYYY/xx	XXXXXXXXXXX	XXXXXXXXXXX	XXXXXXXXXXX

As: Native Asian. Bl: Black or African American. CTMS: Clinical trial management system. eCRF: Electronic case report form. F: Female. Ia: American Indian or Alaskan. M: Male. Ot: Other. Pi: Native Hawaiian or Pacific islanders. Un: Unknown. W: White.
Protocol deviations: Defined as deviation types reported in the CTMS log.
Age (years): As reported in the eCRF.
Relative day: Day relative to day of the first dose of study medication per treatment period (i.e., Treatment period X, Day 1).
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell) and within group by patient ID and then the deviation date.

Output ID: L003

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp

Date: 22JAN2021

Listing 16.2.3.2 Patient Included in Analysis Sets (All Randomized Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.3.2

Patient Included in Analysis Sets

(All Randomized Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

	Analysis Sets				
Patient ID	Randomized	Safety	Full	Completers	Pharmacokinetic
XXXXX	Yes	Yes	Yes	Yes	Yes
XXXXX	Yes	Yes	Yes	No	Yes
…					

Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell) and within group by patient ID.

Output ID: L002

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Document: \\ieedc-vnasc01\biosdata\Verona_Pharma\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 TLF Shells v2.0 - Part B

Version: 2.0

Author: Jennifer Allsopp

Date: 22JAN2021

Listing 16.2.4.7 Demographic Characteristics (All Randomized Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.4.7

Demographic Characteristics

(All Randomized Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Country	Age/Sex/Race	Ethnicity	Weight (kg)	Height (cm)	BMI (kg/m^2)	Re-screened patient	Childbearing potential
XXXXXXXXX	UK	62/F/W	XXXXXXXXX	XX	XXX	XX.X	X	X
XXXXXXXXX	UK	67/M/W	XXXXXXXXX	XX	XXX	XX.X	X	NA

As: Native Asian. Bl: Black or African American. BMI: Body mass index. eCRF: Electronic case report form. F: Female. Ia: American Indian or Alaska. M: Male. NA: Not applicable. Ot: Other. Pi: Native Hawaiian or Pacific Islanders. Un: Unknown. W: White.
Age (years): As calculated relative to informed consent date.
BMI (kg/m^2) = Weight (kg) / Height $(m)^2$.
All measurements listed above are measured at Screening on the Demography eCRF.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes:

Order by treatment group (as per shell) and within group by patient ID.

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Document: \\ieedc-vnasc01\biosdata\Verona_Pharma\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 TLF Shells v2.0 - Part B

Version: 2.0

Author: Jennifer Allsopp

Date: 22JAN2021

Listing 16.2.4.8 Screening Disease Characteristics (All Randomized Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.4.8

Screening Disease Characteristics

(All Randomized Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

		Bronchodilator FEV_1 (L)			Bronchodilator FVC (L)					Reversibility	
Patient ID	Age/Sex /Race	Pre	Post	Predicted FEV_1 (%)	Pre	Post	Post-bronchodi-lator FEV_1/FVC	Assessment performed with four puffs of albuterol	Met reversibility test criteria?	%	mL
XXXX	XX/X/XX X	XX	XX		XX	XX	XX	XX	XX	X.X	XXX

As: Native Asian. Bl: Black or African American. F: Female. FEV_1: Forced expired volume in 1 second. FVC: Forced vital capacity. Ia: American Indian or Alaska. M: Male. Ot: Other. Pi: Native Hawaiian or Pacific islanders. Un: Unknown. W: White.
Pre-, post-bronchodilator and reversibility values are the results of the screening reversibility test.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell) and within group by patient ID.

Output ID: L005

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp

Date: 22JAN2021

Listing 16.2.4.9 COPD and Smoking History (All Randomized Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.4.9

COPD and Smoking History

(All Randomized Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

						Smoking History		
Patient ID	Date COPD first diagnosed	Duration of COPD (years) (time since diagnosis)	Date of most recent exacerbation/ Study day	Bronchitis/ Emphysema	Smoking category	Number of packs per day	Number of years smoking	Smoking exposure (pack-years)
XXXXXXX	DDMMMYYYY	xx	DDMMMYYYY/xx	Yes/Yes	Current Smokers	XX	XX	XX

COPD: Chronic Obstructive Pulmonary Disease.
Smoking exposure (pack-years) = Number of packs per day * Number of years smoking, for patients with a smoking history or a current smoker.
Study day: Relative to first dose of study medication (i.e., Treatment period 1, Day 1).
Duration of COPD (years) (time since diagnosis) = (Randomization date – date COPD first diagnosed)/365.25.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell) and within group by patient ID.

Output ID: L006

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp

Date: 22JAN2021

Listing 16.2.4.10 Medical History (All Randomized Analysis Set in Part B)

Verona Pharma Page X of Y

Protocol: RPL554-MD-201 Part B

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.4.10

Medical History

(All Randomized Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Medical history diagnosis	SOC/PT	Start date/ Study day	End date/ Study day
XXXXXXXXX	XXXXXXXXXXXXXXX	XXXXXXXXXXX/ XXXXXXXXXXXXX	DDMMMYYYY/xx	DDMMMYYYY/xx

MedDRA: Medical Dictionary for Regulatory Activities. PT: Preferred Term. SOC: System Organ Class.
Medical history: Coded using MedDRA (Version 21.0).
Study day: Relative to first dose of study medication (i.e., Treatment period 1, Day 1).
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell) and within group by patient ID.

Output ID: L007

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Listing 16.2.4.11 Surgical Procedure History (All Randomized Analysis Set in Part B)

Listing 16.2.4.11

Surgical Procedure History

(All Randomized Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Reported name of procedure	Purpose of procedure	Start date of procedure/ Study day	End date of procedure/ Study day
XXXXXXXXX	XXXXXXXXXXXXXXX	XXXXXXXXXXXXX	DDMMMYYYY/xx	DDMMMYYYY/xx

Surgical procedure history: Coded using MedDRA (Version 21.0).
Study day: Relative to first dose of study medication (i.e., Treatment period 1, Day 1).
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell) and within group by patient ID.

Output ID: L008

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Listing 16.2.4.12 Prior and Concomitant Medications (All Randomized Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201 Part B

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.4.12

Prior and Concomitant Medications

(All Randomized Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Treatment group	Treatment period	Start date (Study day)/ End date (Study day)	P?[a]/ C?[b]	ATC Level 1/ Preferred term	Indication	Dose (Unit)	Frequency/ Route
XXXX/XXXX	XXXXXXXXX	XXXXXXXXX	DDMMMYYYY (XX)/ DDMMMYYYY(XX)	C	XXXXXXXXXXXXXX/ XXXXXXXXXXXXXX	XXXXXX	XX(XX)	XXXXXXXX/ XXXXXXXX

…

ATC: Anatomical Therapeutic Chemical. C: Concomitant. P: Prior.
[a] Medication taken between Part A and Part B of the study or prior to the start of study medication.
[b] Medication taken between start and stop of study medication.
Study day: Day relative to day of the first dose of study medication (i.e., Treatment period 1, Day 1).
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell) and within group by patient ID
'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:
o Had an onset date on or after the study medication.
o AND ended on or after the date of medication or were ongoing at the end of Part B.

Output ID: L009

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Document: \\ieedc-vnasc01\biosdata\Verona_Pharma\RPL554\EZAA8488\Biostatistics\Documentation\SAP\Verona RPL554-MD-201 TLF Shells v2.0 - Part B
Version: 2.0
Author: Jennifer Allsopp Date: 22JAN2021

Listing 16.2.4.13 Prior COPD Medications (All Randomized Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.4.13

Prior COPD Medications

(All Randomized Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Start date (Study day)/ End date (Study day)	ATC Level 1/ Preferred term	Dose (Unit)	Frequency/ Route
XXXX	DDMMMYYYY(XX)/ DDMMMYYYY(XX)	XXXXXXXXXXXXXX/ XXXXXXXXXXXXXX	XX(XX)	XXXXXXXX/ XXXXXXXX

…

ATC: Anatomical Therapeutic Chemical.
Study day: Day relative to day of the first dose of study medication (i.e., Treatment period 1, Day 1).
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell) and within group by patient ID
'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.
COPD medications are when Indication is "Other" and Other reason for medication is "COPD".

Output ID: L009

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Listing 16.2.5.2 Drug Exposure and Accountability (All Randomized Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.5.2

Drug Exposure and Accountability

(All Randomized Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Treatment group	Treatment period/ Timepoint	Start date and of study medication / Relative day	Start time/ End time of inhalations	Weight of pMDI dispensed (g)	Weight of pMDI returned (g)	Weight of pMDI used (g)
XXXXXXXXX	XXXXXXXXX	XXXXXXXXX/ XXXXXXXXX	DDMMMYYYY/xx	HH:MM/HH:MM	XX	XX	XX
XXXXXXXXX	XXXXXXXXX	XXXXXXXXX/ XXXXXXXXX	DDMMMYYYY/xx	HH:MM/HH:MM	XX	XX	XX

Relative day: Relative to day of the first dose of study medication in each treatment period.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell) and within group by patient ID and treatment period.

Output ID: L010
[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Listing 16.2.6.5 Spirometry: FEV_1 Results (Full Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.6.5

Spirometry: FEV_1 Results

(Full Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Treatment group	Treatment period/ Timepoint	Date and time/ Relative day	Refrained from smoking/Capable of withdrawing from long acting bronchodilators	FEV_1 measurement (L)	Predicted FEV_1 (%)
XXXXX	XXXXX	XXXXXX/ XXXXXX	DDMMYYY HH:MM/xx	XXXXXX/ XXXXXX	X.XXX [a]	XX.X
		XXXXXX				
		…				

FEV_1: Forced expiratory volume in 1 second. PFT: Pulmonary function test.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

The assessment timepoints can be Pre PFT -60 min, Immediately Pre-dose, Post PFT 5min, 15min, 30min, 1h, 1.5h, 2h, 4h, 8h, 12h and EOS. Order by treatment sequence (as per shell) and within group by patient ID and treatment period.

Output ID: L014

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Listing 16.2.6.6 Spirometry: FEV_1 Derived Measurements (Full Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201 Part B

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.6.6

Spirometry: FEV_1 Derived Measurements

(Full Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Treatment group	Treatment period/ Timepoint	Date/ Relative day	Peak FEV_1 4h (CFB)	Morning trough FEV_1 (CFB)	Average FEV_1 (AUC) 4h (CFB)	Average FEV_1 (AUC) 12h (CFB)
XXXXX	XXXXXX	XXXXXXX/ XXXXXXX	DDMMYYY/ xx	X.XXX (X.XXX)	X.XXX (X.XXX)	X.XXX (X.XXX)	X.XXX (X.XXX)
…			…				…

AUC: Area under the curve. CFB: Change from Baseline. FEV_1: Forced expiratory volume in 1 second.
Peak FEV_1: Maximum post-dose value among the values collected up to timepoint of interest hours.
Morning trough FEV_1: average of the FEV_1 pre dose assessments (-60 minutes and -5 minutes) on Day 7.
Average FEV_1 AUC: AUC of the FEV_1 values (maximum value of the three assessments at each timepoint) divided by the length of the time (in hours) interval of interest (per visit).
Relative day: Relative to day of the first dose of study medication in each treatment period.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

The assessment timepoints can be Pre PFT, Post PFT, Pre PFT -60 min, Immediately Pre-dose, Post PFT 5min, 15min, 30min, 1h, 1.5h, 2h, 4h, 8h, 11h, 12h and EOS. Order by treatment sequence (as per shell) and within sequence by patient ID and treatment period.

Output ID: L015

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Listing 16.2.6.7 Spirometry: FEV_1 Time to First Occurrence of Onset of Action (Full Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.6.7

Spirometry: FEV_1 Time to First Occurrence of Onset of Action

(Full Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Treatment group	Date/ Study day	Time of pre-dose (HH:MM)	Time of onset of action (HH:MM)	Time to first occurrence of onset of action (mins)	Censored (Yes/No)*
XXXXXX	XXXXXX	YYYY-MM-DD/XX	HH:MM	HH:MM	XX	XX
XXXXXX	XXXXXX	YYYY-MM-DD/XX	HH:MM	HH:MM	XX	XX
…						

Time to first occurrence of onset of action (mins): Time of onset of action (defined as >10% increase in FEV_1 from pre-first dose) = Time of onset of action (or censoring time) – time of end of inhalation (mins).
* Patients not experiencing onset of action are censored at 120 mins or at time of premature discontinuation (if withdrawn before 120 minutes).
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Output ID: L032

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Listing 16.2.6.8 Dyspnea Scale Score (Full Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.6.8

Dyspnea Scale Score

(Full Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Treatment group	Treatment period/ Timepoint	Assessment performed/ Date and time/ Relative day	Dyspnea scale score
XXXXXX	XXXXXX	XXXXXX/ XXXXXX	XXX/ YYYY-MM-DD/HH:MM/ XX	XX

Dyspnea scale score: Likert scale assessment ranging from 0 to 10, where 10 represents the "worst shortness of breath that you can imagine" and 0 represents "no shortness of breath".
Relative day: Relative to day of the first dose of study medication in each treatment period.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell) and within group by patient ID and treatment period.

Output ID: L033

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp

Date: 22JAN2021

Listing 16.2.6.9 Rescue Medications (All Randomized Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.6.9

Rescue Medications

(All Randomized Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Treatment group	Treatment period	Date of administration/ Relative day	Rescue Medication Taken	Number of puffs
XXXXXX	XXXXXX	XXXXXXX	DDMMMYYYY/x	Yes/No	X

Rescue medications = Short acting bronchodilators used to relieve i.e. rescue symptoms immediately.
Relative day: Relative to day of the first dose of study medication in each treatment period.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell) and within group by patient ID and treatment period.

Output ID: L034

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Listing 16.2.6.10 Rescue Medications Canister Dispensed, Weight and Collection Information (All Randomized Analysis Set in Part B)
Verona Pharma

Protocol: RPL554-MD-201
Part B
RPL554 pressurised Metered Dose Inhaler

Listing 16.2.6.10

Rescue Medications Canister Dispensed, Weight and Collection Information

(All Randomized Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

			Inhaler Dispensed			Inhaler Weighed			Inhaler Collected		
Patient ID	Inhaler number	Treatment Period	Inhaler dispensed? If no, specify	Date/time	Weight(g)	Inhaler weighed? If no, specify	Date/time	Weight(g)	Inhaler collected? If no, specify	Date/time	Weight(g)
XXXXXX	XX	XXXXXXXX	X / XXXXX	DDMMYYYY HH:MM	XX.X	X / XXXXX	DDMMYYYY HH:MM	XX.X	X / XXXXX	DDMMYYYY HH:MM	XX.X

Rescue medications = Short acting bronchodilators used to relieve i.e. rescue symptoms immediately.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell) and within group by patient ID.

Output ID: L038

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0
Author: Jennifer Allsopp
Date: 22JAN2021

Listing 16.2.7.6 List of All Adverse Events (Safety Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.7.6

Listing of All Adverse Events

(Safety Analysis Set in Part B)

Treatment groups: <RPL554 300µg/RPL554 1000µg/RPL554 3000µg/Placebo>

Patient ID	Study day of last dose of study medication [a]	SOC/PT/Reported term [b]	Treatment period	Start/End date or ongoing (Study day) [c]	Sev [d]	Rel [e]	Act [f]	Ser [g]	Out [h]	Chronic-ity [i]	Treatment given	Disconti-nued from study	Blind broken
XXXXX	XX	XXXXXX/XXXXX/ XXXXX	XXXXX	DDMMMYYYYY	MI	Y	NC	N	Rslv	XX/X/X	Yes	Yes	Yes

SOC: System organ class. PT: Preferred Term.
AEs which started within a treatment period are assigned to that treatment period.
[a] Day of last dose of study medication relative to day of the first dose of study medication (i.e., Treatment period 1, Day 1).
[b] An asterisk "*" indicates a non-treatment-emergent adverse event.
[c] Study day: Day relative to day of the first dose of study medication (i.e., Treatment period 1, Day 1).
[d] Severity: MI=Mild, MO=Moderate, SE=Severe.
[e] Related to study drug.
[f] Action taken with respect to study drug: NC = Dose Not Changed, DD = Drug Discontinued, DI = Drug Interrupted, O = Other, NA = Not Applicable.
[g] Serious AE.
[h] Outcome: Fatal = Fatal, NRslv = Not recovered/not resolved, Rslv = Resolved/Recovered, RslvG = Recovering/Resolving, RslvS = Recovered/Resolved with sequelae, Unk = Unknown.
[i] S = Single Occasion, I = Intermittent, P = Persistent.
SOCs and PT are coded using the MedDRA (Version 21.0).

Programming Notes

Order by treatment group (as per shell) and within sequence by patient ID, adverse event start date and adverse event end date (in that order).

Output ID: L016

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp

Date: 22JAN2021

Listing 16.2.7.7 Treatment-emergent Adverse Events Leading to Study Discontinutation (Safety Analysis Set in Part B)

L017: This output uses shell L016 [Listing 16.2.7.6]

Listing 16.2.7.8 Treatment-emergent Adverse Events Leading to Death (Safety Analysis Set in Part B)

L018: This output uses shell L016 [Listing 16.2.7.6]

Listing 16.2.7.9 Serious Treatment-emergent Adverse Events (Safety Analysis Set in Part B)

L019: This output uses shell L016 [Listing 16.2.7.6]

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Version: 2.0
Author: Jennifer Allsopp
Date: 22JAN2021

Listing 16.2.7.10 Serious Treatment-emergent Adverse Events - Details (Safety Analysis Set in Part B)

Listing 16.2.7.10

Serious Treatment-emergent Adverse Events - Details

(Safety Analysis Set in Part B)

Treatment groups: <RPL554 300µg/RPL554 1000µg/RPL554 3000µg/Placebo>

Patient ID	SOC/PT/ Reported Term	SAE details	Answer
XXXXXXXXXXX	XXXXXXX/XXXXXXX/XXXXXX	Date Investigator became aware of SAE	DDMMMYYYY
		Death	XXXXX
		Life-threatening	XXXXX
		Initial or prolonged hospitalization	XXXXX
		Date of admission (DD MMM YYYY)	DDMMMYYYY
		Date of discharge (DD MMM YYYY)	DDMMMYYYY
		Persistent or significant disability/incapacity	XXXXX
		Congenital anomaly/birth defect	XXXXX
		Occurred with overdose	XXXXX
		Other medically important event	XXXXX
		Was the SAE caused by other medication? (e.g. Concomitant medication, background medication, rescue medication)	XXXXX
		If Yes, Please Specify	XXXXX
		Was the SAE caused by study procedure(s)?	XXXXX
		If Yes, Please Specify	XXXXX
		Describe treatment for event including medications (1)	XXXXX
		Describe treatment for event including medications (2)	XXXXX
		Describe treatment for event including medications (3)	XXXXX
		List all diagnostic tests that were done to confirm event (1)	XXXXX
		List all diagnostic tests that were done to confirm event (2)	XXXXX
		List all diagnostic tests that were done to confirm event (3)	XXXXX
		Description of SAE/narrative	XXXXX

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Listing 16.2.7.10

Serious Treatment-emergent Adverse Events - Details

(Safety Analysis Set in Part B)

Treatment groups: <RPL554 300µg/RPL554 1000µg/RPL554 3000µg/Placebo>

Patient ID	SOC/PT/ Reported Term	SAE details	Answer
		Additional information	XXXXX

PT: Preferred Term. SAE: Serious Adverse Event. SOC: System Organ Class.
SOCs and PTs are coded using the MedDRA (version 21.0).

Programming Notes

Order by treatment group (as per shell) and within group by patient ID.

Output ID: L020

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Listing 16.2.8.5 Hematology (Safety Analysis Set in Part B)

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Protocol: RPL554-MD-201 Part B

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.8.5

Hematology

(Safety Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Parameter	Reference Range (Lower-Upper)	Treatment group	Treatment period/ Timepoint	Date/Time of assessment/ Relative day	Value (unit) L/H [a]	Change from Baseline
XXXXXXXXXXX	Hemoglobin	XX.X - XX.X	XXXXXXX	XXXXXXX/ XXXXXXX	DDMMMYYYY/HH:MM/ xx	XX (unit)	XX.X

[a] L = Below low normal range. H = Above high normal range.
Baseline: Defined as the pre-dose assessment for each treatment period.
Relative day: Relative to day of the first dose of study medication in each treatment period.
End of Study: Defined as the last available assessment assigned to study.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell), hematology parameter (in alphabetical order), patient ID and treatment period.

Output ID: L021

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

Listing 16.2.8.6 Biochemistry (Safety Analysis Set in Part B)

L022: This output uses shell L021 [Listing 16.2.8.5]

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Listing 16.2.8.7 Urinalysis (Safety Analysis Set in Part B)

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Protocol: RPL554-MD-201 Part B

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.8.7

Urinalysis

(Safety Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Parameter	Treatment group	Treatment period	Date/Time of assessment/ Relative day	Result [a]
XXXXXXXXXXX	Ketones	XXXXXX	XXXXXX	DDMMMYYYY/HH:MM/xx	NEGATIVE (N)
	Leukocyte Esterase			DDMMMYYYY/HH:MM/xx	TRACE (T)
	Occult Blood			DDMMMYYYY/HH:MM/xx	1+ (P)
	…				

[a] Category assigned and used in the shift table: N = Normal or 'Negative'; T = 'Trace' P = '1+','2+','3+',' or '4+'. The flag appears only for the following parameters: Leucocyte Esterase, Bilirubin, Glucose, Ketones, Occult blood, Protein and Urobilinogen.
Relative day: Relative to day of the first dose of study medication in each treatment period.
Baseline: Defined as the pre-dose assessment for each treatment period.
End of Study: Defined as the last available assessment assigned to study.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell), urinalysis parameter (in alphabetical order) and by patient ID and treatment period.

Output ID: L023

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Listing 16.2.9.11 Electrocardiogram Local Reading Overall Evaluation (Safety Analysis Set in Part B)

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RPL554 pressurised Metered Dose Inhaler

Listing 16.2.9.11

Electrocardiogram Local Reading Overall Evaluation

(Safety Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Treatment group	Treatment Period/Day /Timepoint	Date/Time of assessment/Relative day	Overall ECG Evaluation	Abnormal Significant/ Specify
XXXXXXXXXXX	XXXXXXXXX	XXXX/XXXX	DDMMMYYYY/HH:MM/xx	Normal	Y/XXXXXX
XXXXXXXXXXX	XXXXXXXXX	XXXX/XXXX	DDMMMYYYY/HH:MM/xx	Normal	Y/XXXXXX

ECG: Electrocardiogram.
Relative day: Relative to day of the first dose of study medication in each treatment period.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell) and within group by patient ID and treatment period.

Output ID: L024

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Listing 16.2.9.12 12-lead ECG (Safety Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201

Part B

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.9.12

12-lead ECG

(Safety Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Treatment Group	Treatment Period/Day /Timepoint	Date/Time of assessment/Relative day	ECG parameter (unit)	Result	Baseline	CFB
XXXXXXXXXXXXX	XXXXX	XXXXX	DDMMMYYY/HH:MM/xx	HR (bpm)	XX.X	XX.X	XX.X
				PR interval (msec)	XX.X	XX.X	XX.X
				QRS duration (msec)	XX.X	XX.X	XX.X
				QT interval (msec)	XX.X	XX.X	XX.X
				QTcF	XX.X	XX.X	XX.X
				RR interval (msec)	XX.X	XX.X	XX.X
	XXXXX	XXXXX	DDMMMYYY/HH:MM/xx	…	…	…	…

bpm: beats per minute. CFB: Change from baseline. ECG: Electrocardiogram. HR: Heart rate. QTcF: QT interval using Fridericia's correction formula.
Baseline: Defined as the assessment performed pre-dose for each treatment period.
Relative day: Relative to day of the first dose of study medication in each treatment period.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment group (as per shell) and within group by patient ID.

Output ID: L025

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Version: 2.0

Author: Jennifer Allsopp

Date: 22JAN2021

Listing 16.2.9.13 Vital Signs (Safety Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201 Part B

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.9.13

Vital Signs

(Safety Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Treatment group	Treatment period/ Timepoint	Date/Time of assessment/Relative day	Vital sign parameter (unit)	Result	Baseline	CFB
XXXXXXXXXXX	XXXXX	XXXXX	DDMMMYYYY/HH:MM/xx	SBP (mmHg)	XX.X	XX.X	XX.X
				DBP (mmHg)	XX.X	XX.X	XX.X
				Pulse (beats/min)	XX.X	XX.X	XX.X
		XXXXX	DDMMMYYYY/HH:MM/xx	…	…	…	…

CFB: Change from baseline. DBP: Diastolic blood pressure. SBP: Systolic blood pressure.
Relative day: Relative to day of the first dose of study medication in each treatment period.
Baseline: Defined as the assessment performed pre-dose for each treatment period.
End of Study: Defined as the last available assessment assigned to study.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell) and within group by patient ID and treatment period.

Output ID: L026

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Listing 16.2.9.14 Vital Signs - Patients with at Least One Markedly Abnormal Finding (Safety Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.9.14

Vital Signs - Patients with at Least One Markedly Abnormal Finding

(Safety Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Treatment group	Treatment period/ Timepoint	Date/Time of assessment/Relative day	Vital sign parameter (unit)	Result	Baseline	CFB	Markedly abnormal
XXXXXXXXXXX	XXXXX	XXXXX	DDMMMYYYY/HH:MM/xx	SBP (mmHg)	XX.X	XX.X	XX.X	
				DBP (mmHg)	XX.X	XX.X	XX.X L	Y
				Pulse (beats/min)	XX.X	XX.X	XX.X H	Y
		XXXXX	DDMMMYYYY/HH:MM/xx	…	…	…	…	…

CFB: Change from baseline. DBP: Diastolic Blood Pressure. SBP: Systolic Blood Pressure.
Relative day: Relative to day of the first dose of study medication in each treatment period.
L and H represents marked decrease or increase from baseline.
Baseline: Defined as the assessment performed pre-dose for each treatment period.
End of Study: Defined as the last available assessment assigned to study.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell) and within group by patient ID and treatment period.
Only include subjects who have a markedly abnormal finding.

Output ID: L035

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Listing 16.2.9.15 Derived Safety Measurements (Safety Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.9.15

Derived Safety Measurements

(Safety Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Treatment group	Treatment period	Date/ Relative day	Peak Pulse Rate (bpm) (over 4 hours)
XXXXXXXXXX	XXXXX	XXXXX	DDMMMYYYY/xx	X.XXX
		XXXXX	DDMMMYYYY/xx	…

Peak = Maximum post-dose value among the values collected up to timepoint of interest hours.
Relative day: Relative to day of the first dose of study medication in each treatment period.
Baseline: Defined as the assessment performed pre-dose for each treatment period.
End of Study: Defined as the last available assessment assigned to study.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell) and within group by patient ID and treatment period.

Output ID: L035

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Version: 2.0

Author: Jennifer Allsopp

Date: 22JAN2021

Listing 16.2.9.16 Brief Physical Examination (Safety Analysis Set in Part B)
Verona Pharma
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Protocol: RPL554-MD-201
Part B
RPL554 pressurised Metered Dose Inhaler

Listing 16.2.9.16

Brief Physical Examination

(Safety Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Treatment group	Visit	Date/Time of examination/ Relative day	Body system	Result (if Abnormal, clinical significant), Specify
XXXXXXXXXXX	XXXXX	XXXXX	DDMMMYYYY/HH:MM/xx	XXXXXXXXXXXXXX	XXXXXXXXXXXXX

Relative day: Relative to day of the first dose of study medication in each treatment period.
EOS: End of Study, defined as the last available assessment assigned to study.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell) and within group by patient ID and treatment period.

Output ID: L027

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0
Author: Jennifer Allsopp
Date: 22JAN2021

Listing 16.2.9.17 Full Physical Examination (Safety Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.9.17

Full Physical Examination

(Safety Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Treatment group	Visit	Date/Time of examination/ Relative day	Body system	Result (if Abnormal, clinical significant), Specify
XXXXXXXXXXX	XXXXX	XXXXX	DDMMMYYYY/HH:MM/xx	XXXXXXXXXXXXXX	XXXXXXXXXXXXXX

Relative day: Relative to day of the first dose of study medication in each treatment period.
EOS: End of Study, defined as the last available assessment assigned to study.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell) and within group by patient ID and treatment period.

Output ID: L027

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp

Date: 22JAN2021

Listing 16.2.9.18 Inhalation Training (All Randomized Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.9.18

Inhalation Training

(All Randomized Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Treatment Period	Inhalation training given?	Date of inhalation training/ Relative day
XXXXXXX	XXXXXXX	XXXXXXX	DDMMMYYYY/xx

Relative day: Relative to day of the first dose of study medication in each treatment period.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment sequence (as per shell) and within group by patient ID.

Output ID: L013

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp

Date: 22JAN2021

Listing 16.2.9.19 Pregnancy Urine Test Results (All Randomized Analysis Set in Part B)

Verona Pharma

Protocol: RPL554-MD-201

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.9.19

Pregnancy Urine Test Results

(All Randomized Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Treatment Group	Treatment Period	Urine pregnancy test performed/Date of test/Relative day	Urine pregnancy test result
XXXXXXX	XXXXXXXXXX	XXXXXXX	XX/DDMMMYYYY/xx	XXXXXXX

Relative day: Relative to day of the first dose of study medication in each treatment period.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment group (as per shell) and within group by patient ID.
Consider only female patients.
Multiple pregnancy risk factors and multiple relevant family history will be presented as one result per row, as these are not presented separately in Pregnancy report eCRF.

Output ID: L036

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp Date: 22JAN2021

Listing 16.2.9.20 Pregnancy Report Results (All Randomized Analysis Set in Part B)

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Protocol: RPL554-MD-201 — Part B

RPL554 pressurised Metered Dose Inhaler

Listing 16.2.9.20

Pregnancy Report Results

(All Randomized Analysis Set in Part B)

Treatment sequence: <Seq 1/Seq 2/Seq 3/Seq 4>

Patient ID	Pregnancy report item	Results
XXXXXXXXXXXX	Date of last menstrual period/Relative day	DDMMMYYYY/xx
	Date of expected delivery/Relative day	DDMMMYYYY/xx
	Overall number of previous pregnancies	XX
	Number of normal deliveries	XX
	Number of spontaneous miscarriages	XX
	Number of other previous pregnancies	XX
	Relevant pregnancy risk factors	XXXXXXXXX
	Relevant family history	XXXXXXXXX

Relative day: Relative to day of the first dose of study medication in each treatment period.
Seq 1 = RPL554 300 mcg/RPL554 1000 mcg/RPL554 3000 mcg/Placebo. Seq 2 = RPL554 1000 mcg/Placebo/RPL554 300 mcg/ RPL554 3000 mcg. Seq 3 = RPL554 3000 mcg/RPL554 300 mcg/Placebo/RPL554 1000 mcg. Seq 4 = Placebo/RPL554 3000 mcg/RPL554 1000 mcg/RPL554 300 mcg.

Programming Notes

Order by treatment group (as per shell) and within group by patient ID.
Consider only female patients.
Multiple pregnancy risk factors and multiple relevant family history will be presented as one result per row, as these are not presented separately in Pregnancy report eCRF.

Output ID: L037

[Source: Filepath\Filename.sas] IQVIA DDMMMYYYY HH:MM

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Version: 2.0

Author: Jennifer Allsopp — Date: 22JAN2021