

STATISTICAL ANALYSIS PLAN

RPL554-CO-204

A Phase II, Randomized, Double Blind, Placebo Controlled, Three Way Crossover Study to Assess the Bronchodilator Effect of RPL554 Administered in Addition to Open Label Tiotropium/Olodaterol in Patients with COPD

AUTHOR: NICHOLAS ROUBINIS

VERSION NUMBER AND DATE: V1.0, 18OCT2018

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 18OCT2018) for Protocol RPL554-CO-204.

	Name	Signature	Date
Author:	Nicholas Roubinis		
Position:	Senior Biostatistician		
Company:	IQVIA		

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

	Name	Signature	Date
Approved By:	Ruaan Van Zyl		
Position:	Manager, Biostatistics		
Company:	IQVIA		
Approved By:	Brian Maurer		
Position:	Senior Director, Clinical Operations		
Company:	Verona Pharma		

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	18OCT2018	Nicholas Roubinis	Not Applicable – First Version

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

TABLE OF CONTENTS

1.	INTRODUCTION.....	9
2.	STUDY OBJECTIVES.....	9
2.1.	Primary Objective	9
2.2.	Secondary Objectives	9
2.3.	Exploratory Objectives	10
3.	STUDY DESIGN.....	10
3.1.	General Description	10
3.2.	Schedule of Events	12
3.3.	Changes to Analysis from Protocol	12
4.	PLANNED ANALYSES.....	12
4.1.	Data Monitoring Committee (DMC).....	13
4.2.	Interim Analysis.....	13
4.3.	Final Analysis	13
5.	ANALYSIS SETS.....	14
5.2.	All Patients Randomized Set [RND]	14
5.3.	Safety Analysis Set [SAF]	14

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

5.4.	Full Analysis Set [FAS]	14
5.5.	Completers Analysis Set [CAS]	15
5.6.	Pharmacokinetics [PK] Analysis Set	15
6.	GENERAL CONSIDERATIONS	15
6.1.	Reference Start Date and Study Day	15
6.2.	Baseline	16
6.3.	Repeat/reschedule, Unscheduled Visits and Early Termination Data	16
6.4.	Windowing Conventions	17
6.5.	Statistical Tests	17
6.6.	Common Calculations	17
6.7.	Software Version	18
7.	STATISTICAL CONSIDERATIONS	18
7.1.	Adjustments for Covariates and Factors to be Included in Analyses	18
7.2.	Multicenter Studies	19
7.3.	Missing data	19
7.4.	Multiple Comparisons/ Multiplicity	19
7.5.	Examination of Subgroups	20
8.	OUTPUT PRESENTATIONS	20

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

9.	DISPOSITION AND WITHDRAWALS.....	20
10.	DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS.....	21
10.1.	Derivations	22
11.	SURGICAL, MEDICAL AND COPD/SMOKING HISTORY.....	22
12.	MEDICATIONS	23
13.	STUDY MEDICATION EXPOSURE	25
13.1.	Derivations	26
14.	STUDY MEDICATION COMPLIANCE	26
15.	EFFICACY OUTCOMES.....	26
15.1.	Primary Efficacy	26
15.1.1.	Primary Efficacy Variable(s) & Derivation(s).....	26
15.1.2.	Missing Data Methods for Primary Efficacy Variable(s)	27
15.1.3.	Primary Analysis of Primary Efficacy Variable(s)	27
15.2.	Secondary Efficacy	29
15.2.1.	Secondary Efficacy Variables & Derivations	29
15.2.1.1.	Change from baseline in trough FEV ₁ on Day 4 (mean of 11 and 12 hour values after evening dose on Day 3) (Secondary variable 1).....	29
15.2.1.2.	Determination of AUC _{0-4h} FEV ₁ (Average FEV ₁ over 4 hours) after morning dosing on Day 3 (Secondary variable 2).....	29
15.2.1.3.	Peak FEV ₁ (measured in first 4 hours after dosing) and AUC _{0-12h} FEV ₁ after dosing on Day 1 (Secondary variable 3).....	30
15.2.1.4.	Change from baseline in AUC _{0-8h} , AUC _{0-12h} FEV ₁ measured on Day 3 (Secondary variable 4).....	30
15.2.1.5.	Change from baseline in peak FEV ₁ after evening dose on Day 3 (peak over 4 hours) (Secondary variable 5)	30
15.2.1.6.	Determination of onset of action (>10% increase in FEV ₁ , from pre-first dose, censored at 120 minutes) on Day 1 (Secondary variable 6)	31
15.2.1.7.	RV (Residual volume), FRC (Functional residual capacity) and sG _{aw} (Specific airway conductance) at 1.25 hours on Day 1 and 1.25, 8.25 and 12.25 hours after dosing on Day 3 (Secondary variable	

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

7)	31
15.2.1.8.	RPL554 steady state pharmacokinetics (AUC _{0-12h} , C _{max} , time to maximum concentration [t _{max}]) (Secondary variable 8).....32
15.2.2.	Missing Data Methods for Secondary Efficacy Variable(s)32
15.2.3.	Analysis of Secondary Efficacy Variables.....32
15.2.3.1.	Analysis of Secondary Variables 1, 2, 3, 4, 5 and 7.....32
15.2.3.2.	Analysis of Secondary Variable 6.....32
15.2.3.3.	Analysis of Secondary Variable 8.....33
15.3.	Exploratory Efficacy33
15.3.1.	Exploratory Efficacy Variables & Derivations33
15.3.1.1.	AUC _{0-24h} FEV ₁ on Day 333
15.3.1.2.	Change from baseline in dyspnea scale34
15.3.2.	Missing Data Methods for Exploratory Efficacy Variable(s)34
15.3.3.	Analysis of Exploratory Efficacy Variables34
16.	SAFETY OUTCOMES 35
16.1.	Adverse Events.....35
16.1.1.	All TEAEs36
16.1.1.1.	Severity36
16.1.1.2.	Relationship to Study Medication.....36
16.1.2.	TEAEs Leading to Discontinuation of Study Medication36
16.1.3.	Serious Adverse Events37
16.1.4.	Adverse Events Leading to Death.....37
16.2.	Laboratory Evaluations37
16.2.1.	Laboratory Reference Ranges and Markedly Abnormal Criteria38
16.3.	ECG Evaluations38
16.4.	Vital Signs.....39
16.5.	Physical Examination39
16.6.	Other Safety Assessments40

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

17. REFERENCES.....	41
APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS.....	42
IQVIA Output Conventions.....	42
Table and Listing Output Conventions	42
Figure Output Conventions	44
Dates & Times.....	44
Spelling Format.....	45
Presentation of Treatment Groups	45
Presentation of Treatment Sequences.....	45
Presentation of Visits.....	46
Listings	46
 APPENDIX 2. PARTIAL DATE CONVENTIONS	 46
Algorithm for Treatment Emergence of Adverse Events.....	47
Algorithm for Prior / Concomitant Medications	48

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for protocol RPL554-CO-204. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. The statistical analysis plan (SAP) is based on the final protocol version 2.0, dated 10JUL2018.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of this study is to investigate the bronchodilator effect on peak forced expiratory volume in 1 second (FEV₁) (measured in the first 4 hours after dosing) of nebulized RPL554 dosed twice daily for 3 days, as compared to placebo, when administered in addition to once daily tiotropium/olodaterol. The peak FEV₁ is measured after the morning dose on Day 3.

2.2. SECONDARY OBJECTIVES

The secondary objectives are as follows:

- To assess the bronchodilator effect on peak FEV₁ (measured in the first 4 hours after dosing) and average (measured as the area under the curve [AUC]) FEV₁ over 12 hours of nebulized RPL554 after the first dose (on Day 1) as compared to placebo, when administered in addition to tiotropium/olodaterol
- To investigate the effect of twice daily nebulized doses of RPL554, as compared to placebo, when administered in addition to tiotropium/olodaterol on morning trough FEV₁ (mean of values 11 and 12 hours after last dose of RPL554) on Day 4
- To investigate the effect of twice daily nebulized doses of RPL554, as compared to placebo, when administered

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

in addition to tiotropium/olodaterol on average (measured as AUC) FEV₁ over 4, 8 and 12 hours after morning dosing on Day 3

- To assess the bronchodilator effect on peak FEV₁ measured within 4 hours after the evening dosing of RPL554 on Day 3
- To analyze plasma concentrations and assess the steady state pharmacokinetics (PK) of RPL554 when administered in addition to tiotropium/olodaterol
- To assess the tolerability and safety of twice daily nebulized doses of RPL554 in addition to tiotropium/olodaterol
- To determine the onset of action of RPL554 when administered with tiotropium/olodaterol (after the first dose)
- To investigate the effects of RPL554 on specific airway conductance (sG_{aw}) and lung volumes (residual volume [RV], functional residual capacity [FRC]) when administered in addition to tiotropium/olodaterol

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives are as follows:

- To assess the dose response of RPL554 on peak and average (measured as AUC over 12 hours) after morning dose on Day 3, and morning trough FEV₁ (mean of values at 11 and 12 hours after last dose of RPL554) on Day 4, when dosed in addition to tiotropium/olodaterol
- To examine the effect of RPL554 on top of tiotropium/olodaterol on average (measured as AUC) FEV₁ over 24 hours after 3 days of dosing
- To examine the effect of RPL554 on top of tiotropium/olodaterol on a Likert dyspnea scale

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a Phase II, randomized, double blind, placebo controlled, complete block three-way crossover study to

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

investigate treatment with nebulized RPL554 and tiotropium/olodaterol Respimat[®] in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

A total of approximately 70 male or female 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 across up to 4 sites, in the United States (US) and the United Kingdom (UK). All patients will receive 3 combinations of study treatment (1.5 mg RPL554, 6 mg RPL554 and placebo) in a randomized, crossover design; therefore, each patient will act as his or her own control in the study. There are 6 possible treatment sequences a patient can be randomized to: a) RPL544 1.5 mg / RPL544 6.0 mg/Placebo, b) RPL544 1.5 mg / Placebo / RPL544 6.0 mg, c) RPL544 6.0 mg / RPL544 1.5 mg / Placebo, d) RPL544 6.0 mg / Placebo / RPL544 1.5 mg, e) Placebo / RPL544 1.5 mg / RPL544 6.0 mg and f) Placebo / RPL544 6.0 mg / RPL544 1.5 mg, with the ratio of patients to treatment groups / treatment sequences being 1:1:1:1:1:1.

Patients will be screened for eligibility, including a reversibility test with salbutamol (in UK) or albuterol (in US) and ipratropium between 7 and 14 days before the first dose of study treatment. Eligible patients will then attend 3 separate treatment periods (Treatment periods 1 to 3), with each lasting 3 days and separated by a 7 to 14-day washout period. Figure 1 below summarizes these details.

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

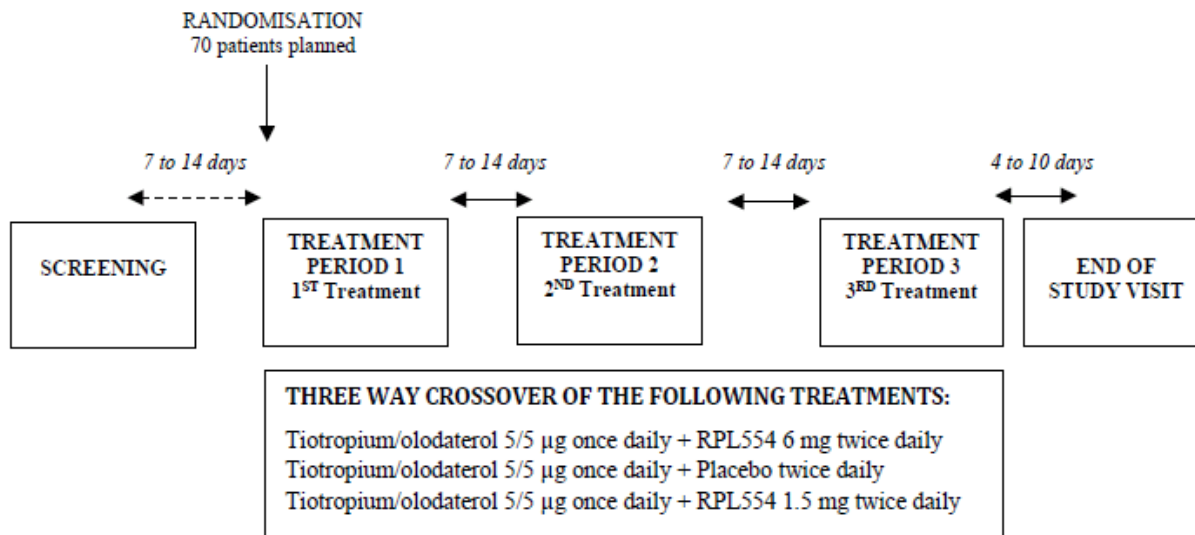
Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Figure 1 Study Flow Chart



3.2. SCHEDULE OF EVENTS

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

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

Not applicable.

4. PLANNED ANALYSES

There are no data monitoring committee (DMC) or interim analyses to be performed for this study. Only a final

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

analysis 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. FINAL ANALYSIS

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

- All outstanding data issues and queries resolved.
- All irresolvable data issues documented in the Data Handling Report (DHR) from Data Management.
- All coding of medications and AEs completed.
- Serious adverse event (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 all verbatim text from the eCRF will be presented in outputs “as is” with no “manual hard coding” corrections for such data.

PK analysis will be performed by another party (third party vendor), however details of this analysis will be specified in this SAP.

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

5. ANALYSIS SETS

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

5.1. ALL SUBJECTS ENROLLED SET [ENR]

The all subjects enrolled (ENR) set will contain all subjects 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 receive at least 1 dose of study medication and patients will be classified according to 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 sufficient data collected after intake of study medication to compute the pharmacodynamic parameters (FEV_1 , sG_{aw} , RV, FRC measurements) on at least 2 treatment periods. For analyses and displays based on FAS, patients will be classified according to actual treatment.

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

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 3 treatment periods per schedule of events (see section 6 of the protocol for schedule details).

5.6. PHARMACOKINETICS [PK] ANALYSIS SET

The PK analysis set will contain all patients in the RND analysis set who have a blood sampling performed after at least 1 dose of RPL544 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 first dose of study medication (e.g., treatment period 1, Day 1 is the day of the first dose of study medication in treatment period 1), 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).

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

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 3). Baseline pre-dose FEV₁/FVC will be derived from 3 acceptable readings (performed up to 8 times to obtain these), with the highest being used for analysis. For safety laboratory tests (hematology, biochemistry, urinalysis) and 24-hour Holter monitoring screening assessment, performed 7 to 14 days before randomization, will be considered as baseline.

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 FEV₁ or other reason, the repeated/rescheduled visit, will be listed and summarized as the valid visit (same visit number assigned), at the discretion of the Investigator. Unscheduled measurements will not be included in by-visit summaries, but will contribute to the endpoint value, at the discretion of the Investigator. For example, if an unscheduled visit occurred at 10 hours post-dose on Day 3, then this value will be considered in the calculation of the average FEV₁ over 12 hours (AUC_{0-12h} FEV₁) on Day 3. 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 early termination occurs pre-first dose (after baseline), then it is summarized at the actual visit. If

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

termination is after first dose in period or during the following wash-out period, data collected remains at the visit performed. However, if the patient returns for end of study, then this data will be mapped to end of study visit.

If AE data occurs in the 7 to 14-day gap between treatment periods, these will be mapped to the earlier of the two treatment periods. Similarly, the AE will be mapped to the last treatment group received. If AE data occurs in the post-treatment period, these will be mapped to the last treatment period and last treatment group received.

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. < 0.05) will be flagged by means of an “*” 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 time point – pre-dose at each treatment period value.

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

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).
- Morning trough FEV_1 calculated as mean of the 11 and 12-hour FEV_1 measurements following the pre-evening dose.

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 1.5mg
 - RPL554 6.0mg
 - Placebo

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

- Treatment period (fixed).
 - Treatment period 1
 - Treatment period 2
 - Treatment period 3
- Baseline value of analyzed variable (covariate).

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at up to 4 study centers, in US and UK. Randomization to treatment groups is not stratified by country/center.

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 analysis plan. Partial date imputations will be handled as specified in [Appendix 2](#).

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

Significance of treatment effect will be tested for the primary and secondary efficacy endpoints and will be done for each of the 2 doses of RPL554 against placebo, starting with the highest dose (6 mg). To this end, the fixed-sequence testing approach (Maurer et al., 1995; Westfall & Krishen, 2001) will be used.

Let $i = 0, 1$ and 2 represent increasing dose levels, 0 denoting placebo. Also, let μ_i , $i = 0, 1$ and 2 , denote the mean change from baseline in peak FEV₁ at Day 3 (measured in first 4 hours after morning dosing) for placebo and each increasing active dose level, respectively. The primary null hypotheses are defined as:

$H_i: \mu_j - \mu_0 = 0$ and will be tested against the 2-sided alternative $K_i: \mu_j - \mu_0 \neq 0$, $j = 1$ and 2

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Finally, let p_1 and p_2 denote the marginal p-values obtained from the statistical tests associated with H_1 and H_2 (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 accepted without testing.

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

- Step 1: If $p_2 \leq \alpha$ reject H_2 and go to Step 2. Otherwise, fail to reject H_2 and H_1 and stop.
- Step 2: 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.

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.

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Patient disposition, withdrawals and reasons for exclusion from each analysis set and protocol deviations, including inclusion and exclusion criteria will be presented for all patients, including those with screen failures and summarized by treatment sequence. Number of patients treated and discontinued in each treatment period will also be presented. Discontinued patients are assigned to treatment period based on the last day of treatment + 1 from study start: treatment period 1, treatment period 2 (7 to 14 days after treatment period 1), treatment period 3 (7 to 14 days after treatment period 2). If the patient discontinued/withdrawn, he/she will be allocated to the last treatment period attended and last treatment administered.

All protocol deviations collected will be divided into critical, major or minor categories and will be assigned to the treatment group the patient is on according to when the protocol deviation occurred. Critical and/or major protocol deviations affect the integrity of the drug activity data and will be obtained by the clinical research associates (CRAs) and documented in a log. The deviations will be discussed at monthly calls with the sponsor to determine the accuracy of classification and severity and to determine if any changes are needed to the wording of the descriptions. Major deviations however, are discussed as soon as they arise.

Preliminary assignment to each analysis population (therefore whether a patient is included/excluded in each analysis population [excluding the PK and PK/PD 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 will be reviewed by Verona and assignments/comments will be discussed and an agreement should be reached prior to the Database Lock of the study. After agreement is reached, the EXCEL sheet should be authorized by means of a customer authorization form (CAF).

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics (including screening disease characteristics) will be presented for the all analysis sets (RND, SAF, FAS, CAS, PK) by the treatment sequences. No statistical testing will be carried out for demographic or other baseline characteristics.

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

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

- Age (years)
- Sex
- Childbearing potential
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- BMI (kg/m²)
- Pre (prior to dosing at baseline)/post (post dosing at baseline) bronchodilator FEV₁ (both in liters and in percentage of predicted normal)
- Post-bronchodilator FEV₁/ forced vital capacity (FVC)
- FEV₁ reversibility test (mL and %)

10.1. DERIVATIONS

- Age (years) = (Randomization date – informed consent date)
- Height (cm) = height (cm) (if recorded in cm) OR height (inches) x 2.54 (if recorded in inches)
- Weight (kg) = weight (kg) (if recorded in kg) OR weight (lbs) x 0.453592 (if recorded in lbs)
- BMI (kg/m²) = weight (kg)/ height (m)²

Demographic and other baseline characteristics without derivations are recorded on the eCRF and used as is on the eCRF.

11. SURGICAL, MEDICAL AND COPD/SMOKING HISTORY

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

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

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

12. MEDICATIONS

Medications will be coded using WHO-DD version specified in the data management plan and will be presented by Anatomical Therapeutic Chemical (ATC) (the 1st level of the ATC code) and PT for the RND analysis set.

Medications may be assigned to multiple treatment groups based on their occurrence date, due to the cross-over design of the study. 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.

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

concomitant.

- ‘Prior’ medications are medications which started and stopped in the 3 months prior to the first dose of study medication and are recorded at Screening.
- ‘Concomitant’ medications are medications which:
 - Started 3 months prior to first dose of each study medication and on or after the first dose of each study medication.
 - AND ended on or after the date of first dose of study medication or were ongoing at the end of the study.
 - A patient can report more than 1 concomitant medication with the same PT, but concomitant medication will be counted only once. Similarly, if a patient reported more than 1 concomitant within the same primary ATC Level 1, the patient will be counted only once. However, a medication can be counted once per treatment period, if it occurs in multiple treatment periods.

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

- Rescue medications will be recorded on the Rescue Medication page of the eCRF. These are short acting bronchodilators and will be sourced by the study center and dispensed at the Screening visit. Rescue medication used during each treatment period must be separately documented on the eCRF (medication, dose, route, date and time of each administration). Protocol procedures must continue even if rescue medication has been taken. Salbutamol/albuterol is to be used for primary rescue use. Salbutamol/albuterol and ipratropium (or Combivent®) must be withheld for at least 8 hours prior to spirometry (per below), and this is to be confirmed in the eCRF at the start of each treatment period. If this withhold is not met, the patient should be rescheduled for a repeat visit within permitted windows. Short acting bronchodilators should be withheld as follows:
 - 8 hours prior to pre-reversibility spirometry for Screening
 - 8 hours prior to pre-dose spirometry for Day 1, Day 2 and Day 3
 - Post dose:
 - Day 1 until after +12 hours spirometry.
 - Day 2 until after + 12 hours spirometry.
 - Day 3 until after + 24 hours spirometry (Day 4 morning).

Rescue medications used (during the treatment periods) will be summarized by treatment group and the type of

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

rescue medications, presented in a table. Time to first use of rescue medication will also be estimated for each treatment group, where start time is considered the time of first dose administration in treatment period 1 and end time the time when first rescue medication was used or the time of last spirometry (24 h after evening dose 3) performed in the period. Kaplan-Meier estimates, if calculable, for median time to first overall fall with 95% confidence interval, minimum, 25th and 75th percentiles and maximum will be presented for each treatment group. An accompanying Kaplan-Meier figure will also be presented, including all available rescue medications recoded from patients. Patients not experiencing a use of rescue medications will be censored at the time of last spirometry within treatment period or premature discontinuation. If rescue medication usage is deemed to be low (number of patients using rescue medications < 10%), as expected, the Kaplan-Meier estimates and accompanying figure will not be presented. Rescue medications will also be presented in a listing.

13. STUDY MEDICATION EXPOSURE

Exposure to study medication in days will be presented by treatment sequence for the RND analysis set. The date of first study medication administration (tiotropium/olodaterol dosing) will be taken from the Drug Exposure eCRF page for treatment period 1. The date of last study medication will be taken from the Disposition eCRF page based on date of completion/discontinuation. Interruptions/washout periods between treatment periods (7 to 14 days) are not considered for duration of exposure. The mean duration of exposure in days will also be summarized. Total exposure (in mL) will be based on the volume of residual product for AM dose of the first nebulization (RPL554 or Placebo dosing), or residual product of first and second nebulization (RPL554 or Placebo dosing), if applicable, and will also be summarized.

Drug accountability will also be summarized by treatment sequence for the RND analysis set. The number of vials dispensed will be compared to the number of unused vials returned, as measured on the Drug accountability eCRF page.

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

13.1. DERIVATIONS

- Duration of exposure (days) = date of last study medication administration – date of first study medication administration – number of washout period days between treatment periods (21 to 42 days) + 1.
- Total exposure (mL) = (number of vials dispensed x contents of each vial) – residual product for AM dose of first (and second, if applicable) nebulization.
- Drug accountability (number of vials) = Number of vials dispensed - number of unused vials returned.

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)

The primary efficacy variable is peak FEV₁ (measured in first 4 hours after morning dosing). This will be measured after dosing on Day 3 and is collected on the Spirometry Study measurements eCRF page.

Three acceptable readings are performed at each of the timepoints in first 4 hours after morning dosing on Day 3 (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 FEV₁ is derived as the highest of all these readings.

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Descriptive statistics (see [Appendix 1](#) [Programming conventions for outputs]) for peak FEV₁ will be presented for all patients assigned to FAS, at each assessment and change from baseline at each assessment and overall (where overall is regardless of treatment period, day and timepoint to assess treatment group as a whole) as relevant. All summaries will be presented for each treatment group. In addition, a figure (bar graph) representing mean change from baseline FEV₁ to peak FEV₁ by treatment will be presented, including the standard error of the mean.

Change from baseline FEV₁ to peak FEV₁ (over 4 hours) at Day 3 will be derived to test the hypothesis described in [section 15.1.3](#) with baseline defined as the FEV₁ pre-dose assessment (-5 minutes) collected on Day 1 of each treatment period. Peak FEV₁ at Day 3 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 3 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 + tiotropium/olodaterol treatment group (RPL554 6mg + tiotropium/olodaterol and/or RPL554 1.5 mg + tiotropium/olodaterol) will increase peak FEV₁ (change from Baseline) compared to RPL554 placebo + tiotropium/olodaterol at Day 3 (measured in first 4 hours after morning dosing) by rejecting the null hypothesis described below at significance level $\alpha=0.05$ 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 FEV₁ at Day 3 (measured in first 4 hours after morning dosing) for 1 RPL554 + tiotropium/olodaterol treatment group (RPL554 6mg + tiotropium/olodaterol and/or RPL554 1.5 mg + tiotropium/olodaterol) and RPL554 placebo + tiotropium/olodaterol respectively.

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

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 3 as response variable, and treatment, treatment period and baseline FEV_1 as covariates. Analyses will be implemented using the SAS® procedure MIXED as follows:

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

where CHG = difference in log (peak FEV_1) – log (baseline FEV_1) i.e. log (peak FEV_1 / baseline FEV_1)

TREATMENT = treatment group (1.5 mg RPL554, 6 mg RPL554 and placebo)

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

BASELINE = log (baseline FEV_1)

USUBJID = subject ID

The primary comparison will be the contrast (difference in least squares mean [LSMEAN]) between 6 mg RPL554 and placebo on Day 3 (in first 4 hours after morning dosing).

Peak FEV_1 and baseline FEV_1 will be log-transformed prior to analysis using natural logarithm. The difference between the two (log [peak FEV_1] – log [baseline FEV_1]) equals log (peak FEV_1 / baseline FEV_1). The covariate, baseline FEV_1 , 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.

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

Summary statistics for FEV₁ will be presented for baseline, peak on Day 3 (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.

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 from baseline in trough FEV₁ on Day 4 (mean of 11 and 12 hour values after evening dose on Day 3) (Secondary variable 1)

Morning trough FEV₁ is defined as mean of values 11 and 12 hours after the evening dose of RPL554 on Day 3.

15.2.1.2. Determination of AUC_{0-4h} FEV₁ (Average FEV₁ over 4 hours) after morning dosing on Day 3 (Secondary variable 2)

Average FEV₁ after morning dosing on Day 3 is defined as the AUC_{0-4h} FEV₁ collected during Day 3 under analysis, divided by the length of the time (in hours). AUC_{0-4h} FEV₁ is derived using the following formula:

$$AUC = \frac{1}{2}(t_1 - t_0)(y_1 + y_0) + \frac{1}{2}(t_2 - t_1)(y_2 + y_1) + \dots$$

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 FEV₁ values. The AUC result will then be divided by the actual time (the time elapsed since morning dosing on Day 3, until the time of assessment) at 4-hour assessment (as this can occur \pm 10 minutes) to obtain the average FEV₁. For analysis purposes, it will be assumed that the pre-dose value occurred at time 0 when computing pharmacodynamic parameters.

If a patient misses' hours 2 and 4 then the AUC₀₋₄ is set to missing.

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

15.2.1.3. Peak FEV₁ (measured in first 4 hours after dosing) and AUC_{0-12h} FEV₁ after dosing on Day 1 (Secondary variable 3)

Peak FEV₁ (after 4 hours of dosing) on Day 1 is defined as the change from baseline to peak FEV₁ and derived similarly to primary analysis (see [section 15.1.3](#)), but instead at Day 1.

AUC_{0-12h} FEV₁ on Day 1 is also defined and derived similarly to secondary endpoint above (see [section 15.2.1.2](#)), but at Day 1. Parameters will be calculated over 12 hours (on Day 1 of each treatment period). If patient misses hours 8 and 12 then the AUC_{0-12h} is set to missing.

15.2.1.4. Change from baseline in AUC_{0-8h}, AUC_{0-12h} FEV₁ measured on Day 3 (Secondary variable 4)

AUC_{0-8h} and AUC_{0-12h} FEV₁ on Day 3 is defined and derived similarly to secondary endpoint in [section 15.2.1.2](#), but at Day 3. Parameters will be calculated over 8 and 12 hours (on Day 3 of each treatment period), respectively. If patient misses hours 4 and 8 then AUC_{0-8h} is set to missing. Similarly, if 8 and 12 then the AUC_{0-12h} is set to missing.

15.2.1.5. Change from baseline in peak FEV₁ after evening dose on Day 3 (peak over 4 hours) (Secondary variable 5)

Peak FEV₁ on Day 3 evening is defined as the maximum value among the 13, 14 and 16-hour assessments collected after pre-evening dose of each treatment period.

Change from baseline to peak FEV₁ on Day 3 evening (over 4 hours) will be derived to test the hypothesis described in [section 15.1.3](#).

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

15.2.1.6. Determination of onset of action (>10% increase in FEV₁, from pre-first dose, censored at 120 minutes) on Day 1 (Secondary variable 6)

Onset of action is defined as a >10% increase in FEV₁ 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 onset of action is deemed to be low (number of patients with onset of action < 10%), the Kaplan-Meier estimates and accompanying figure will not be presented, similar to rescue medications.

15.2.1.7. RV (Residual volume), FRC (Functional residual capacity) and sG_{aw} (Specific airway conductance) at 1.25 hours on Day 1 and 1.25, 8.25 and 12.25 hours after dosing on Day 3 (Secondary variable 7)

RV, FRC, sG_{aw} (1.25 hours) on Day 1 are defined as the lung volume/specific airway conductance assessments recorded pre-dose and 1.25 hours post-dose (on Day 1 of each treatment period). Similarly, RV, FRC, sG_{aw} (pre-dose, 1.25, 8.25 and 12.25 hours) on Day 3 are defined as the lung volume/specific airway conductance assessments recorded pre-dose and 1.25, 8.25 and 12.25 hours, respectively post-dose (on Day 3 of each treatment period).

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

15.2.1.8. RPL554 steady state pharmacokinetics (AUC_{0-12h} , C_{max} , time to maximum concentration [t_{max}]) (Secondary variable 8)

Concentration of RPL554 (AUC_{0-12h} , C_{max} [maximum concentration], t_{max} [time to maximum concentration]) on Day 3 of each treatment period (pre-dose, 5, 30 and 45 minutes and 1, 1.5, 2, 4, 8 and 12-hours post dose).

15.2.2. MISSING DATA METHODS FOR SECONDARY EFFICACY VARIABLE(S)

Missing data will not be imputed similarly to primary endpoint, where applicable (see [section 15.1.2](#)).

15.2.3. ANALYSIS OF SECONDARY EFFICACY VARIABLES

15.2.3.1. Analysis of Secondary Variables 1, 2, 3, 4, 5 and 7

The secondary endpoints listed above will be analyzed in the same way as the primary endpoint. In the analyses using AUC of the FEV_1 , the average FEV_1 at the each timepoint of interest will be used. Similarly, to the primary analysis, average AUC of the FEV_1 and baseline FEV_1 will be log-transformed prior to analysis using natural logarithm and the difference between the two will be estimated, with $\log(\text{baseline } FEV_1)$, being a covariate.

In the analysis of the RV, FRC and sG_{aw} the pre-dose will be used as baseline in the model and the dependent endpoint will be the change at each timepoint of interest (1.25 hours after dosing on Day 1 and 1.25, 8.25 and 12.25 hours after dosing on Day 3).

15.2.3.2. Analysis of Secondary Variable 6

Onset of action will be summarized by treatment and a Kaplan-Meier plot illustrating time to onset constructed. The SAS® procedure LIFETEST including covariates, if relevant, will be used as follows:

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.


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

where ONSET = time to onset of action

TRT = treatment group

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

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).

15.2.3.3. Analysis of Secondary Variable 8

Summary statistics (number of observations, geometric mean, CV [coefficient of variation], minimum and maximum) will be presented for the concentrations of RPL554, specifically AUC_{0-12h} , C_{max} and t_{max} on the PK analysis set population.

15.3. EXPLORATORY EFFICACY

15.3.1. EXPLORATORY EFFICACY VARIABLES & DERIVATIONS

15.3.1.1. AUC_{0-24h} FEV₁ on Day 3

AUC_{0-24h} FEV₁ after evening dose on Day 3 is defined and derived similarly to secondary endpoint in [section 15.2.1.3](#). Parameters will be calculated over 24 hours (on Day 4 of each treatment period). If patient misses hours 12 and 24 then the AUC_{0-24h} is set to missing.

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

15.3.1.2. Change from baseline in dyspnea scale

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 1 pre-dose and 5, 15, and 30 minutes post-dose; and on Day 3 pre-dose and 5, 15, 30 minutes and 24 hours post-dose. Baseline will be considered the pre-dose assessment on Day 1 of each treatment period and change from baseline will be assessed at 30 min post-dose on Day 1 and Day 3 and 24hours post-dose on Day 3.

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

Missing data will not be imputed similarly to primary endpoint, where applicable (see [section 15.1.2](#)).

15.3.3. ANALYSIS OF EXPLORATORY EFFICACY VARIABLES

The analysis relating the to the average FEV₁ on Day 3 over 24 hours will be analyzed in the same way as the primary endpoint.

Dyspnea score and the change in dyspnea score will be summarized at each timepoint of interest (30 min post-dose on Day 1 and Day 3 and 24hours post-dose on Day 3).

In addition, Wilcoxon signed rank test for pair-wise comparisons between baseline and the relevant post-baseline assessment, will be applied to identify differences.

The SAS® procedure NPAR1WAY will be used as follows, to conduct the Wilcoxon rank sum test:

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

```
PROC NPAR1WAY DATA=... WILCOXON;  
  CLASS TREATMENT;  
  VAR DIFF;  
  EXACT WILCOXON;  
RUN;
```

where

DIFF = difference in dyspnea score between baseline and each post-baseline assessment

TREATMENT = treatment group

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF.

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

16.1. ADVERSE EVENTS

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

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

See [Appendix 2](#) for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

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 OF STUDY MEDICATION

TEAEs leading to permanent discontinuation of study medication 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 of study medication, summaries of incidence rates (frequencies and

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

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.

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 central 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 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 each treatment period) to each post-dose time point (for quantitative measurements), including overall (where overall is regardless of treatment period, day and timepoint to assess treatment group as a whole).
- Incidence of abnormal values according to normal range criteria
- Shift from baseline according to normal range criteria (for quantitative measurements and categorical

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

measurements)

- Listing of abnormal values occurring after the first dose of study treatment.

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 safety (and other) laboratory assessments will also be identified by the Investigator by manually annotating a print out of the results.

16.3. ECG EVALUATIONS

Overall results from the central ECG (Electrocardiogram) Reading Center 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)

The following summaries will be provided for ECG data:

- Actual assessments at 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).

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

- Shift of overall assessment baseline to post-dose time points according to markedly abnormal criteria
- Incidence of markedly abnormal criteria
- Listing of patients meeting markedly abnormal criteria

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).

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
- Incidence of abnormalities at end of study
- Changes in abnormalities between screening and end of study

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

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

- Incidence of abnormalities prior to discharge from the study center on Day 4
- Changes in abnormalities between pre-dose on Day 1 and prior to discharge from the study center on Day 4

16.6. OTHER SAFETY ASSESSMENTS

24-hour Holter monitoring screening assessment, performed 7 to 14 days before randomization (with patients returning the next day for the removal of the Holter monitor), and on Day 3 pre-dose will be performed. The results of these assessments will be summarized by treatment group and time point of collection.

The Screening Holter report must have a minimum of 18 hours recording that is evaluable for rhythm analysis and the report must be reviewed as part of the inclusion criteria prior to randomization.

Alcohol breath test and trainings (including whole body plethysmography training and inhalation training) results will be presented in a listing only.

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

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.

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

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.
- If possible, include 100% frequencies in the table shell, so that it is clear what the denominator is for percentage calculations.
- All listing outputs should be sorted (preferably by Treatment, Site Number and Subject Number).
- Exponentiation will be expressed using a double asterisk, i.e., mm³ will be written as mm**3.
- 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, Median, Minimum, Maximum)

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

- 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:

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

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

Ratios:

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

Spacing:

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

Denominators:

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

Missing values

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

FIGURE OUTPUT CONVENTIONS

- Figures should be provided in RTF files using the SAS Output Delivery System (ODS), as Computer Graphics Metafile (CGM) formatted graphical output generated by SAS.
- The CGM file itself 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 DDMMYYYY THH:MM:SS.

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

SPELLING FORMAT

English US.

PRESENTATION OF TREATMENT GROUPS

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

Treatment Group	For Tables, Graphs and Listings
Tiotropium/olodaterol 5 µg /5 µg once daily + RPL554 1.5 mg	RPL554 1.5 mg
Tiotropium/olodaterol 5 µg /5 µg once daily + RPL554 6.0 mg	RPL554 6.0 mg
Tiotropium/olodaterol 5 µg /5 µg once daily + Placebo twice daily	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
RPL544 1.5 mg / RPL544 6.0 mg / Placebo	Seq 1
RPL544 1.5 mg / Placebo / RPL544 6.0 mg	Seq 2
RPL544 6.0 mg / RPL544 1.5 mg / Placebo	Seq 3
RPL544 6.0 mg / Placebo / RPL544 1.5 mg	Seq 4
Placebo / RPL544 1.5 mg / RPL544 6.0 mg	Seq 5
Placebo / RPL544 6.0 mg / RPL544 1.5 mg	Seq 6
Non-randomized (where applicable)	Non-randomized

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order, considering there will be 3 treatment periods (1 to 3):

Long Name (default)	Short Name
Screening	Scr
Day 1	Day 1
Day 2	Day 2
Day 3	Day 3
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.

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

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 If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

START DATE	STOP DATE	ACTION
		If stop date \geq 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 \geq 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 \geq study med start date and start date \leq end of treatment, assign as concomitant If stop date \geq 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 \geq study med start date and start date \leq end of treatment, assign as concomitant If stop date \geq 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 \leq end of treatment, assign as concomitant If start date $>$ end of treatment, assign as post treatment

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

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

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.

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

Document: Z:\RPL554\UYA25849\Biostatistics\Documentation\SAP\Verona RPL554-CO-204 SAP v1.0

Author: Nicholas Roubinis

Version Number: 1.0

Version Date: [18OCT2018]

Template No.: CS_TP_BS016 Revision 5

Reference: CS_WI_BS005

Effective Date: 01Apr2018

Copyright © 2009, 2010, 2012, 2016, 2018 IQVIA. All rights reserved. The contents of this document are confidential and proprietary to IQVIA Holdings Inc. and its subsidiaries. Unauthorized use, disclosure or reproduction is strictly prohibited.