Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for a 24- week randomised, double-blind and placebo-controlled study to evaluate the efficacy and safety of 62.5 mcg Umeclidinium Inhalation Powder delivered once-daily via a Novel Dry Powder Inhaler in subjects with Chronic Obstructive Pulmonary Disease
Compound Number	:	GSK573719
Effective Date	:	26-DEC-2017

Description:

- The purpose of this RAP is to describe the planned analyses and output to be performed on all subjects enrolled from China and Korea and on the subjects enrolled in China alone: A China subgroup analysis for Protocol AC4117410.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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TABLE OF CONTENTS

PAGE

1. REPORTING & ANALYSIS PLAN SYNPOSIS 6

2. SUMMARY OF KEY PROTOCOL INFORMATION 8
   2.1. Changes to the Protocol Defined Statistical Analysis Plan 8
   2.2. Study Objective(s) and Endpoint(s) 8
   2.3. Study Design 10
   2.4. Statistical Hypotheses 10

3. PLANNED ANALYSES 11
   3.1. Interim Analyses 11
   3.2. Final Analyses 11

4. ANALYSIS POPULATIONS 11
   4.1. Protocol Deviations 13

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS 14

6. STUDY POPULATION ANALYSES 15
   6.1. Overview of Planned Analyses 15

7. PRIMARY STATISTICAL ANALYSES 17
   7.1. Primary Efficacy Analyses 17
      7.1.1. Overview of Planned Primary Efficacy Analyses 17
      7.1.2. Planned Primary Efficacy Statistical Analyses 18
      7.1.3. Planned Missing Data Sensitivity Statistical Analyses for Trough FEV1 20
   7.2. Secondary Efficacy Analyses 20
      7.2.1. Overview of Planned Secondary Efficacy Analyses 20
      7.2.2. Planned Secondary Efficacy Statistical Analyses 21
         7.2.2.1. 0-6 h Weighted Mean FEV1 on Day 1 21
         7.2.2.2. TDI 22
   7.3. Other Efficacy Analyses 23
      7.3.1. Overview of Planned Other Efficacy Analyses 23
      7.3.2. Planned Other Efficacy Statistical Analyses 24
         7.3.2.1. Time to Onset and Time to First COPD Exacerbation 24
         7.3.2.2. Proportion Endpoints 25
         7.3.2.3. Serial FEV1/FVC and Trough FVC 26
         7.3.2.4. Rescue Salbutamol Use (mean puffs/days) 26
   7.4. Health Outcomes Analyses 27
      7.4.1. Overview of Planned Health Outcomes Analyses 27
      7.4.2. Planned Health Outcomes Statistical Analyses 28

8. SAFETY ANALYSES 29
   8.1. Adverse Events Analyses 29
      8.1.1. Overview of Planned Adverse Events Analyses 29
   8.2. Clinical Laboratory Analyses 30
      8.2.1. Overview of Planned Clinical Laboratory Analyses 30

8.3. Other Safety Analyses 31
8.3.1. Overview of Planned Other Safety Analyses 31
8.3.2. Planned Safety Statistical Analyses 32

9. REFERENCES 33

10. APPENDICES 34
10.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population 35
10.1.1. Exclusion of Data from Modified Intent-to-treat Analyses 35
10.1.2. Exclusions of Data from Per Protocol Analyses 35
10.1.2.1 Inclusion/exclusion/randomisation Criteria Deviations 35
10.1.3. Programmed Checks to Identify Non-medication Deviations 36
10.1.4. Programmed Checks to Identify Medication Deviations 38
10.2. Appendix 2: Time & Events 40
10.2.1. Protocol Defined Time & Events 40
10.3. Appendix 3: Assessment Windows 42
10.4. Appendix 4: Treatment States and Phases 43
10.4.1. Treatment Phases 43
10.4.2. Treatment States 43
10.4.2.1. Treatment States for Concomitant Medications Data 43
10.4.2.2. Treatment States for AE Data 43
10.4.2.3. Treatment States for COPD exacerbation 44
10.5. Appendix 5: Data Display Standards & Handling Conventions 45
10.5.1. Study Treatment & Sub-group Display Descriptors 45
10.5.2. Baseline Definition & Derivations 45
10.5.2.1. Baseline Definitions 45
10.5.2.2. Derivations and Handling of Missing Baseline Data 45
10.5.3. Reporting Process & Standards 46
10.6. Appendix 6: Derived and Transformed Data 48
10.6.1. General 48
10.6.2. Study Population 48
10.6.3. Safety 50
10.6.4. Health- Related Quality of Life 53
10.6.5. Efficacy 54
10.7. Appendix 7: Premature Withdrawals & Handling of Missing Data 58
10.7.1. Premature Withdrawals 58
10.7.2. Handling of Missing Data 58
10.7.2.1. Handling of Missing Responder 58
10.7.2.2. Handing of Missing Dates 59
10.7.2.3. Handling of Partial Dates 59
10.7.2.4. Handling of Missing Data for Statistical Analysis 60
10.8. Appendix 8: Values of Potential Clinical Importance 61
10.8.1. Laboratory Values 61
10.8.2. ECG 61
10.8.3. Vital Signs 61
10.9. Appendix 9: Multicenter Studies 62
10.10. Appendix 10: Examination of Covariates, Subgroups & Other Strata 63

10.11. Appendix 11: Multiple Comparisons & Multiplicity 64
10.12. Appendix 12: Model Checking and Diagnostics for Statistical Analyses 65
10.12.1. Statistical Analysis Assumptions 65
10.13. Appendix 13 – Abbreviations & Trade Marks 67
10.13.1. Abbreviations 67
10.13.2. Trademarks 68
10.14. Appendix 14: List of Data Displays 69
10.14.1. Data Display Numbering 69
10.14.2. Mock Example Shell Referencing 69
10.14.3. Deliverable [Priority] 69
10.14.4. Study Population Tables 70
10.14.5. Study Population Figures 75
10.14.6. Efficacy Tables 76
10.14.7. Efficacy Figures 82
10.14.8. Safety Tables 85
10.14.9. Safety Figures 90
10.14.10. ICH Listings 92
10.14.11. Non-ICH Listings 95
10.15. Appendix 15: Example Mock Shells for Data Displays 98

1. REPORTING & ANALYSIS PLAN SYNPOSIS

Overview	Key Elements of the RAP
Purpose	• This RAP describes the analysis to be performed on all subjects enrolled from China, Korea and also the subjects enrolled in China alone: a China subgroup analysis for study AC4117410.
Protocol	• This RAP is based on the protocol amendment 03 [(Dated: 11/Nov/2015) of study AC4117410 (GSK Document Number. 2013N159587_03] and eCRF Version (1.3).
Primary Objective	• Evaluate the efficacy of Umeclidinium Inhalation Powder at 62.5 mcg compared with placebo when administered once-daily via ELLIPTA™ over a 24-week treatment period in subjects with COPD
Primary Endpoint	• Change from baseline of clinic visit trough (pre-bronchodilator) FEV1 on Treatment Day 169 Trough FEV1 on Treatment Day 169 is defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on Treatment Day 168 (i.e. at Week 24). [Note: This has been altered from the Protocol GSK Document Number 2013N159587_03 where the endpoint was not clarified change from baseline]
Study Design	• 24-week, phase III multicenter, randomized, double-blind, placebo-controlled, parallel-group study. • Planned total number of approximately 288 randomized subjects will be randomised to UMEC 62.5 mcg and placebo treatment group in a 2:1 ratio. • A total of 10 study clinic visits are planned to be conducted on an outpatient basis but may be less if subjects withdraw from study. • The total duration of subject participation, including follow-up will be approximately 27 weeks. • All subjects will be provided with albuterol/salbutamol for use on an “as-needed” basis throughout the Pre-screen, Run-in and study Treatment periods.
Planned Analyses	• All decisions regarding final analysis, as defined in this RAP document, will be made prior to Database Freeze (unblinding) of the study data.
Analysis Populations	• The All Subjects Enrolled Population will be used for reporting subject disposition, AE listing and treatment misallocations listing. • The Screen and Run in Failure population will be used for the tabulation of reasons for screen and run-in failure and for inclusion, exclusion and randomisation criteria failed. • The Modified Intent-to-treat (ITT) Population will constitute the primary population for all data analyses and displays. • The Per Protocol (PP) Population will be used for confirmatory analyses of the primary endpoint only, irrespective of how many subjects are in the PP population.

Overview	Key Elements of the RAP
Hypothesis	For each test on each efficacy endpoint: • The null hypothesis is that there is no difference between Umeclidinium 62.5 mcg and placebo. $H_0: T_1 - T_2 = 0$ • The alternative hypothesis is there is a difference between Umeclidinium 62.5 mcg and placebo. $H_1: T_1 - T_2 \neq 0$
Primary Analyses	• The primary endpoint of change from baseline trough in FEV1 on Day 169 will be analysed for the Modified Intent-to-treat Population using a mixed model repeated measures (MMRM) analysis, including trough FEV1 recorded at each of Days 2, 28, 56, 84, 112, 168 and 169.
Secondary Analyses	• The analysis of the mean Transition Dyspnea Index (TDI) focal score on Days 28, 84 and 168 will use the same methodology as that for the primary endpoint. • Weighted mean clinic visit FEV1 over 0 to 6 hours post-dose at Visit 2 (Day 1) will be analysed using analysis of covariance (ANCOVA).

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There was one change to the originally planned statistical analysis specified in the protocol amendment 03 (Dated: 11-NOV-2015) of study AC4117410 (GSK Document Number 2013N159587_03). This change was made so that primary endpoint description is consistent across all documents.

In the following section of the protocol, the primary endpoint is Clinic visit trough (pre-bronchodilator) FEV1 on Treatment Day 169.

PROTOCOL SUMMARY
OBJECTIVE(S) and Endpoints (Section 2)
Efficacy (Section 6.2)
Hypotheses （Section 8.1）
Sample Size Assumptions (Section 8.2.1)

In Efficacy Analyses Section (8.3.5.1), it is clarified that the primary endpoint is change from baseline trough in FEV1 on Day 169.

Actually, the primary endpoint of this study is change from baseline in trough FEV1 on Day 169. The sample size calculation was based on this endpoint. To avoid any confusion, the primary endpoint has been defined as change from baseline in trough FEV1 on Day 169 in this RAP.

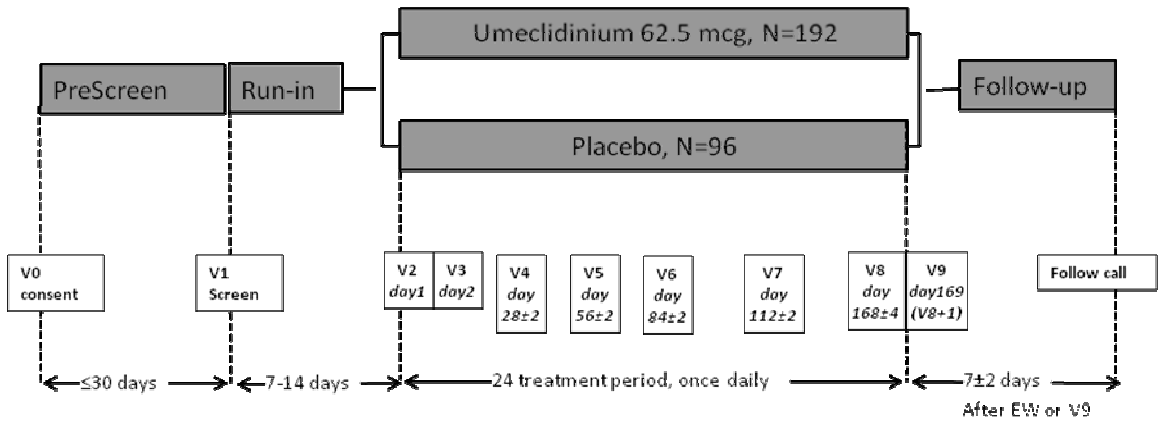
2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	
• To evaluate the efficacy of Umeclidinium 62.5 mcg compared with placebo when administrated once-daily via the ELLIPTATM over a 24-week treatment period in subjects with COPD	**Primary Efficacy Endpoints:**
	• Change from Baseline of Clinic visit trough (pre-bronchodilator) FEV_1 on Treatment Day 169 Trough FEV_1 on Treatment Day 169 is defined as the mean of the FEV_1 values obtained 23 and 24 hours after dosing on Treatment Day 168 (i.e. at Week 24).
	Secondary Efficacy Endpoints:
	• TDI focal score at Week 24 (Day 168)
	• Weighted mean clinic visit FEV_1 over 0 to 6 hours post-dose at visit 2 (Randomization visit, Day 1)
	Other Efficacy Endpoints:
	• Trough FEV_1 and TDI focal score at other time points
	• Rescue albuterol/salbutamol use (percentage of rescue-free days and puffs/day)
	• Time to onset (defined as an increase of 100mL above baseline in FEV_1) during 0-6hr post-dose on Treatment Day 1 (Visit 2)
	• Proportion of subjects achieving an increase in FEV_1 of ≥12% and ≥200mL above baseline at any time during 0 to 6hr post-dose on Treatment Day 1 (Visit 2)

Objectives	Endpoints
	• Proportion of subjects achieving an increase in FEV_1 of ≥100mL above baseline in trough FEV_1
	• Serial FEV_1 over 0 to 6 hours post-dose (on Day 1)
	• Serial and trough Forced Vital Capacity (FVC)
	• Proportion of responders to TDI. (a responder to TDI will be defined as a subject with TDI score of 1 unit or more)
	• Time to first COPD exacerbation
Secondary Objectives	
• To evaluate the safety of Umeclidinium 62.5 mcg compared with placebo when administrated once-daily via ELLIPTA over a 24-week treatment period in subjects with COPD	• Incidence of adverse events
	• Vital signs (pulse rate, systolic and diastolic blood pressure)
	• 12-lead ECG parameters
	• Clinical chemistry and haematology parameters and routine urinalysis
• To evaluate health-related quality of life Umeclidinium 62.5 mcg compared with placebo when administrated once-daily via ELLIPTA over a 24-week treatment period in subjects with COPD	• St. George's Respiratory Questionnaire (SGRQ)
	• COPD Assessment Test (CAT)
	• Healthcare resource utilisation

2.3. Study Design

Overview of Study Design and Key Features



Design Features	• Multicenter, randomized, double-blind, parallel group study to evaluate the efficacy and safety of umeclidinium 62.5 mcg administered once-daily via ELLIPTA™ compared with placebo over 24 weeks in subjects with COPD.
Dosing	• Umeclidinium (GSK573719) 62.5 mcg Inhalation Powder administered QD via a ELLIPTA™ in the morning • Placebo administered QD via a ELLIPTA™ I in the morning
Treatment Assignment	• Eligible subjects will be randomized 2:1 to receive active drug or placebo
Interim Analysis	• No interim analysis is planned.

2.4. Statistical Hypotheses

The objective of this study is to assess the efficacy and safety of 24 weeks' treatment with Umeclidinium 62.5 mcg Inhalation Powder compared with placebo, when administered once-daily in subjects with COPD. The primary endpoint is change from baseline of trough FEV1 at Day 169. The comparisons of interest for the primary analysis are Umeclidinium 62.5 mcg vs. placebo.

For each test on each efficacy endpoint, the null hypothesis is that there is no difference between treatment groups.

H0: $T1 - T2 = 0$

The alternative hypothesis is there is a difference between treatment groups.

H1: $T1 - T2 \neq 0$

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analysis is planned.

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.
3. All criteria for unblinding the randomisation codes have been met.
4. Randomisation codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population for analysis to be performed on all subjects enrolled from China and Korea.

Population	Definition / Criteria	Analyses Evaluated
All Subjects Enrolled	• Comprise of all subjects, for whom a record exists on the study database, including pre-screen/screen failures and any subject who was not screened but experienced an SAE between the date of informed consent and the planned date of the Screening Visit.	• Reporting subject disposition, AE listing and treatment misallocations listing
Screen and Run in Failure	• Comprise of all subjects in the All Subjects Enrolled Population who are recorded as screen failures or run-in failures in the electronic case report form (eCRF)	• Tabulation of reasons for screen and run-in failure and for inclusion, exclusion and randomisation criteria failed
Modified Intent-To-Treat	• Comprise of all subjects randomized to treatment who received at least one dose of randomized study medication in the treatment period. • Randomized subjects will be assumed to have received study medication unless definitive evidence to the contrary exists. • Outcomes will be reported according to the randomized treatment allocation. • All scheduled data collected until the	• Constitute the primary population for all data analyses and displays.

Population	Definition / Criteria	Analyses Evaluated
	time of study discontinuation will be included in the Modified Intent-to-treat analysis for subjects who withdraw from the study.	
Per-Protocol	• Comprise all subjects in the Modified ITT Population who are not identified as full protocol violators. • Subjects identified as partial protocol violators will be included in the PP Population but will have their data excluded from PP analyses from the time of violation onwards. • The definition of full and partial violations will be included in Section 4.1 (Protocol Deviations) and Appendix 1 (Protocol Deviation Management and Definition for Per-Protocol Population). • The decision to exclude a subject from the PP Population or a subject's data from PP analyses will be made prior to breaking the blind.	• Confirmatory analyses of the primary efficacy endpoint only, irrespective of how many subjects are in the PP population.

NOTES :

- Please refer to Appendix 14: List of Data Displays which details the population to be used for each display being generated.

Population for analysis to be performed on subjects enrolled in China alone: a China subgroup analysis.

Population	Definition / Criteria	Analyses Evaluated
China All Subjects Enrolled	• Comprise of all subjects as defined in the above table in All Subjects Enrolled population, but will include only those subjects at sites in China.	• The same as above table for All Subjects Enrolled Population.
China Screen and Run in Failure	• Comprise of all subjects as defined in the above table in Screen and Run in Failure population, but will include only those subjects at sites in China	• The same as above table for Screen and Run in Failure Population.
China Modified Intent-To-Treat	• Comprise of all subjects as defined in the above table in Modified Intent-To-Treat Population, but will include only those subjects at sites in China.	The same as above table for Modified Intent-To-Treat Population.
China Per-Protocol	• Comprise all subjects as defined in the above table in Per-Protocol Population, but will include only those	• The same as above table for Per-Protocol Population.

Population	Definition / Criteria	Analyses Evaluated
	subjects at sites in China.	

NOTES :
Please refer to Appendix 14: List of Data Displays which details the population to be used for each display being generated.

4.1. Protocol Deviations

- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.
- Important deviations which result in exclusion from the analysis population will also be summarised and listed. (Please refer to Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
    - Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
    - This dataset will be the basis for the summaries and listings of protocol deviations.
- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 Overview of Appendices

Section	Appendix
RAP Section 4 : Analysis Populations	
Section 10.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 10.2	Appendix 2: Time and Events
Section 10.3	Appendix 3: Assessment Windows
Section 10.4	Appendix 4: Treatment States & Phases
Section 10.5	Appendix 5: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 10.6	Appendix 6: Derived and Transformed Data • General, Study Population & Safety • Efficacy
Section 10.7	Appendix 7: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 10.8	Appendix 8: Values of Potential Clinical Importance
Section 10.9	Appendix 9: Multicentre Studies
Section 10.10	Appendix 10: Examination of Covariates and Subgroups
Section 10.11	Appendix 11: Multiple Comparisons and Multiplicity
Section 10.12	Appendix 12: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
Section 10.13	Appendix 13: Abbreviations & Trade Marks
Section 10.14	Appendix 14: List of Data Displays
Section 10.15	Appendix 15: Example Mock Shells for Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the Modified Intent-To-Treat population for the analysis on all countries overall and on China Modified Intent-To-Treat population for the analysis of China subgroup alone, unless otherwise specified.

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 14: List of Data Displays. All the planned study population analyses will be done on all countries overall, and China subgroup alone (with the exception of those displays specified by country).

Table 2 Overview of Planned Study Population Analyses

Endpoint/ Parameter/ Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Populations			
Subject Populations	Y		
Subject Disposition			
Subject Disposition	Y		
Reasons for Screen Failure/Run-in Failures	Y		Y
Subjects by Country and Centre	Y		
Reasons for Subject Withdrawal	Y		Y
Subjects for Whom the Treatment Blind was Broken			Y
Planned and Actual Treatments			Y
Subjects Attending Each Clinic Visit	Y		
Subjects Withdrawals over Time		Y	
Protocol Deviations			
Subjects with Inclusion/ Exclusion/Randomisation Criteria Deviations	Y		Y[1]
Important Protocol Deviations	Y		Y[1]
All Protocol Deviations			Y
Exclusions from the Per protocol Population	Y		
Demography and Baseline Characteristics			
Demographics Characteristics	Y		Y
Race and Racial Combinations	Y		Y[2]
Race and Racial Combination Details	Y		
Medical Condition			
Medical Conditions (Current/Past)	Y		Y
Past Cholecystectomies	Y		Y
Family History of Cardiovascular Risk Factors	Y		Y
COPD History	Y		Y
COPD Exacerbation	Y		Y
Smoking History and Status	Y		Y
Lung Function Test at Screening	Y		Y
GOLD Stage and Reversibility/Responsiveness	Y		Y
Scores for Modified Medical Research Council dyspnoea	Y		Y
Concomitant Medication			

Endpoint/ Parameter/ Display Type	Data Displays Generated		
	Table	Figure	Listing
COPD medications not given for an exacerbation taken pre-treatment	Y		
COPD medications not given for an exacerbation taken on-treatment	Y		
COPD medications not given for an exacerbation taken post-treatment	Y		
Medications given for an exacerbation taken pre-treatment	Y		
Medications given for an exacerbation taken on-treatment	Y		
Medications given for an exacerbation taken post-treatment	Y		
Non-COPD medications taken pre-treatment	Y		
Non-COPD medications taken on-treatment	Y		
Non-COPD medications taken post-treatment	Y		
Relationship between ATC Level 1, Ingredient and Verbatim Text			Y
COPD medications			Y
Non-COPD medications			Y
Treatment Compliance			
Treatment compliance	Y		Y

NOTES :

- Y = Yes display generated.
- All summaries tables will be presented by treatment group and overall.
- COPD History and COPD Exacerbation will be listed together.
- Screening lung function data, GOLD stage, reversibility to salbutamol and reversibility to salbutamol and ipratropium will be listed together.
- COPD and non-COPD medications will be listed separately. The COPD medications listing will indicate whether each medication was taken for an exacerbation. Both listings will indicate in which study phases each medication was taken (pre-treatment, ontreatment and/or post-treatment).

[1] Flag shall be provided to identify if the subject is excluded from PP Population or excluded from PP population analysis.

[2] Listing of race.

7. PRIMARY STATISTICAL ANALYSES

7.1. Primary Efficacy Analyses

7.1.1. Overview of Planned Primary Efficacy Analyses

The primary efficacy analyses will be based on the Modified Intent-To-Treat population, for the analysis on all countries overall and on China Modified Intent-To-Treat population for the analysis on China subgroup alone, unless otherwise specified.

Table 3 provides an overview of the planned efficacy analyses, with full details of data displays being presented in Appendix 14: List of Data Displays. All the planned primary efficacy analyses will be done on all countries overall, and China subgroup alone (with the exception of those displays specified by country).

Table 3 Overview of Planned Efficacy Analyses

Endpoints	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Primary Efficacy Analyses														
Baseline FEV_1				Y[1]			Y							
Trough FEV_1 on Day 169	Y[1]			Y[1]			Y	Y[1]	Y		Y[1]	Y		Y
Trough FEV_1 on Day 169 (Using LOCF)	Y			Y				Y			Y			
Trough FEV1 at other time points	Y			Y			Y	Y	Y		Y			Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- All the tables will be presented by treatment group.

[1]: Will be repeated for PP population.

7.1.2. Planned Primary Efficacy Statistical Analyses

Primary Statistical Analyses

Endpoint(s)

- Change from baseline in trough FEV1

Model Specification

- Mixed Models Repeated Measures (MMRM) model.

- While missing data are not explicitly imputed in the primary MMRM analyses, there is an underlying assumption that the data are missing at random. All available scheduled postbaseline assessments will be utilized and via modeling of the within-subject correlation structure, the derived treatment differences will be adjusted to account for missing data.

- The MMRM analysis for trough FEV1 will include on-treatment FEV1 measurements at Days 2, 28, 56, 84, 112, 168 and 169.

- Terms fitted the model:

Response	:trough FEV1 on each day or Change from baseline in trough FEV1 on each Day
Categorical	:Treatment, Smoking Status (screening), Country [1], Day
Continuous	:Baseline FEV1
Interaction	: baseline*Day, treatment*Day
Repeated	: Day (nominal)

- The model will be fit with an unstructured variance-covariance matrix.
- The Kenward and Roger method (KR) for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used. In the event the model fails to run using the KR method, then the residual method will be used instead.
- Baseline is defined in Section 10.5.2.1
- Two models will be fitted; one with trough FEV1 on each Day and one with Change from baseline in trough FEV1 on each Day.

Model Checking & Diagnostics

- Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.

Model Results Presentation

- Least-square (LS) means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors.
- Estimated treatment differences along with corresponding 95 % confidence intervals (CIs) and p-values for Days 2, 28, 56, 84,112, 168 and 169 will be presented for the treatment comparisons
- The LS means from the model for change from baseline in trough FEV1 for each treatment on Days 2, 28, 56, 84, 112, 168 and 169, along with the corresponding 95 % CIs, will be plotted.
- The LS mean treatment differences, along with the corresponding 95 % CIs, for change from baseline in trough FEV1 on Days 2, 28, 56, 84, 112, 168 and 169 will be plotted for active treatment group versus placebo.
- The type III tests of fixed effects and the covariance parameter estimates from the model will

Primary Statistical Analyses
be presented in two tables in the statistical appendix.
Example SAS Code

proc mixed data=dsetin;
class trtcd visit subjid smk country[1];
model endpoint=trtcd baseline smk country[1] day day*baseline day*trtcd / ddfm =kr;
repeated visit / subject=subjid type=un;
lsmeans trtcd*visit / cl diff e om=OMdset at (baseline)=(&blm.);
ods output lsmeans=lsmeans;
ods output diffs=diffs;
run;
[where OMdset is a dataset with a row for every subject-visit combination that contains all of the covariates and blm is a macro variable containing the mean baseline for the subjects used in the analysis. This is used to derive the LS means using coefficients which are based on the subjects used in the analysis.]

Note: [1]: In China subgroup analysis, Country will be removed.

Sensitivity and Supportive Statistical Analyses
• The summaries, figures and analysis detailed in Section 7.1.1 (Overview of Planned Efficacy Analyses) and above primary statistical analyses, except for the summary figures (box plot and empirical distribution function plot, details please refer to Appendix 14), will be repeated for the PP population for the analysis on all countries overall and on China PP population for the analysis on China subgroup alone as the supportive analysis of primary efficacy analyses. • An assessment of whether the effect of treatment on trough FEV1 is modified by smoking status at screening, country [1] or baseline will be made by fitting separate repeated measures models, identical to the model described in the above primary statistical analyses, but also including additional terms for the treatment by smoking status interaction, treatment by country (for the all countries analysis only) interaction and treatment by baseline interaction respectively. • Additionally, an assessment will be made of whether the effect of treatment on trough FEV1 is modified by the following factors, ICS use at screening. Reversibility to salbutamol at screening. Post-salbutamol percent predicted FEV1 at screening This will be made by fitting separate repeated measures models, identical to the model described in Primary Statistical Analyses of Section 7.1.2 but also including additional terms for the factor and the factor by treatment interaction. • If any interaction from these analyses is significant at the 10 % level, further investigation and characterisation of the interaction will be undertaken. • The interaction p-values from these analyses will be included in the statistical appendix.

Note: [1]: In China subgroup analysis, Country will be removed.

7.1.3. Planned Missing Data Sensitivity Statistical Analyses for Trough FEV1

Missing Trough FEV1 on Day 169 will be imputed using LOCF. This only include post-baseline measurements at on-treatment scheduled clinic visits.

Sensitivity Statistical Analyses – LOCF
Endpoint(s)
• Change from baseline in trough FEV1 on Day 169
Model Specification

• Analysis of Covariance (ANCOVA) model using LOCF
 	
• Terms in the model:
  • **Response**: trough FEV1 or change from baseline in trough FEV1 on Day 169.
  • **Categorical**: treatment group, smoking status (screening), country[1]
  • **Continuous**: baseline FEV1
 	
• Baseline is defined in Section 10.5.2.1
• Two models will be fitted; one with trough FEV1 on Day 169 and one with Change from baseline in trough FEV1 on Day 169.

Model Results Presentation
• Least-square (LS) means and LS mean change from baseline values for treatment group will be presented with their associated standard errors. • The estimated treatment difference along with corresponding standard error, 95% CI and p-value will be presented.
Example SAS Code
proc mixed data=dsetin; *class trtcd smk country[1] ;* *model endpoint=trtcd baseline smk country[1] / ddfm =kr;* *lsmeans trtcd / cl diff e;* *ods output lsmeans=lsmeans;* *ods output diffs=diffs;* *run;*

Note: [1]: In China subgroup analysis, Country will be removed.

7.2. Secondary Efficacy Analyses

7.2.1. Overview of Planned Secondary Efficacy Analyses

The secondary efficacy analyses will be based on the Modified Intent-To-Treat population, for the analysis on all countries overall and on China Modified Intent-To-Treat population for the analysis on China subgroup alone, unless otherwise specified.

Table 4 provides an overview of the planned efficacy analyses, with further details of data displays being presented in Appendix 14: List of Data Displays. All the planned secondary efficacy analyses will be done on all countries overall, and China subgroup alone (with the exception of those displays specified by country).

Table 4 Overview of Planned Efficacy Analyses

Endpoint	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
0-6 h Weighted Mean FEV1 on Day 1	Y			Y			Y	Y			Y			Y
Baseline Dyspnea Index (BDI)				Y			Y							
Transition Dyspnea Index (TDI)	Y	Y		Y			Y							

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- All the tables will be presented by treatment group.

7.2.2. Planned Secondary Efficacy Statistical Analyses

7.2.2.1. 0-6 h Weighted Mean FEV1 on Day 1

Statistical Analyses
Endpoint(s)
• 0-6 h Weighted Mean FEV1
Model Specification
• ANCOVA Model • The absolute and change from baseline value of 0-6 h weighted mean FEV1 on Day 1 will be analysed. • Terms fitted in the ANCOVA model will be include: Response :Absolute value or change from baseline value of 0-6 h weighted mean FEV1 on Day 1 Categorical :Treatment, Smoking Status (Screening), Country[1] Continuous :Baseline FEV1 • Baseline is defined in Section 10.5.2.1 • Two models will be fitted; one with a response variable of change from baseline and one with the response variable as absolute value.
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• LS mean and LS mean change from baseline values for each treatment group will be presented with their associated standard errors. • Estimated treatment differences along with corresponding 95 % CIs and p-values for Day 1 will be presented for the treatment comparisons.
Example SAS Code
proc mixed data=dsetin;

Statistical Analyses

class trtcd subjid smk country[1];
model endpoint=trtcd baseline smk country[1] / ddfm =kr;
lsmeans trtcd / cl diff e om;
ods output lsmeans=lsmeans;
ods output diffs=diffs;
run;

Note: [1]: In China subgroup analysis, Country will be removed.

7.2.2.2. TDI

Statistical Analyses	
Endpoint(s)	
• TDI	
Model Specification	
• MMRM • The model will use all available TDI focal scores recorded on Days 28, 84 and 168. • Terms fitted in the model will be include:	
Response	: TDI focal scores on each day
Categorical	:Treatment, Smoking Status (screening), Country[1], Day
Continuous	:BDI focal score
Interaction	: BDI focal score *Day, treatment*Day
Repeated	: Day (nominal)
Model Checking & Diagnostics	
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.	
Model Results Presentation	
• LS means values for each treatment group will be presented with their associated standard errors. • Estimated treatment differences along with corresponding 95 % CIs and p-values for Days 28, 84 and 168 will be presented for the treatment comparisons. • The LS means from the model for TDI focal score for Days 28, 84 and 168, along with the corresponding 95 % CIs, will be plotted ✓ The LS mean treatment differences, along with the corresponding 95 % CIs for Days 28, 84 and 168 will be plotted for active treatment group versus placebo	
Example SAS Code	
Similar like the code in Section 7.1.2.	

7.3. Other Efficacy Analyses

7.3.1. Overview of Planned Other Efficacy Analyses

Other efficacy analyses will be based on the Modified Intent-To-Treat population, for the analysis on all countries overall and on China Modified Intent-To-Treat population for the analysis on China subgroup alone, unless otherwise specified.

Table 5 provides an overview of the planned other efficacy analyses, with further details of data displays being presented in Appendix 14: List of Data Displays. All the planned study population analyses will be done on all countries overall, and China subgroup alone (with the exception of those displays specified by country).

Table 5 Overview of Planned Other Efficacy Analyses

Endpoint	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Time to Onset (an increase of 100mL in FEV1 above baseline) during 0-6 h post-dose on Day 1	Y	Y		Y			Y							
Proportion Achieving Increase in FEV1 of ≥12 % and ≥200 mL above Baseline at any Time During 0-6 h Post-dose on Day 1	Y			Y			Y							
Proportion Achieving Increase of ≥100 mL above Baseline in Trough FEV1	Y			Y			Y							
Serial FEV1	Y	Y		Y			Y	Y	Y		Y			
Trough FVC	Y			Y			Y	Y	Y		Y			
Serial FVC	Y	Y		Y			Y	Y	Y		Y			
Rescue Salbutamol Use (Percentage of Rescue-Free Days)[1]				Y			Y				Y			
Rescue Salbutamol Use (mean puffs/days)[1]	Y			Y			Y	Y			Y			Y
Proportion of Responders According to TDI Focal Score[2]	Y			Y			Y							
Time to First COPD Exacerbation	Y	Y		Y			Y							
On-Treatment COPD Exacerbations[3]				Y										
Post-Treatment COPD Exacerbations[3]				Y										

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- All the tables will be presented by treatment group.
- [1]: Absolute summary will be done on each at baseline, during each four weeks of treatment and over the entire 24-week treatment period. The change from baseline values will also be summarised by treatment, for each four weeks of treatment and the entire 24-week treatment period.
- [2]: A responder to TDI will be defined as a subject with TDI score of 1 unit or more
- [3]: The number and percentage of subjects reporting 0, 1, 2 or >2 on-treatment COPD exacerbations and the total number of exacerbations will be presented by treatment group. The number and percentage of exacerbations with each outcome category, the number and percentage of exacerbations leading to withdrawal and the number and percentage of exacerbations treated by oral/systemic corticosteroids, antibiotics, or which resulted in a visit to the emergency room or hospitalisation will also be presented. In addition, the exacerbation duration will be summarised.

7.3.2. Planned Other Efficacy Statistical Analyses

7.3.2.1. Time to Onset and Time to First COPD Exacerbation

Statistical Analyses
Endpoint(s)
• Time to Onset (an increase of 100mL in FEV1 above baseline) during 0-6 h post-dose on Day 1 • Time to First COPD Exacerbation
Model Specification
• Cox's proportional hazards model • Terms in the model: Dependent variable: Time to Onset or time to first COPD exacerbation Categorical: treatment group, smoking status (screening), and Country[1]. • Use the 'exact' method for handling ties. (If the analysis will not run using the 'exact' method, then the 'Efron' method for handling ties will be used instead.)
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Hazard ratios for each of the treatment comparisons with associated 95 % CIs and p-values, will be presented. • Kaplan-Meier survivor functions of the proportion of subjects with onset over time will be obtained for each treatment group separately and will be plotted on the same figure. • The median time to onset on Day 1 (taken from the Kaplan Meier analysis) will also be presented in the summary table.
Example SAS code
• Cox's proportional hazards model

Statistical Analyses

proc phreg data=dsetin ;
model timeto1*eventflag(0)=treatment smokehis country[1]
/ risklimits ties=exact;
run;
 	
• Kaplan-Meier survivor functions
 	
proc lifetest data=wdw outsurv=survest;
time timeto1*eventflag(0);
strata treatment;
run;
quit;

Note: [1]: In China subgroup analysis, Country will be removed.

7.3.2.2. Proportion Endpoints

Statistical Analyses
Endpoint(s)
• Proportion Achieving Increase in FEV1 of ≥12 % and ≥200 mL above Baseline at any Time During 0-6 h Post-dose on Day 1 • Proportion Achieving Increase of ≥100 mL above Baseline in Trough FEV1 • Proportion of Responders According to TDI Focal Score
Model Specification
Proportion Endpoints • Logistic Regression Model • At each of Days 2, 28, 56, 84, 112, 168 and 169, the proportion of subjects who achieved an increase of 100 mL above baseline in trough FEV1 will be analysed using a separate logistic regression model. • At each visit, the proportion of responders according to TDI focal score will be analysed using a separate logistic regression model. • Terms in the model: Dependent Variable : Proportion Categorical :Treatment, Smoking Status (screening), Country[1] Continuous :Baseline FEV1 or BDI
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• For each treatment comparison, the odds ratio, 95 % CI and p-value will be presented.
Example SAS code

proc logistic data=fevaanal descending;
class treatment (ref='1') smokehis country[1] / param=ref;
model respond=treatment base smokehis country[1] / clodds=wald expb;
ods output logistic.oddsratios=odds1
(where=(index(effect,'TREATMENT')>0

Statistical Analyses

or index(effect,'treatment')>0));
ods output logistic.parameterestimates=pval1
(keep=probchisq variable classval0
where=(variable in ('TREATMENT','treatment')));
run;

Note: [1]: In China subgroup analysis, Country will be removed.

7.3.2.3. Serial FEV1/FVC and Trough FVC

Statistical Analyses
Endpoint(s)
• Serial FEV1 (including post dose 15 and 30 min, 1, 3 and 6 h post-dose measurements on Day 1) • Trough FVC (including Days 2, 28, 56, 84, 112, 168 and 169) • Serial FVC (including post dose 15 and 30 min, 1, 3 and 6 h post-dose measurements on Day 1)
Model Specification, Checking, Results Presentation and SAS code
• Similar to trough FEV1 in Section 7.1.2
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.

7.3.2.4. Rescue Salbutamol Use (mean puffs/days)

Statistical Analyses	
Endpoint(s)	
• Rescue Salbutamol Use (mean puffs/days) (absolute and change from baseline value)	
Model Specification	
ANCOVA model • The mean number of puffs of rescue medication per day over each four weeks of treatment and the entire 24 week treatment period will be analyzed. • Terms in model:	
Response	: Rescue Salbutamol Use (mean puffs/days) (absolute or change from baseline value)
Fixed Categorical	:Treatment, Smoking Status, Country[1]
Fixed Continuous Covariates	:Baseline
• Baseline is defined in Section 10.6.5 Rescue Use part. • Two models will be fitted; one with absolute value and one with change from baseline value.	
Model Checking & Diagnostics	
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.	
Model Results Presentation	
• LS means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors. • Estimated treatment differences along with corresponding 95 % CIs and p-values will be presented for the treatment comparisons.	
Example SAS code	

Statistical Analyses

proc mixed data=start;
by week;
class treatment smokehis country[1];
model endpoint=treatment baseline smokehis country[1];
lsmeans treatment / cl diff e om;
ods output lsmeans=lsmeans;
ods output diffs=diffs;
run;

Note: [1]: In China subgroup analysis, Country will be removed.

7.4. Health Outcomes Analyses

7.4.1. Overview of Planned Health Outcomes Analyses

Health outcomes analyses will be based on the Modified Intent-To-Treat population, for the analysis on all countries overall and on China Modified Intent-To-Treat population for the analysis on China subgroup alone, unless otherwise specified.

Table 6 provides an overview of the planned health outcomes analyses, with further details of data displays being presented in Appendix 14: List of Data Displays. All the planned study population analyses will be done on all countries overall, and China subgroup alone (with the exception of those displays specified by country).

Table 6 Overview of Planned Health Outcomes Analyses

Endpoint	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Baseline SGRQ (Total and each domain)				Y			Y[1]							
SGRQ total score	Y			Y			Y	Y	Y		Y	Y		Y
SGRQ each domain score				Y			Y				Y			
Proportion of responders according to SGRQ total score	Y			Y										
Baseline COPD Assessment Test (CAT) score				Y										
CAT score	Y			Y	Y[2]		Y	Y			Y			Y
Proportion of Responders according to CAT Score	Y			Y										
Healthcare Resource Utilisation				Y			Y							

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- All the tables will be presented by treatment group.
- [1]: Only total baseline score will be listed.
- [2]: Two scatter plots will be generated:
  Change from baseline CAT score at day 168 vs Change from baseline FEV1 at 168
  Baseline CAT scores versus baseline FEV1

7.4.2. Planned Health Outcomes Statistical Analyses

Primary Statistical Analyses
Endpoint(s)
• SGRQ • CAT score • Proportion of responders according to SGRQ total score
Model Specification, Checking, Results Presentation and SAS code
SGRQ, **CAT score** • Similar to trough FEV1 in Section 7.1.2 **Proportion of responders according to SGRQ total score** **Proportion of Responders according to CAT Score** • Similar to proportion endpoint in Section 7.3.2.2

8. SAFETY ANALYSES

8.1. Adverse Events Analyses

8.1.1. Overview of Planned Adverse Events Analyses

The safety analyses will be based on the Modified Intent-To-Treat population, for the analysis on all countries overall and on China Modified Intent-To-Treat population for the analysis on China subgroup alone, unless otherwise specified.

In case of treatment misallocation, additional outputs for safety analyses may be provided, showing the subjects impacted by misallocation and the treatments they actually received.

Table 7 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 14: List of Data Displays. All the planned study population analyses will be done on all countries overall, and China subgroup alone (with the exception of those displays specified by country).

Table 7 Overview of Planned Adverse Event Analyses

Endpoint	Absolute		
	Summary		Individual
	T	F	L
Exposure			
Exposure to Study Treatment	Y		Y
Adverse Events (AEs)			
Overview of AE incidence			
All AEs by SOC	Y		Y
Common AEs by Overall Frequency	Y	Y	
All Drug-Related AEs by SOC	Y		
Subject Numbers for Individual AEs			Y
Relationship Between AE SOCs, PT & Verbatim Text			Y
On-Treatment AEs by SOC	Y		
Post-Treatment AEs by SOC	Y		
On-Treatment AEs experienced by 3% (after rounding) or more of subjects in any treatment group	Y		
Common On-Treatment non-serious AEs[1]	Y		
On-treatment Drug-Related AE's	Y		
On-treatment Non-Serious Drug Related Adverse Events	Y		
All AEs			Y
Serious and Other Significant AEs			
Fatal SAEs[1]	Y		Y
Non-Fatal SAEs	Y		Y
Pre-treatment fatal SAEs	Y		
Pre-treatment non-fatal SAEs	Y		Y
On-treatment non-fatal SAEs	Y		Y
Post-treatment Non-fatal SAEs	Y		Y
SAEs by SOC	Y		
Drug related serious AE	Y		

Endpoint	Absolute		
	Summary		Individual
	T	F	L
Drug related SAEs by SOC			Y
Pre-treatment AEs leading to withdrawal from the study	Y		Y
On-treatment AEs leading to permanent discontinuation of study treatment or withdrawal from the study	Y		Y
On-Treatment AE of Special Interest	Y		Y
Fatal SAE of Special Interest	Y		
On-treatment Non-Fatal SAE of Special Interest	Y		
Drug Related Fatal SAEs	Y		
On-treatment Non-Fatal Drug Related SAEs	Y		
Reasons for potential ELLIPTA malfunctions			Y

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- All the tables will be presented by treatment group.

[1]: A cut-off of 3% for 'common' will be used, but for this purpose it should be applied without rounding, i.e. an event experienced by 2.8% subjects should not be included. This table also needs a 'number of subjects with any event' row which only counts subjects experiencing any event in the body of the table.

8.2. Clinical Laboratory Analyses

8.2.1. Overview of Planned Clinical Laboratory Analyses

The safety analyses will be based on the Modified Intent-To-Treat population, for the analysis on all countries overall and on China Modified Intent-To-Treat population for the analysis on China subgroup alone, unless otherwise specified.

Table 8 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 14: List of Data Displays. All the planned study population analyses will be done on all countries overall, and China subgroup alone (with the exception of those displays specified by country).

Table 8 Overview of Planned Clinical Laboratory Analyses

Endpoint	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Chemistry								
Laboratory Values								
Clinical Chemistry	Y				Y			
Clinical Chemistry values outside the normal range	Y			Y				
Clinical Chemistry change from baseline value relative to the normal range	Y							
Clinical Chemistry maximum post-baseline value		Y				Y		
Clinical Chemistry minimum post-baseline value		Y				Y		
Hematology								
Hematology	Y				Y			
Hematology values outside the normal range	Y			Y				

Endpoint	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Hematology change from baseline value relative to the normal range	Y							
Hematology maximum post-baseline value		Y				Y		
Hematology minimum post-baseline value		Y				Y		
Urinalysis								
Urinalysis data	Y			Y				
Hepatobiliary (Liver)								
Liver Event				Y				

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, PCI = Potential Clinical Importance
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

8.3. Other Safety Analyses

8.3.1. Overview of Planned Other Safety Analyses

The safety analyses will be based on the Modified Intent-To-Treat population, for the analysis on all countries overall and on China Modified Intent-To-Treat population for the analysis on China subgroup alone, unless otherwise specified.

Table 9 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 14: List of Data Displays. All the planned study population analyses will be done on all countries overall, and China subgroup alone (with the exception of those displays specified by country).

Table 9 Overview of Planned Other Safety Analyses

Endpoint	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Vital Signs														
Pulse rate	Y	Y		Y			Y	Y			Y			Y
Systolic	Y	Y		Y			Y	Y			Y			Y
Diastolic blood pressure	Y	Y		Y			Y	Y			Y			Y
12-Lead ECG														
QTc(F)	Y	Y		Y	Y			Y			Y	Y		
QTc(B)				Y							Y			
PR interval	Y	Y		Y				Y			Y			
Heart Rate	Y	Y		Y				Y			Y			
ECG interpretation				Y										
ECG abnormalities				Y			Y							

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- All the tables will be presented by treatment group.

8.3.2. Planned Safety Statistical Analyses

Primary Statistical Analyses
Endpoint(s)
• Pulse rate • Systolic • Diastolic blood pressure • QTc(F) • PR interval • Heart Rate
Model Specification
• ANCOVA model • The absolute and change from baseline value of each endpoint will be statistically analysed at each scheduled time point after the start of treatment separately. • Terms fitted in the ANCOVA model will be include: Response : Absolute value or change from baseline value at each scheduled time point. Fixed Categorical :Treatment, Smoking Status(Screening), Country[1] Fixed Continuous Covariates :Baseline • Baseline is defined in Section 10.5.2.1. • Two models will be fitted; one with a response variable of change from baseline and one with the response variable as absolute value.
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Treatment group LS mean values and LS mean change from baseline values with associated standard errors will be presented for each scheduled on-treatment time point for each endpoint. • LS mean treatment differences for comparisons will be presented with associated 95 % CIs. • LS mean change from baseline and associated 95 % CIs for pre-dose values at each scheduled time point by treatment group will be presented graphically.
Example SAS Code
Similar to the code in Section 7.2.2.2

Note: [1]: In China subgroup analysis, Country will be removed.

9. REFERENCES

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10. APPENDICES

Section	Appendix
RAP Section 4 : Analysis Populations	
Section 10.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 10.2	Appendix 2: Time and Events
Section 10.3	Appendix 3: Assessment Windows
Section 10.4	Appendix 4: Treatment States & Phases
Section 10.5	Appendix 5: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 10.6	Appendix 6: Derived and Transformed Data • General, Study Population & Safety • Efficacy
Section 10.7	Appendix 7: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 10.8	Appendix 8: Values of Potential Clinical Importance
Section 10.9	Appendix 9: Multicentre Studies
Section 10.10	Appendix 10: Examination of Covariates and Subgroups
Section 10.11	Appendix 11: Multiple Comparisons and Multiplicity
Section 10.12	Appendix 12: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
Section 10.13	Appendix 13: Abbreviations & Trade Marks
Section 10.14	Appendix 14: List of Data Displays
Section 10.15	Appendix 15: Example Mock Shells for Data Displays

10.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

Protocol deviations identified in this section are those considered to affect the primary outcome of the study. All decisions on whether to exclude a subject or a subject's data from analysis will be made prior to breaking the blind, with the exception of subjects receiving incorrect treatment container. If, after breaking the blind, the container was found to have contained the correct randomised treatment, no data will be excluded from analyses.

10.1.1. Exclusion of Data from Modified Intent-to-treat Analyses

In general, all data recorded for subjects who were randomised and received at least one dose of study medication will be included in Modified ITT analyses. The following deviations will result in exclusion of data from Modified ITT analyses:

If a 23 h or 24 h post-dose FEV1 or FVC assessment is actually performed after the following day's dose, the value will be excluded from Modified ITT analyses.

If a 15 or 30 min, 1, 3, or 6 h FEV1 or FVC assessment is actually performed before dosing, the value will be excluded from Modified ITT analyses.

Derived endpoints will be calculated from remaining assessment values. Exclusion of a value from Modified ITT analyses does not necessarily mean the subject will not have a value for the derived endpoints.

10.1.2. Exclusions of Data from Per Protocol Analyses

Subjects with full protocol deviations identified below will be excluded from the PP population. Subjects with partial protocol deviations will generally be included in the PP population but have data excluded from PP analyses from the time of the deviation onwards. The exception to this is a partial deviation which occurred prior to the start of treatment – in this case the subject will be excluded from the PP population. Subjects with time-point specific deviations will have only the affected data excluded from PP analyses.

10.1.2.1 Inclusion/exclusion/randomisation Criteria Deviations

Failure of criteria will be considered a full protocol deviations as detailed in Table 10:

Table 10 Inclusion/exclusion/randomisation criteria deviations considered to affect the primary outcome

Reason for exclusion	Full protocol deviation considered to affect primary outcome
Inclusion criterion	
Type of subject	No
Informed consent	No
Age	Yes
Gender	No
COPD History	Yes
Tobacco Use and Smoking history	Yes
Severity of disease	Yes
Dyspnoea (mMRC)	Yes
Exclusion criterion	
Pregnancy	No
Asthma	Yes
Other respiratory disorders	Yes
Other diseases/abnormalities	No
Chest X-ray	Yes
Contraindications	No
Hospitalisation	Yes
Lung resection	Yes
12-lead ECG	No
Screening labs	No
Medication prior to spirometry	Yes
Medication prior to screening	Yes
Oxygen	Yes
Nebulised therapy	No
Pulmonary rehabilitation	Yes
Drug or alcohol abuse	No
Affiliation with investigator site	No
Compliance	No
Randomisation criterion	
Pre-dose 12-Lead ECG at Visit 2	No
COPD exacerbation	Yes
ICS	Yes
Prohibited Medications	Yes

10.1.3. Programmed Checks to Identify Non-medication Deviations

The data checks identified in Table 11 will be performed to further identify protocol deviations.

Table 11 Programmed non-medication checks

Reason for exclusion	Check performed	Deviation Type
Age	(visit date – date of birth) < 40 at pre-screening	Full
Smoking history	number of pack-years < 10 at screening[1] or only use a pipe and/or cigar	Full
Severity of disease: FEV1/FVC	Pre-salbutamol or Post-salbutamol FEV_1/FVC ≥0.7 or any one missing at screening	Full
Severity of disease: % predicted	Pre-salbutamol or Post-salbutamol FEVPDPC > 70% or any one missing at screening	Full
Dyspnea (mMRC)	mMRC < 2 at screening or missing	Full
COPD exacerbation during run-in	Exacerbation onset date between dates of screening and start of treatment	Full
Compliance with treatment	Overall compliance < 80 % or > 120 % or missing	Full
Incorrect treatment	At any point	Partial; data excluded from start of incorrect treatment onwards
Blind broken[3]	At any point	Partial; data excluded from date of breaking of blind
COPD exacerbation during treatment and not withdrawn	Exacerbation onset date between treatment start and stop date +1 with measurement of primary efficacy endpoint after onset date[2]	Partial; data excluded from date of onset onwards
Meet other withdrawn criteria defined in the protocol but not withdrawn	Manual Review	Partial; data excluded from date of PD happened.
Trough FEV1 outside window	23 h or 24 h FEV1 assessment outside window of 22.5-24.5h after previous day's dose	Time-point specific

Note:

1. Pipe and/or cigar use cannot be used to calculate pack-year history.
2. Subject experiences an exacerbation during the treatment period requiring the use of any systemic or oral corticosteroids with prescribed or non-prescribed (self-administered) antibiotics, and/or requiring emergency treatment or hospitalisation. If subjects used either prescribed or non-prescribed (self-administered) antibiotics only for the treatment of exacerbation, they were permitted to remain in the study under PI's discretion according to the study protocol therefore the use of only antibiotics will not be defined as a protocol deviation.
3. Subjects whose blind was broken by someone external to GSK (i.e. site staff).

10.1.4. Programmed Checks to Identify Medication Deviations

Medications will be classified into Respiratory Medication Class (RMC) as identified in concomitant medications part of Section 10.6.3.

Following agreement of the correct classification, medications taken prior to or on-treatment (i.e. medication start date on or before treatment stop date) in the intervals identified in Table 12 will be reviewed to identify data which should be excluded from analysis. If the disallowed medication started within the specified window prior to Visit 2 the deviation will be considered full and the subject will be excluded from the PP population. Otherwise the deviation will be considered partial and the subject's data will be excluded from PP analyses from the start of the disallowed medication onwards.

Table 12 Programmed medication checks

RMC	Disallowed rule
Depot corticosteroids	Started on-treatment; stopped after 12 weeks prior to V1
Systemic, oral, parenteral and intra-articular corticosteroids	Started on-treatment; stopped after 4 weeks prior to V1.
Antibiotics[1]	Stopped after 4 weeks prior to V1, and reason is LRTI[1]
ICS[2]	Started on-treatment; stopped after 30 days prior to V1[2]
PDE4 inhibitors	Started on-treatment; stopped after 14 days prior to V1
Long-acting anticholinergics	Started on-treatment; stopped after 7 days prior to V1
Xanthines	Started on-treatment; stopped after 12 hours prior to each visit
Leukotriene receptor antagonists	Started on-treatment; stopped after 2 days prior to V1
Oral beta-2 agonists – long acting[3]	Started on-treatment; stopped after 2 days prior to V1
Oral beta-2 agonists - short-acting	Started on-treatment; stopped after day of V1
Inhaled beta-2 agonists – long acting[3]	Started on-treatment; stopped after 2 days prior to V1
Nedocromil or sodium cromoglycate	Started on-treatment; stopped after 1 day prior to V1 and route is inhaled
Other investigational medication for COPD	Started on-treatment; stopped after 30 days prior to V1
Any investigational medication	30 days or 5 half lives, whichever is longer
Oxygen	Greater than 12 hours a day
Herbal medicine for respiratory diseases	Manual Review

1. All antibiotics will be identified; manual review to identify those with reason for administration of LRTI. After v1, antibiotics used for acute infection <=2weeks is permitted.
2. All ICS will be identified; manual review to identify ICS:
Started but not as switch from ICS/LABA or not within allowed dose range
Dose>1000 mcg fluticasone propionate or equivalent
Stopped with no change to an alternative steroid in the same dose range within 14 days of stopping
Change dose before treatment or change of more than one dose range on the treatment
3. The definition of LABA has now changed and split in to three categories which are now:
'Long-acting beta-2 agonist – Group 1';

'Long-acting beta-2 agonist – Group 2 (Olodaterol or Indacaterol)';
'Long-acting beta-2 agonist – Group 3 (Salmeterol and Formoterol)';

The final decision on exclusion will be made following manual review and will be documented prior to unblinding.

10.2. Appendix 2: Time & Events

10.2.1. Protocol Defined Time & Events

		Run-in	Double-blind treatment period									
Visit	Visit 0 (Pre-Screen)	Screening Visit (Visit 1)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Early With-drawal (EW) Visit	Follow-Up (Phone contact)
Day		Day -7 to -14	Day 1	Day 2	Day 28±2	Day 56±4	Day 84±4	Day 112±4	Day 168±4	Day 169 (Visit 8 +1 day)		7±2 days after Visit 9 or EW
Week		-1	0	0	4	8	12	16	24			
Written Informed Consent[1]	x											
Demography/ COPD History	X											
Medical History		X										
Physical Examination		X							X		X	
Smoking Status		X							X		X	
Smoking Cessation Counselling		X							X		X	
Chest X-ray[2]		X										
Inclusion/exclusion criteria		X										
Randomization criteria			X									
Screening spirometry (including post-bronchodilator testing)[3]		X										
mMRC questionnaire		X										
Register visit in IVSR	x	x	x	x	x	x	x	x	x	x	x	x
Diary Card Dispense or Collection/Review		X	X	X	X	X	X	X	X	X	X	

		Run-in	Double-blind treatment period									
Visit	Visit 0 (Pre-Screen)	Screening Visit (Visit 1)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Early With-drawal (EW) Visit	Follow-Up (Phone contact)
Day		Day -7 to -14	Day 1	Day 2	Day 28±2	Day 56±4	Day 84±4	Day 112±4	Day 168±4	Day 169 (Visit 8 +1 day)		7±2 days after Visit 9 or EW
Week		-1	0	0	4	8	12	16	24			
Efficacy assessments												
Trough Spirometry[4]				X	X	X	X	X	X	X		
Serial Spirometry[5]			X									
COPD exacerbation assessment	x	X	X	X	X	X	X	X	X	X	X	X
Baseline Dyspnea Index (BDI)			X									
Transition Dyspnea Index (TDI)					X		X		X			
SGRQ			X		X		X		X			
COPD Assessment Test (CAT)			X		X		X		X			
Healthcare resource utilization[6]			◄	———	———	———	———	———	———	►		
Safety Assessments												
12-Lead ECG		X	X[7]				X[7]		X[7]		X	
Vital Signs (blood pressure and pulse rate)[8]		X	X	X	X	X	X	X	X	X	X	
Adverse Event /Con-Med Assessment		X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments												
Pharmacogenetics sample[9]			X									
Routine urine		X							X		X	
Urine Pregnancy Test		X	X				X		X		X	X
Clinical Laboratory tests[10]		X					X		X		X	
Medication												
COPD and Concurrent Medication Assessment	x	X	X	X	X	X	X	X	X	X	X	

		Run-in	Double-blind treatment period									
Visit	Visit 0 (Pre-Screen)	Screening Visit (Visit 1)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Early With-drawal (EW) Visit	Follow-Up (Phone contact)
Day		Day -7 to -14	Day 1	Day 2	Day 28±2	Day 56±4	Day 84±4	Day 112±4	Day 168±4	Day 169 (Visit 8 +1 day)		7±2 days after Visit 9 or EW
Week		-1	0	0	4	8	12	16	24			
Dispense/collect rescue salbutamol/albuterol		X	X	X	X	X	X	X	X	X	X	
Dispense double-blind study drug			X		X	X	X	X				
Collect double-blind study drug					X	X	X	X	X		X	
Assess double-blind study drug compliance					X	X	X	X	X		X	

1. Written informed consent must be obtained prior to performing any Visit 1 procedures or initiating any alterations in a subject's medications. Subjects will be assigned a study number at the time the ICF is signed. Visit 0 and Visit 1 may occur on the same day if applicable.
2. To be performed only if there is no chest X-ray or CT scan available within 6 months prior to Visit 1
3. Spirometry to be conducted as follows: pre-bronchodilator testing following by post-albuterol/salbutamol testing, followed by post-ipratropium testing. Post albuterol/salbutamol testing conducted 10 to 30 min after subject self-administration of 4 puffs of albuterol/salbutmol via MDI with a spacer. Subject will then self administer 4 puffs of ipratropium bromide via MDI and spacer, followed by spirometry testing 30 to 60 min later.
4. Trough spirometry obtained twice: at 23 and 24 hours after the previous day's morning dose.
5. 6 hr serial spirometry: Performed post-dose at 15 and 30 min and 1, 3 and 6 hours. At Visit 2 (Day 1), pre-dose measurements will be obtained -30min and -5min pre-dose.
6. Healthcare resource utilization will be collected and entered in the e-CRF as required during the study, collection of this data to be aided by the subject documentation in the paper diary of any contact with the doctor or nurse about their lung condition which was unrelated to study participation.
7. ECG conducted pre-dose and 10 and 45 minutes post-dose
8. Vital signs to be measured pre-dose and 10 and 45 minutes post-dose at visit 2, and measured only pre- dose at other visits (prior to spirometry).
9. PGx sample preferably to be obtained at Visit 2 after randomization, but can also be obtained at a subsequent study visit. PGx consent must be obtained prior to sampling.
10. Haematology, and clinical chemistry.

10.3. Appendix 3: Assessment Windows

Data are generally reported according to the nominal time of clinic visits and assessments as specified in the protocol, and time windows for exclusion will not be defined. For example, if a subject recorded values for the Week 4 visit that were actually made on the 21st day of treatment, they will be presented as Week 4 values in the summary tables.

For the 23 and 24 h post-dose trough FEV1 measurements, a time window of 22.5-24.5 h is allowed for the actual time of an assessment relative to time of dosing. Values falling outside of this window will not be used in the PP analysis of the primary endpoint, but will still be included in all Modified ITT analyses.

10.4. Appendix 4: Treatment States and Phases

10.4.1. Treatment Phases

Assessments and events will be classified according to the time of occurrence relative to study treatment, unless otherwise specified.

Treatment Phase	Definition
Pre-Treatment	Date < Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ Date ≤ Study Treatment Stop Date
Post-Treatment	Date > Study Treatment Stop Date

NOTES:

- If the study treatment stop date is missing then the assessment will be considered to be On-Treatment

10.4.2. Treatment States

Assessments and events will be classified according to time of occurrence relative to the start and/or stop date of the study treatment.

10.4.2.1. Treatment States for Concomitant Medications Data

Treatment State	Definition
Pre-Treatment	Medication start date < Study Treatment Start Date
On-Treatment	Medication start date ≤ Study Treatment Stop Date and Medication stop date≥ Study Treatment Start Date
Post-Treatment	Medication stop date > Study Treatment Stop Date

NOTES:

- A medication will be classed in every period of the study in which it was taken.
- For medications with partial start and stop dates or missing start/stop dates, the medication will be classed in every period of the study in which it could have been taken.
- If the study treatment stop date is missing then the medication will be considered to be On-Treatment.
- The answers to the questions "Taken Prior to Study?" and "Ongoing?" which are recorded on the eCRF will also be taken into consideration to determine if the medication was started pre-treatment or continued post-treatment. In each case, should the answers suggest a different classification than the dates, the medication will be summarised in all possible classifications (pre/on/post) in which it could conceivably have been taken.

10.4.2.2. Treatment States for AE Data

Treatment State	Definition
Pre-Treatment	AE Start Date < Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop **+1**
Post-Treatment	AE Start Date > Study Treatment Stop Date**+1**
Onset Time Since 1st Dose (Days)	If Treatment Start Date > AE Onset Date **= AE Onset Date - Treatment Start Date** If Treatment Start Date ≤ AE Onset Date **= AE Onset Date - Treatment Start Date +1** Missing otherwise.

Treatment State	Definition
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	If relationship is marked 'YES' on Inform/CRF OR value is missing.

NOTES:

- If the study treatment stop date is missing then the AE will be considered to be On-Treatment.
- If the AE onset date is missing or partial then the AE will be considered on-treatment unless there is evidence to the contrary (e.g. the month of the onset date is present and is less than the month of the first dose of study treatment).
- AEs reported by subjects who did not receive treatment will be considered pre-treatment.
- Any SAEs for screen failures, run-in failures or subjects who were randomised but did not receive treatment will be classified as pre-treatment SAEs.

10.4.2.3. Treatment States for COPD exacerbation

Treatment State	Definition
Pre-Treatment	Exacerbations Onset Date < Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ Exacerbations Onset Date ≤ Study Treatment Stop **+1**
Post-Treatment	Exacerbations Onset Date > Study Treatment Stop Date**+1**
Time to first on-treatment exacerbation	= Exacerbation Onset Date of first on-treatment exacerbation - Treatment Start Date +1 Missing otherwise.
Duration (Days)	Exacerbation resolution date or date of death – Exacerbation Onset Date + 1

NOTES:

- If the study treatment stop date is missing then the exacerbation will be considered to be On-Treatment.
- If the exacerbation onset date is missing or partial then the exacerbation will be considered on-treatment unless there is evidence to the contrary (e.g. the month of the onset date is present and is less than the month of the first dose of study treatment).
- Exacerbations reported by subjects who did not receive treatment will be considered pre-treatment.

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
A	UMEC 62.5 mcg	UMEC 62.5 mcg	2
P	Placebo	Placebo	1

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.

10.5.2. Baseline Definition & Derivations

10.5.2.1. Baseline Definitions

For all endpoints (expect FEV1 and FVC) the baseline value will be the latest pre-dose assessment at schedule visit. Unless otherwise stated, the mean of replicate assessments at any given time point will be used as the value for that time point.

The baseline value for FEV1 and FVC is calculated from the values measured 30 min and 5 min pre-dose on Day 1. If the actual time of an assessment is after the time of dosing on Day 1, the value at that assessment will be set to missing prior to calculating baseline. If one of the values is missing then the baseline will be the single remaining value; otherwise the baseline will be the mean of the two values.

10.5.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= On-treatment Value – Baseline value
% Change from Baseline	= 100 x [(On-treatment Value – Baseline value) / Baseline value]
Maximum Change from Baseline	= Calculate the change from baseline at each given timepoint and determine the maximum change

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 10.5.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- If either the baseline or on-treatment value is missing then the change from baseline will be set to missing.
- The change from baseline will not be calculated for baseline records or records prior to baseline

10.5.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Area	: \arenv\arprod\gsk573719\ac4117410\final
QC Spreadsheet	: arenv\arprod\gsk573719\ac4117410\final\qc
Analysis Datasets	
• Analysis datasets will be created according to Integrated Data Standards Library standards.	
Generation of RTF Files	
• RTF files will be generated.	

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics
Formats
• All data will be reported according to the randomized treatment the subject received unless otherwise stated. However, there may be additional adhoc displays for individual subjects using the actual treatment received. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time
• Reporting for tables, figures and formal statistical analyses : • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. • Reporting for Data Listings: • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). • Unscheduled or unplanned readings will be presented within the subject's listings.
Unscheduled Visits
• Unscheduled visits will not be included in summary tables except as part of a 'worst case post-baseline' assessment.

Reporting Standards	
• Unscheduled visits will not be included in figures. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

10.6. Appendix 6: Derived and Transformed Data

10.6.1. General

Multiple Measurements at One Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time window the value closest to the target day for that window will be used. If values are the same distance from the target then the mean will be taken. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day
Calculated as the number of days from randomisation date : • Ref Date = Missing → Study Day = Missing • Ref Date < Start of treatment date → Study Day = Ref Date – Start of treatment date • Ref Data ≥ Start of treatment date → Study Day = Ref Date – (Start of treatment date) + 1
Date of Completion/Withdrawal
The date of completion/withdrawal will be derived as follows: • For subjects who complete the last on-treatment study visit, the date of completion/withdrawal will be the date of that visit (Visit 9). • For subjects who withdraw from the study, the date of completion/withdrawal will be the latest of the date of the last attended scheduled clinic visit (excluding follow-up), the date of the EW visit (if present) and the last dose date.

10.6.2. Study Population

Demographics
Age

• Age will be calculated based on the Pre-screening visit date.
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  ○ Any subject with a missing day will have this imputed as day '15'.
  ○ Any subject with a missing date and month will have this imputed as '30th June'.
• Birth date will be presented in listings as 'YYYY'.

Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)^2**

Smoking Status

At Screening, subjects who were identified as former smokers but who last smoked within 6 months prior to Screening will be re-classified as current smokers prior to summarizing. Subject listings will include original and re-classified status.

During the study, smoking status will be derived from smoking status at Screening and records of change in smoking status at visits. A subject identified as a current smoker at Screening who stopped smoking during the study will be assessed as a former smoker only at visits which are at least 6 months after the date the subject last smoked. Former smokers who started smoking will be considered current smokers at all visits after the date the subject started smoking.

In order to assess the last time a subject smoked the partial date will be imputed to earliest date within the month or year e.g. If a subject has only remembered the year they last smoked (-----2010) then impute to 01JAN2010. If a subject has remembered the month and year that they last smoked (--SEP2010) then impute to 01SEP2010.

Concomitant Medications

COPD concomitant medications will be grouped into the following RMCs based on pre-defined code lists derived from ATC classifications:

```
Short-acting anticholinergic
Short-acting beta-2 agonist
Long-acting anticholinergic
Long-acting beta-2 agonist - Group 1
Long-acting beta-2 agonist - Group 2 (Olodaterol or Indacaterol)
Long-acting beta-2 agonist - Group 3 (Salmeterol and Formoterol)
Xanthine
PDE4 Inhibitors
Corticosteroid - Inhaled
Corticosteroid - Depot
Corticosteroid - Systemic, oral, parenteral and intra-articular
Corticosteroid - Other
Leukotriene Receptor Antagonist
Nedocromil or Cromolyn Sodium
Mucolytics
Cytochrome P450 3A4 Strong Inhibitors
Oxygen
Antiinfectives (antibiotics, antifungals, antivirals, antiseptics)
Other medication given for exacerbation
Other COPD medication
Other
```

COPD concomitant medications that were stopped more than 30 days prior to Screening and non COPD concomitant medications that were stopped prior to Screening will not be presented in any tables or listings.

For reporting purposes, the LABA groups will be combined in the concomitant medication tables.

Treatment Compliance

The number of doses of study treatment taken by each subject from each inhaler will be calculated from the dose counter start and stop counts for each inhaler used. If a dose counter start count is missing then it will be assumed to be 30. If all dose counter stop counts are non-missing then the percentage compliance will be calculated as:

$$\text{Compliance} = \frac{\text{sum of all (dose counter start} - \text{dose counter stop)} \times 100}{\text{(exposure stop date} - \text{exposure start date} + 1)}$$

If any dose counter stop is missing then the treatment compliance will be set to missing for that subject.

Overall compliance will be categorised as follows:

< 80 %
≥ 80 % to < 95 %
≥ 95 % to ≤105 %
>105 % to ≤120 %
>120 %.

If a subject received a treatment other than the randomised treatment during the study, the compliance will still be calculated using data from all containers received and overall exposure start and stop dates.

10.6.3. Safety

Extent of Exposure

- Number of days of exposure to study drug will be calculated based on the formula:
  Duration of Exposure in Days = Overall Treatment Stop Date – Overall Treatment Start Date + 1
- If there are any treatment breaks during the study, exposure data will be adjusted accordingly.
- If overall treatment stop date is missing it will be imputed as follows:
  - For subjects who attended a Study Treatment Discontinuation visit, use the date of the Study Treatment Discontinuation visit
  - For subjects who attended the last on-treatment visit, use the Visit 8 (Week 24) date.
  - For subjects who died and did not attend a Study Treatment Discontinuation visit or the last on-treatment visit, use the date of death
  - For all other subjects, use the last recorded exposure start or stop date.
- If a subject's overall exposure start date is missing then it will be assumed to be their Day 1 visit date.
- If a subject received a treatment other than the randomised treatment during the study, the exposure will still be calculated based on overall exposure start and stop dates.

Adverse Events

- The most frequent on-treatment AEs will be defined as the on-treatment AEs experienced by 3 % (after rounding) or more of subjects in any treatment group.

  - AE groups of special interest have been defined as AEs which have specified areas of interest for UMEC. The following table presents the special interest AE groups and subgroups. The complete list, including the PTs which contribute to each of the groups will be provided by Global Clinical Safety and Pharmacovigilance (GCSP) using the MedDRA version current at the time of reporting. This will be finalized prior to unblinding.

Special Interest AE Group	Special Interest AE Subgroup
Cardiovascular effects	Cardiac Arrhythmia Cardiac Failure Cardiac Ischaemia Hypertension Stroke
Urinary Retention	
Pneumonia	
Anticholinergic syndrome	
Gastrointestinal obstruction	
Hypersensitivity	
LRTI excluding pneumonia	
Ocular effects (antimuscarinic)	
Paradoxical bronchospasm	
gallbladder disorders	

- A flag will be derived to identify on-treatment AEs of special interest. In order to ensure consistency with the umeclidinium Global ISS, all outputs will use the same MedDRA version (i.e. v 15.0) and the same list of special interest terms as was used for the umeclidinium Global ISS.
- The AESI category designated as Pneumonia and LRTI will include lower respiratory tract infections and related diseases. Also, the category designated as “Anticholinergic Syndrome” will be referenced as “Anticholinergic Effects” since the Anticholinergic Syndrome SMQ which was used to located terms includes events that are often associated with anticholinergic or antimuscarinic medication, but are not necessarily diagnostic for anticholinergic syndrome.

Laboratory Parameters

- The baseline value for a parameter will be the most recent recorded value for that parameter before dosing on Day 1 at schedule visit.

Laboratory Parameters

- Laboratory data values will be classified as 'low', 'normal' or 'high' with reference to normal ranges.
- An 'any visit post-baseline' classification will be derived, in which subjects will be counted in the 'low' and 'high' categories if they reported a low or high value at any scheduled, unscheduled or EW visit made after the start of study treatment, up to a maximum of two weeks after the last dose of study treatment. Subjects who did not report a low or high value at any visit after the start of study treatment will be counted in the 'normal' category.
- Change from baseline values will be classified relative to the normal range as 'to low', 'to normal or no change' or 'to high'. Subjects who do not change categories or move from out-of-range to normal will be classified as 'to normal or no change'.
- An 'any visit post-baseline' change classification will be derived, in which subjects will be counted in the 'to low' and 'to high' categories if they reported a change from a 'normal' baseline to a value below or above the normal range (respectively) at any scheduled, unscheduled or EW visit made after the start of study treatment, up to a maximum of 2 weeks after the last dose of study treatment. Subjects who did not report a change to a value outside the normal range at any visit after the start of study treatment will be counted in the 'to normal or no change' category.
- If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.
  - Example 1: 2 Significant Digits = '< x ' becomes x – 0.01
  - Example 2: 1 Significant Digit = '> x' becomes x + 0.1
  - Example 3: 0 Significant Digits = '< x' becomes x – 1

Vital Signs

- The baseline value for a vital sign endpoint will be the most recent recorded value for that endpoint before dosing on Day 1 at schedule visit.
- The 'maximum/minimum post-baseline' value will be the maximum value for pulse rate and systolic blood pressure, or the minimum value for diastolic blood pressure, recorded at any scheduled, unscheduled or EW visit made after the start of study treatment.

12-Lead ECG

- The baseline value for an ECG endpoint will be the most recent recorded value for that endpoint before dosing on Day 1 at schedule visit.
- A 'maximum post-baseline' QTc(F), QTc(B), PR interval and heart rate value will be derived as the maximum value recorded at any scheduled, unscheduled or EW visit made after the start of study treatment.
- QTc(F) values (including 'maximum post-baseline') will be categorised as follows:
  - ≤ 450 msec
  - > 450 to ≤ 480 msec
  - > 480 to ≤ 500 msec

12-Lead ECG
> 500 msec. • Change from baseline QTc(F) values (including change to 'maximum post baseline') will be categorised as follows: < -60 msec ≥ -60 to < -30 msec ≥ -30 to < 0 msec ≥ 0 to < 30 msec ≥ 30 to < 60 msec ≥60 msec. • An 'any time post-baseline' ECG interpretation will be derived as the worst interpretation recorded at a scheduled, unscheduled or EW visit made after the start of study treatment. The order of severity from worst to best for ECG interpretation is: abnormal: clinically significant, abnormal: not clinically significant, normal, unable to interpret. • Any ECG abnormality recorded by a subject with an ECG interpretation of 'abnormal: clinically significant' after the start of study treatment will be included in an 'any-time post-baseline' record of ECG abnormalities. • Any ECG abnormality recorded by a subject after the start of study treatment will be included in an 'any-time post-baseline' record of all ECG abnormalities.

10.6.4. Health- Related Quality of Life

St. George's Respiratory Questionnaire
• The SGRQ contains 76 items grouped into three domains (Symptoms, Activity and Impacts). The domain score will be calculated as the sum of the weighted scores for the non-missing items within each domain, dividing by the maximum possible score for those non-missing items and multiplying by 100. The SGRQ total score will be calculated as the sum of the weighted scores from all 76 items and dividing by the maximum possible score for the SGRQ and multiplying by 100. This calculation is outlined in the developer's guide (St. George's Respiratory Questionnaire Manual, 2009). • If a subject has more than one response to a given item at a particular time point then the response will be taken as the average of the responses prior to calculating domain and total scores. • If a subject has given both responses to a dichotomous question (yes/ no, true/false) the response to that question will be set to missing. • If more than 25 % of items are missing from a domain, then the domain total will be set to missing. This equates to no more than two missed questions for the Symptom domain, no more than four missed questions for the Activity domain and no more than six missed questions for the Impacts domain. If any domain score is missing, then the total score will be set to missing. • If the language of the SGRQ conducted during the study is different to the language used at Day 1, all SGRQ scores will be set to missing. • The baseline SGRQ domain and total scores are those recorded on Day 1. • A subject will be considered a 'responder' according to his SGRQ total score at each visit if the difference from the visit score to the baseline score was -4 units or lower. A subject will be

St. George's Respiratory Questionnaire
considered a 'non-responder' if the difference from the visit score to the baseline score was greater than -4 units. . • For the classification of responders, subjects with missing SGRQ total scores will be handled as detailed in Section 10.7.2.1 (Handling of Missing Responder).

CAT
• The CAT consists of eight items each formatted as a six-point differential scale: 0 (no impact) to 5 (high impact). A CAT score will be calculated by summing the non-missing scores on the eight items. If one or two items are missing, then the score for those items is set as the average of the non-missing items. If more than two items are missing, then the CAT score will be set to missing. • The baseline CAT score will be that recorded on Day 1. • A subject will be a responder if their on-treatment CAT score has decreased at least 2 units from baseline CAT total score. • A subject will be considered a non-responder if their on-treatment CAT score has decreased by less than 2 units, has not changed, or has increased compared to baseline. • For the classification of responders will be handled as detailed in Section 10.7.2.1 (Handling of Missing Responder).

Healthcare Resource Utilisation
• The total number of visits for each type of healthcare contact (telephone contacts, home visits (day), home visits (night), office/practice visits, urgent care/outpatient clinic visits, emergency room visits and the number of days in intensive care and in general hospital wards will be derived.

10.6.5. Efficacy

Post-ipratropium FEV1
• The difference between post-ipratropium FEV1 and pre-salbutamol FEV1 will be calculated.

Reversibility and GOLD Stage
• A subject's responsiveness to salbutamol at Screening will be classified as 'Reversible' or 'Non-reversible' based on the difference between their pre-salbutamol assessment of FEV1 and their post-salbutamol assessment of FEV1 as follows: o Reversible, if they had an difference in FEV1 of ≥12 % and ≥200 mL, or o Non-reversible, if they had a difference in FEV1 of < 200 mL or a ≥200 mL difference that was <12 % of the pre-salbutamol FEV1. • A subject's responsiveness to salbutamol and ipratropium at Screening will be classified as 'Reversible' or 'Non-reversible' based on the difference between their pre-salbutamol assessment of FEV1 and their post-ipratropium assessment of FEV1 as follows: o Reversible, if they had a difference in FEV1 of ≥12 % and ≥200 mL, or o Non-reversible, if they had a difference in FEV1 of < 200 mL or a ≥200 mL difference that

was < 12 % of the pre-salbutamol FEV1.

- Subjects will be classified according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage (GOLD classification, [GOLD, 2011]): defined using the post-salbutamol percent predicted FEV1 assessed at Screening (Visit 1). Subjects will be classified as:
  - GOLD1: Mild FEV1 ≥80% predicted
  - GOLD 2: Moderate 50% ≤FEV1 < 80% predicted
  - GOLD3: Severe 30% ≤FEV1 < 50% predicted
  - GOLD4: Very Severe FEV1 <30% predicted

Trough FEV1 and FVC

- The trough value for FEV1 and FVC at each of Days 2, 28, 56, 84, 112, 168 and 169 is calculated from the values at the assessments made 23 h and 24 h after dosing on the previous day. If the actual time of an assessment is after the time of dosing on the current day, the value will not be used in the calculation of trough. For the PP population, a value will additionally be excluded from the trough calculation if the assessment is outside the time window of 22.5-24.5 h after dosing on the previous day (see Section 10.1.2 (Exclusions of Data from Per Protocol Analyses)). If one of the values is missing or excluded then the trough will be the single remaining value; otherwise the trough will be the mean of the two values.

BDI/TDI

- The baseline dyspnoea index (BDI) focal score will be calculated as the sum of the ratings recorded for each of the three individual scales (Baseline Functional Impairment, Baseline Magnitude of Task, Baseline Magnitude of Effort). Each of these scales has five possible scores ranging from 0 to 4 (with lower scores indicating more impairment), so the range of the BDI focal score is 0 to 12. If a score is missing (or has a value of W, X or Y) for any of the three scales, then the BDI focal score will be set to missing.
- The TDI focal score will be calculated as the sum of the ratings recorded for each of the three individual scales (Change in Functional Impairment, Change in Magnitude of Task, Change in Magnitude of Effort). Each of these scales has seven possible scores ranging from -3 (major deterioration) to +3 (major improvement), so the range of the TDI focal score is -9 to +9. If a score is missing (or has a value of Z) for any of the three scales, then the TDI focal score will be set to missing.
- A subject will be considered a 'responder' according to TDI at each visit if the TDI focal score was at least 1 unit at that visit. A subject will be considered a 'non-responder' if the score was less than 1 unit.
- For the classification of responders, subjects with missing TDI assessments will be handled as detailed in Section 10.7.2.1 (Handing of Missing Responder).

Weighted Mean FEV1 and FVC

- Weighted mean FEV1 and FVC will be calculated over the nominal 0-6 h post dose period. Values from post-dose assessments which are actually before the time of dosing will be excluded from the calculation.
- The 0 h value is the average value obtained 30 min and 5 min pre-dose, and both the 0 h and 6 h values must be present for a 0-6 h weighted mean to be calculated.
- The 0-6 h weighted mean will be derived by calculating the area under the FEV1 or FVC/time

Weighted Mean FEV1 and FVC

curve over the nominal time points of 0 h (as defined above), 15 and 30 min, 1, 3 and 6 h, using the trapezoidal rule, and then dividing by the actual time between dosing and the 6 h assessment. For post-dose observations the actual time of assessment relative to the time of dosing will be used for the calculation.

$$\text{Weighted Mean (0-6h)} = \left[\frac{1}{2}\sum_{i=1}^{I-1}(t_{i+1}-t_i)(y_i+y_{i+1})\right]/\left[t_l - t_f\right]$$

where

y_i represents the value of the endpoint at the ith timepoint,

t_i represents the actual relative time at the ith timepoint,

t_f represents the actual relative time at the first timepoint (t_f = 0 as the pre-dose measurement is used),

t_l represents the actual relative time at the last timepoint (the 6h timepoint),

I represents the number of timepoints used in the AUC calculation.

If missing values are present in data required for the calculation of the weighted means, the following approach will be employed:

- If more than a third of the observations are missing then the weighted mean will be set to missing for that subject.
- If an observation is missing between two non-missing observations, the value will be interpolated between the two non-missing values.
- If there are two or more missing points that occur consecutively then the weighted mean will be set to missing.
- If the first time-point is missing then the weighted mean will be set to missing.
- If the last time-point is missing then the weighted mean will be set to missing.

Rescue Use

- For rescue use, 'day' refers to the period (24 hours) between one record of rescue use and the next in the database.
- The total puffs of rescue for each day will be calculated as number of salbutamol puffs. If the number of puffs are missing then the total puffs will be set to missing for that day.
- Rescue use will be summarised over the periods defined in below table:

Period	First day	Last day
Baseline	Latest of 6 days before Visit 2 and day after Visit 1	Day of Visit 2
Week 1-4	Study day 2 (day after Visit 2)	Study day 29
Week 5-8	Study day 30	Study day 57

Rescue Use

Week 9-12	Study day 58	Study day 85
Week 13-16	Study day 86	Study day 113
Week 17-20	Study day 114	Study day 141
Week 21-24	Study day 142	Earliest of Study day 169 and day before Visit 9
Week 1-24	Study day 2 (day after Visit 2)	Earliest of Study day 169 and day before Visit 9

- For each summary period, the mean number of puffs per day and the percentage of rescue-free days will be calculated, provided at least half the days within the summary period have non-missing values for the endpoint.
- Any data recorded after study day 169 (but before Visit 9) will not be included in any summaries.

Time to Onset on Day 1

- The time to onset on Day 1 is calculated as the time (both nominal and actual) that the first post-dose FEV1 during the 0-6 h post-dose period is ≥100 mL above baseline FEV1. Post-dose assessments that are actually pre-dose will be considered missing in the calculation.
- Subjects who have at least one FEV1 assessment within the 0-6 h post-dose period but do not achieve a ≥100 mL increase from baseline over 0-6 h post-dose will be considered censored.

Increase in FEV1 of ≥12% and ≥200 mL above Baseline at any Time During 0-6 h Post-dose on Day 1

- A flag will be derived to identify whether or not a subject achieved an increase in FEV1 of ≥12% and ≥200 mL above baseline at any time during 0-6 h post-dose on Day 1. The flag will have values as follows:
  - 1, if any FEV1 value recorded at 15 or 30 min, 1, 3 or 6 h was ≥12 % and ≥200 mL above baseline.
  - 0, if no FEV1 value recorded at 15 or 30 min, 1, 3 or 6 h was ≥12 % and ≥200 mL above baseline.

Increase of ≥100 mL above Baseline in Trough FEV1

- A flag will be derived to identify whether or not a subject achieved an increase of ≥100 mL above baseline in trough FEV1 at each of Days 2, 28, 56, 84, 112, 168 and 169. The flag will have values as follows:
  - 1, if the trough FEV1 was ≥100 mL above baseline.
  - 0, if the trough FEV1 was < 100 mL above baseline, or the trough FEV1 was missing with no subsequent non-missing trough FEV1 values.
  - Missing, if the trough FEV1 was missing but subsequent trough FEV1 values were non-missing.

10.7. Appendix 7: Premature Withdrawals & Handling of Missing Data

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as on completion of final on-treatment clinic visit (Visit 9). • Withdrawn subjects will not be replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • In general, the minimum data required will be a baseline evaluation and at least one post-baseline evaluation. • If a subject withdraws at a scheduled treatment visit, then any data collected at that visit associated with scheduled visit procedures will be used (under the scheduled visit assignment) in all summaries and analyses wherever possible. • All other data collected as part of the early withdrawal at a scheduled visit, or at a standalone EW visit, will only be used in summary or analysis tables as part of the 'worst case post baseline' summary/analysis. • Early withdrawal data will be included in any relevant listing.

10.7.2. Handling of Missing Data

Element	Reporting Detail
General	• For efficacy endpoints, missing data is expected to arise mainly from subjects missing complete visits or time points. • The amount of occasional missing data for covariates included in the statistical analysis is expected to be minimal. Missing data will not be directly imputed in primary analysis of each endpoint. • For analysis of trough FEV1 at Day 169, sensitivity analyses with LOCF will be produced for supportive analysis.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

10.7.2.1. Handling of Missing Responder

Element	Reporting Detail
Responder	• Subjects with missing data and a subsequent non-missing assessment will not be considered a responder or non-responder but will be left as missing. • Subjects with missing data and no subsequent assessments will be considered a non-responder. • No extra visits will be added and no imputation performed in the original dataset. • The analysis dataset will initially contain rows for each visit at which at least one

Element	Reporting Detail
	derived variable (excluding baseline) is able to be calculated. For these rows, IMPFLAG will be 1 (not imputed). • For subjects who do not provide data at the final visit, additional rows will be created for each subsequent visit after their final visit (i.e. their time of withdrawal) with non-missing data which is planned to be included in the responder analysis. For these rows, IMPFLAG will be 0 (imputed) and responder status will be 'Non-responder'. • If the final visit containing non-missing data does not provide enough data to calculate the derived variable on which the responder status is based (e.g. some domains of the SGRQ are present but not all, so the total score cannot be created), then IMPFLAG will be changed to 0 (imputed) and responder status will be 'Non-responder' on that row. • Apart from derived FEV1 and FVC, the listings should not contain any rows where all the derived variables are missing, except for the rows which are imputed. (The FEV1 listing may have a blank row between two non-missing rows because all FEV1 derived variables are missing but FVC derived variables are present – IMPFLAG should still be 1 for these rows.) • If the baseline value is missing, or there are no post-baseline non-missing assessments, no imputation will be performed • No visits will be imputed if they are between two visits with non-missing assessments

10.7.2.2. Handing of Missing Dates

Element	Reporting Detail
General	• Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

10.7.2.3. Handling of Partial Dates

Element	Reporting Detail
Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month o If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.
Adverse Events	• Any partial dates for adverse events will be raised to data management. If the full date cannot be ascertained, the following assumptions will be made: o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month.

Element	Reporting Detail
	○ However, if these results in a date prior to Week 1 Day 1 and the event could possibly have occurred during treatment from the partial information, then the Week 1 Day 1 date will be assumed to be the start date. ○ The AE will then be considered to start on-treatment (worst case). ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • The recorded partial date will be displayed in listings.

10.7.2.4. Handling of Missing Data for Statistical Analysis

Element	Reporting Detail
MMRM	• Missing data will not be directly imputed in this analysis; however, all non-missing data for a subject will be used within the analysis to estimate the treatment effect
ANCOVA	• For analysis of trough FEV1 at Day 169, sensitivity analyses with LOCF to imputed missing data will be produced for supportive analysis. • Missing data will not be imputed for other analysis.
Cox's proportional Analysis	• Missing data will not be imputed.
Logistic regression Analysis	• Missing data will not be imputed.

10.8. Appendix 8: Values of Potential Clinical Importance

10.8.1. Laboratory Values

Threshold values for liver function test results, which are considered values of potential clinical importance, are:

- 3 times the upper limit of normal (ULN) for Alanine Aminotransferase (ALT)
- 2 times the ULN for Total Bilirubin (BILT).

Graphical displays of liver function test results will be produced as described in Section 8.2 (Clinical Laboratory Analyses) to identify any results above the thresholds.

Laboratory values will be flagged relative to the normal range. Clinical concern ranges will not be used.

10.8.2. ECG

Clinical concern ranges will not be used.

10.8.3. Vital Signs

Clinical concern ranges will not be used.

10.9. Appendix 9: Multicenter Studies

This study was randomized centrally within country. No strata were defined.

Country will be considered a fixed effect in all analyses on overall population. For primary efficacy analysis, interaction with treatment will be explored by fitting a model with an additional treatment by country interaction term; any interaction found to be statistically significant at the 10 % level will be further investigated and characterised. Center will not be included as a covariate in China subgroup statistical analyses.

All results will be produced for all countries combined. In addition, summary statistics of demography, screening lung function, primary and secondary endpoints will be produced by country.

10.10. Appendix 10: Examination of Covariates, Subgroups & Other Strata

The details of covariates that will be used in statistical analyses have been clarified in Section 7.1 (Primary Statistical Analyses), Section 7.2 (Secondary Statistical Analyses) and Section 7.3 (Other Statistical Analyses).

Consistency of treatment effect across covariates fitted in the primary efficacy endpoint analysis models will be examined by fitting separate models to examine treatment by baseline, treatment by country (not done for China alone sub-group analysis) and treatment by smoking status at screening interactions. Separate analysis models will also be fitted to examine treatment by ICS use, treatment by reversibility to salbutamol and treatment by percent predicted FEV_1.

No formal statistical analysis of sub-groups of the study population for either the overall analysis or the China subgroup analysis will be performed.

10.11. Appendix 11: Multiple Comparisons & Multiplicity

There is no adjustment for multiplicity to be applied in this study for the analysis on all countries overall as there is only one primary endpoint (Clinic visit trough (pre-bronchodilator) FEV1 on Treatment Day 169) and only one primary comparison (UMEC62.5 mcg vs. placebo) of interest. Treatment comparisons for secondary and other endpoints will be considered exploratory.

For China subgroup analysis, as the China subgroup analysis is powered, the inference on the primary endpoint on China subgroup is dependent on statistical significance having been achieved for the primary endpoint on the analysis on all countries overall. Treatment comparisons for secondary and other endpoints in China subgroup analysis will also be considered exploratory.

10.12. Appendix 12: Model Checking and Diagnostics for Statistical Analyses

10.12.1. Statistical Analysis Assumptions

Endpoint(s)	• Trough FEV1 • Trough FVC • TDI Focal Score • Serial FEV1 • Serial FVC
Analysis	• MMRM

- The Kenward and Roger method (KR) for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
  - In the event the model fails to run using the KR method, then the residual method will be used instead.
- Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

Endpoint(s)	• 0-6 h weighted mean FEV1 on Day 1 • Mean number of puffs of rescue medication per day over each treatment period • Pulse rate • Systolic • Diastolic blood pressure • QTc(F) • PR interval • Heart rate
Analysis	• ANCOVA

Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

Endpoint(s)	• Time to Onset (an increase of 100mL in FEV1 above baseline) during 0-6 h post-dose on Day 1 • Time to First COPD Exacerbation
Analysis	• Cox's proportional hazards model

The proportional hazards assumption for this method of analysis will be examined by obtaining the Kaplan-Meier estimates of the survival function S(t) over time separately for treatment group. Under the assumption of proportional hazard between the treatment

groups, ln{−ln[S(t)]} for the two groups should be parallel to each other and the distance between them constant. If the curves are approximately parallel, then the proportional hazard assumption is not violated. If these curves cross each other or diverge greatly from the assumption of parallel lines, then the assumption is not met.

Endpoint(s)	• Proportion Achieving Increase in FEV1 of ≥12 % and ≥200 mL above Baseline at any Time During 0-6 h Post-dose on Day 1 • Proportion Achieving Increase of ⩾ 100 mL above Baseline in Trough FEV1 • Proportion of Responders According to TDI Focal Score
Analysis	• Logistic regression model
• Computation of confidence intervals for the odds ratios is based on the individual Wald tests. • BUD/FOR will be used as the reference level for treatment • Goodness-of-fit of the logistic model will be examined using the LACKFIT option for the model statement in SAS. Index plots of the Pearson residuals and deviance criteria residuals will be plotted by using the IPLOTS option for the model statement in SAS.	

10.13. Appendix 13 – Abbreviations & Trade Marks

10.13.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
GUI	Guidance
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
GSK	GlaxoSmithKline

10.13.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies	Trademarks not owned by the GlaxoSmithKline Group of Companies
HARP	SAS
RAMOS	S-PLUS
RANDALL	

10.14. Appendix 14: List of Data Displays

10.14.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population (Overall Analysis)	1.1 to 1.37	1.1 to 1.1
Study Population (China Subgroup Analysis)	1.1 to 1.35	1.1 to 1.1
Efficacy(Overall Analysis)	2.1 to 2.56	2.1 to 2.21
Efficacy (China Subgroup Analysis)	2.1 to 2.49	2.1 to 2.21
Safety (Overall Analysis)	3.1 to 3.48	3.1 to 3.17
Safety (China Subgroup Analysis)	3.1 to 3.48	3.1 to 3.17
Section	**Listings**	
ICH Listings	1 to 25	
Other Listings	26 to 54	

10.14.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in Appendix 15: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Efficacy	NA	NA	EFF_L1

NOTES:

- Non-Standard displays are indicated in the 'IDSL / TST ID / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

10.14.3. Deliverable [Priority]

Delivery [Priority] [1]	Description
SAC [1]	Final Statistical Analysis Complete

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort.

10.14.4. Study Population Tables

Study Population Tables						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.1.	1.1.	All Subjects Enrolled	DB2114634 5.01	Summary of Subject Populations		SAC
1.2.	1.2.	Modified ITT	DB2114634 5.09	Summary of Exclusions from the Per Protocol Analysis		SAC
1.3.	1.3.	Modified ITT	DB2114634 5.02	Summary of Attendance at Each Clinic Visit		SAC
1.4.	1.4.	Modified ITT	DB2114634 5.03	Summary of Subject Disposition		SAC[1]
1.5.	1.5.	Screen and Run-in Failure	DB2114634 5.04	Summary of Reasons for Screen Failures		SAC
1.6.	1.6.	Screen and Run-in Failure	DB2114634 5.05	Summary of Reasons for Run-in Failures		SAC
1.7.	1.7.	Modified ITT	DB2114634 5.06	Summary of Number of Subjects by Country and Centre	For China subgroup, Country will be omitted from the title.	SAC
1.8.	1.8.	Screen and Run-in Failure	DB2114634 5.07	Summary of Inclusion/Exclusion/Randomisation Criteria Deviations for Screen or Run-in Failures		SAC
1.9.	1.9.	Modified ITT	DB2114634 5.08	Summary of Inclusion/Exclusion/Randomisation Criteria Deviations for Modified Intent-to-treat Subjects		SAC

Study Population Tables						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.10.	1.10.	Modified ITT	DB2114634 5.09	Summary of Important Protocol Deviations	Remove rows of Full Protocol Deviations, Partial Protocol Deviations and Time-point Specific Protocol Deviations and summarize all PDs with DVIMPFL marked as "Y".	SAC
1.11.	1.11.	Modified ITT	DB2114634 5.10	Summary of Demographic Characteristics		SAC[1]
1.12.	NA	Modified ITT	DB2114634 5.11	Summary of Demographic Characteristics by Country		SAC
1.13.	1.12.	PP	DB2114634 5.12	Summary of Demographic Characteristics		SAC
1.14.	1.13.	Modified ITT	DB2114634 5.13	Summary of Race and Racial Combinations		SAC
1.15.	1.14.	Modified ITT	DB2114634 5.14	Summary of Race and Racial Combination Details		SAC
1.16.	1.15.	Modified ITT	DB2114634 5.15	Summary of Current Medical Conditions		SAC

Study Population Tables						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.17.	1.16.	Modified ITT	DB2114634 5.16	Summary of Past Medical Conditions		SAC
1.18.	1.17.	Modified ITT	DB2114634 5.17	Summary of Past Cholecystectomies		SAC
1.19.	1.18.	Modified ITT	DB2114634 5.18	Summary of Family History of Cardiovascular Risk Factors		SAC
1.20.	1.19.	Modified ITT	DB2114634 5.19	Summary of COPD History		SAC
1.21.	1.20.	Modified ITT	DB2114634 5.20	Summary of COPD Exacerbation History		SAC
1.22.	1.21.	Modified ITT	DB2114634 5.21	Summary of Smoking History		SAC
1.23.	1.22.	Modified ITT	DB2114634 5.22	Summary of Smoking Status		SAC
1.24.	1.23.	Modified ITT	DB2114634 5.23	Summary of Screening Lung Function Test Results		SAC
1.25.	NA	Modified ITT	DB2114634 5.24	Summary of Screening Lung Function Test Results by Country/Region		SAC

Study Population Tables						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.26.	1.24.	Modified ITT	DB2114634 5.25	Summary of GOLD Stage, Percentage of Reversible Subjects and ICS Use at Screening		SAC
1.27.	1.25.	Modified ITT	DB2114634 5.26	Summary of mMRC Dyspnoea Scale		SAC
1.28.	1.26.	Modified ITT	DB2114634 5.27	Summary of COPD Concomitant Medications Not Given for an Exacerbation Taken Pre-treatment		SAC
1.29.	1.27.	Modified ITT	DB2114634 5.28	Summary of COPD Concomitant Medications Not Given for an Exacerbation Taken On-treatment		SAC
1.30.	1.28.	Modified ITT	DB2114634 5.29	Summary of COPD Concomitant Medications Not Given for an Exacerbation Taken Post-treatment		SAC
1.31.	1.29.	Modified ITT	DB2114634 5.30	Summary of Concomitant Medications Given for an Exacerbation Taken Pre-treatment		SAC
1.32.	1.30.	Modified ITT	DB2114634 5.31	Summary of Concomitant Medications Given for an Exacerbation Taken On-treatment		SAC
1.33.	1.31.	Modified ITT	DB2114634 5.32	Summary of Concomitant Medications Given for an Exacerbation Taken Post-treatment		SAC
1.34.	1.32.	Modified ITT	DB2114634 5.33	Summary of Non-COPD Concomitant Medications Taken Pre-treatment		SAC

Study Population Tables						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.35.	1.33.	Modified ITT	DB2114634 5.34	Summary of Non-COPD Concomitant Medications Taken On-treatment		SAC
1.36.	1.34.	Modified ITT	DB2114634 5.35	Summary of Non-COPD Concomitant Medications Taken Post-treatment		SAC
1.37.	1.35.	Modified ITT	DB2114634 5.36	Summary of Overall Percentage Treatment Compliance		SAC

10.14.5. Study Population Figures

Study Population: Figures						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.1	1.1	Modified ITT	DB2114634 5.01	Subject Withdrawals over Time		SAC

10.14.6. Efficacy Tables

Efficacy: Tables						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.1.	2.1	Modified ITT	DB2114634 6.01	Summary of Baseline FEV1 (L), Modified Intent-to-treat		SAC[1]
2.2.	NA	Modified ITT	DB2114634 6.02	Summary of Baseline FEV1 (L) by Country/Region, Intent-to-treat		SAC
2.3.	2.2	Modified ITT	DB2114634 6.03	Summary of Trough FEV1 (L), Modified Intent-to-treat		SAC[1]
2.4.	NA	Modified ITT	DB2114634 6.04	Summary of Trough FEV1 (L) by Country/Region, Modified Intent-to-treat		SAC
2.5.	2.3	Modified ITT	DB2114634 6.05	Analysis of Trough FEV1 (L), Modified Intent-to-treat, Repeated Measures		SAC[1]
2.6.	2.4	PP	DB2114634 6.06	Summary of Baseline FEV1 (L), Per Protocol		SAC
2.7.	NA	PP	DB2114634 6.07	Summary of Baseline FEV1 (L) by Country/Region, Per Protocol		SAC
2.8.	2.5	PP	DB2114634 6.08	Summary of Trough FEV1 (L), Per Protocol		SAC
2.9.	NA	PP	DB2114634 6.09	Summary of Trough FEV1 (L) by Country/Region, Per Protocol		SAC
2.10.	2.6	PP	DB2114634 6.10	Analysis of Trough FEV1 (L), Per Protocol, Repeated Measures		SAC

Efficacy: Tables						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.11.	2.7	Modified ITT	HZC113684 6.07	Summary of Trough FEV1 (L) at Day 169 LOCF		SAC
2.12.	2.8	Modified ITT	HZC113684 6.08	Statistical Analysis of Trough FEV1 (L) at Day 169 using LOCF		SAC
2.13.	2.9	Modified ITT	DB2114634 6.11	Summary of 0-6 h Weighted Mean FEV1 (L)		SAC
2.14.	NA	Modified ITT	DB2114634 6.12	Summary of 0-6 h Weighted Mean (L) by Country/Region		SAC
2.15.	2.10	Modified ITT	DB2114634 6.13	Analysis of 0-6 h Weighted Mean FEV1 (L)		SAC
2.16.	2.11	Modified ITT	DB2114634 6.14	Summary of Time to Onset (an increase of 100mL in FEV1 above baseline) on Day 1		SAC
2.17.	2.12	Modified ITT	DB2114634 6.15	Analysis of Time to Onset (min) (an increase of 100mL in FEV1 above baseline) on Day 1		SAC
2.18.	2.13	Modified ITT	DB2114634 6.16	Summary and Analysis of Proportion of Subjects Achieving Increase in FEV1 of >= 12 % and >= 200 mL above Baseline at Any Time during 0-6 h Post-dose on Day 1		SAC
2.19.	2.14	Modified ITT	DB2114634 6.17	Summary and Analysis of Proportion of Subjects Achieving Increase in Trough FEV1 of >= 100 mL above Baseline		SAC
2.20.	2.15	Modified ITT	DB2114634 6.18	Summary of Serial FEV1 (L)		SAC

Efficacy: Tables						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.21.	2.16	Modified ITT	DB2114634 6.19	Summary of Change from Baseline in Serial FEV1 (L)		SAC
2.22.	2.17	Modified ITT	DB2114634 6.20	Analysis of Serial FEV1 (L) on Day 1		SAC
2.23.	2.18	Modified ITT	DB2114634 6.21	Summary of Baseline FVC (L)		SAC
2.24.	2.19	Modified ITT	DB2114634 6.22	Summary of Trough FVC (L)		SAC
2.25.	2.20	Modified ITT	DB2114634 6.23	Analysis of Trough FVC (L)		SAC
2.26.	2.21	Modified ITT	DB2114634 6.24	Summary of Serial FVC (L)		SAC
2.27.	2.22	Modified ITT	DB2114634 6.25	Summary of Change from Baseline in Serial FVC (L)		SAC
2.28.	2.23	Modified ITT	DB2114634 6.26	Analysis of Serial FVC (L) on Day 1		SAC
2.29.	2.24	Modified ITT	DB2114634 6.27	Summary of Percentage of Rescue-Free Days		SAC
2.30.	2.25	Modified ITT	DB2114634 6.28	Summary of Mean Number of Puffs of Rescue Medication per Day		SAC
2.31.	2.26	Modified ITT	DB2114634 6.29	Analysis of Mean Number of Puffs of Rescue Medication per Day		SAC

Efficacy: Tables						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.32.	2.27	Modified ITT	DB2114634 6.30	Summary of BDI Focal Score		SAC[1]
2.33.	NA	Modified ITT	DB2114634 6.31	Summary of BDI Focal Score by Country/Region		SAC
2.34.	2.28	Modified ITT	DB2114634 6.32	Summary of TDI Focal Score		SAC[1]
2.35.	NA	Modified ITT	DB2114634 6.33	Summary of TDI Focal Score by Country/Region		SAC
2.36.	2.29	Modified ITT	DB2114634 6.34	Analysis of TDI Focal Score, Repeated Measures		SAC[1]
2.37.	2.30	Modified ITT	DB2114634 6.35	Summary and Analysis of Proportion of Responders According to TDI		SAC
2.38.	2.31	Modified ITT	DB2114634 6.36	Summary of Baseline SGRQ Scores		SAC
2.39.	2.32	Modified ITT	DB2114634 6.37	Summary of SGRQ Total Score		SAC
2.40.	2.33	Modified ITT	DB2114634 6.38	Summary of SGRQ Symptoms Domain Score		SAC
2.41.	2.34	Modified ITT	DB2114634 6.39	Summary of SGRQ Activity Domain Score		SAC
2.42.	2.35	Modified ITT	DB2114634 6.40	Summary of SGRQ Impacts Domain Score		SAC

Efficacy: Tables						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.43.	2.36	Modified ITT	DB2114634 6.41	Analysis of SGRQ Total Score		SAC
2.44.	2.37	Modified ITT	DB2114634 6.42	Summary and Analysis of Proportion of Responders According to SGRQ Total Score		SAC
2.45.	2.38	Modified ITT	DB2114634 6.43	Summary of Healthcare Resource Utilisation		SAC
2.46.	2.39	Modified ITT	DB2114634 6.44	Summary of Baseline CAT Score		SAC
2.47.	2.40	Modified ITT	DB2114634 6.45	Summary of CAT Score		SAC
2.48.	2.41	Modified ITT	DB2114634 6.41	Analysis of CAT Score		SAC
2.49.	2.42	Modified ITT	DB2114634 6.42	Summary and Analysis of Proportion of Responders According to CAT Score up to Week 24		SAC
2.50.	2.43	Modified ITT	DB2114634 6.46	Summary of On-treatment COPD Exacerbations		SAC
2.51.	2.44	Modified ITT	DB2114634 6.47	Summary of Post-treatment COPD Exacerbations		SAC
2.52.	2.45	Modified ITT	DB2114634 6.48	Summary and Analysis of Time to First On-treatment Exacerbation (days)		SAC
Stats Appendix						
2.53.	2.46	Modified ITT	DB2114634 10.01	Type III Tests of Fixed Effects for Repeated Measures Analysis of Trough FEV1		SAC

Efficacy: Tables						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.54.	2.47	Modified ITT	DB2114634 10.02	Covariance Parameter Estimates for Repeated Measures Analysis of Trough FEV1		SAC
2.55.	2.48	Modified ITT	DB2114634 10.03	Significance Levels for Interactions of Treatment with Smoking Status, country and Baseline for Trough FEV1		SAC
2.56.	2.49	Modified ITT	DB2114634 10.04	Significance Levels for Interactions of Treatment with ICS Use, Reversibility, Percent Predicted FEV1 for Trough FEV1		SAC

10.14.7. Efficacy Figures

Efficacy: Figures						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.1.	2.1	Modified ITT	DB2114634 6.01	Box Plot of Change from Baseline in Trough FEV1 (L) at Day 169		SAC
2.2.	2.2	Modified ITT	DB2114634 6.02	Empirical Distribution Function Plot of Change from Baseline in Trough FEV1 (L) at Day 169		SAC
2.3.	2.3	Modified ITT	DB2114634 6.03	Least Squares Mean (95% CI) Change from Baseline in Trough FEV1 (L), Modified Intent-to-treat		SAC
2.4.	2.4	Modified ITT	DB2114634 6.04	Least Squares Mean (95% CI) Treatment Differences from Placebo in Change from Baseline in Trough FEV1 (L), Modified Intent-to-treat		SAC
2.5.	2.5	PP	DB2114634 6.05	Least Squares Mean (95% CI) Change from Baseline in Trough FEV1 (L), Per Protocol		SAC
2.6.	2.6	PP	DB2114634 6.06	Least Squares Mean (95% CI) Treatment Differences from Placebo in Change from Baseline in Trough FEV1 (L), Per Protocol		SAC
2.7.	2.7	Modified ITT	DB2114634 6.07	Kaplan-Meier Estimates of Time to Onset (min) on Day 1		SAC
2.8.	2.8	Modified ITT	DB2114634 6.08	Least Squares Mean (95% CI) Change from Baseline in FEV1 (L) Over Time on Day 1		SAC
2.9.	2.9	Modified ITT	DB2114634 6.09	Least Squares Mean (95% CI) Treatment Differences from Placebo in Change from Baseline in FEV1 (L) Over Time on Day 1		SAC
2.10.	2.10	Modified ITT	DB2114634 6.10	Least Squares Mean (95% CI) Change from Baseline in Trough FVC (L)		SAC

Efficacy: Figures						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.11.	2.11	Modified ITT	DB2114634 6.11	Least Squares Mean (95% CI) Treatment Differences from Placebo in Change from Baseline in Trough FVC (L)		SAC
2.12.	2.12	Modified ITT	DB2114634 6.12	Least Squares Mean (95% CI) Change from Baseline in FVC (L) Over Time on Day 1		SAC
2.13.	2.13	Modified ITT	DB2114634 6.13	Least Squares Mean (95% CI) Treatment Differences from Placebo in Change from Baseline in FVC (L) Over Time on Day 1		SAC
2.14.	2.14	Modified ITT	DB2114634 6.14	Least Squares Mean (95% CI) TDI Focal Score		SAC
2.15.	2.15	Modified ITT	DB2114634 6.15	Least Squares Mean (95% CI) Treatment Differences from Placebo in TDI Focal Score		SAC
2.16.	2.16	Modified ITT	DB2114634 6.16	Empirical Distribution Function of Change from Baseline in SGRQ Total Score at Day 168		SAC
2.17.	2.17	Modified ITT	DB2114634 6.17	Least Squares Means (95% CI) Change from Baseline in SGRQ Total Score		SAC
2.18.	2.18	Modified ITT	DB2114634 6.18	Least Squares Mean (95% CI) Treatment Differences from Placebo in Change from Baseline in SGRQ Total Score		SAC
2.19.	2.19	Modified ITT	DB2114634 6.19	Time to First On-treatment COPD Exacerbation (days)		SAC
2.20.	2.20	Modified ITT	DB2114634 6.20	Scatter plot of Change from Baseline CAT scores versus Change from Baseline Trough FEV1 at Day 168		SAC

Efficacy: Figures						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.21.	2.21	Modified ITT	DB2114634 6.21	Scatter Plot of Baseline CAT scores versus Baseline FEV1		SAC

10.14.8. Safety Tables

Safety : Tables						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.1.	3.1	Modified ITT	DB2114634	Summary of Exposure		SAC
3.2.	3.2	Modified ITT	DB2114634 7.02	Overview of Adverse Events		SAC[1]
3.3.	3.3	Modified ITT	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term		SAC
3.4.	3.4	Modified ITT	AE3	Summary of Common Adverse Events by Overall Frequency	A common AE is one reported by 3% or more of subjects in any treatment group	SAC
3.5.	3.5	Modified ITT	DB2114634 7.03	Summary of On-treatment Adverse Events		SAC
3.6.	3.6	Modified ITT	DB2114634 7.04	Summary of Post-treatment Adverse Events		SAC
3.7.	3.7	Modified ITT	DB2114634 7.05	Summary of On-treatment Adverse Events Reported by 3 % (after rounding) or More Subjects in Any Treatment Group		SAC
3.8.	3.8	Modified ITT	DB2114634 7.06	Summary of On-treatment Common Non-serious Adverse Events	A common AE is one reported by 3% or more of subjects in any treatment group.	SAC
3.9.	3.9	Modified ITT	DB2114634 7.07	Summary of On-treatment Drug-related Adverse Events		SAC

Safety : Tables						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.10.	3.10	Modified ITT	DB2114634 7.07	Summary of On-treatment Non-Serious Drug Related Adverse Events		SAC
3.11.	3.11	Screen and Run-in Failure	DB2114634 7.09	Summary of Pre-treatment Fatal Serious Adverse Events, Screen and Run-in Failure		SAC
3.12.	3.12	Screen and Run-in Failure	DB2114634 7.10	Summary of Pre-treatment Non-Fatal Serious Adverse Events, Screen and Run-in Failure		SAC
3.13.	3.13	Modified ITT	DB2114634 7.11	Summary of Pre-Treatment Non-Fatal Serious Adverse Events, Modified Intent-to-treat		SAC
3.14.	3.14	Modified ITT	DB2114634 7.12	Summary of Fatal Serious Adverse Events		SAC[1]
3.15.	3.15	Modified ITT	DB2114634 7.07	Summary of Serious Adverse Events by System Organ Class		SAC[1]
3.16.	3.16	Modified ITT	DB2114634 7.07	Summary of Drug-Related Serious Adverse Events by System Organ Class		SAC
3.17.	3.17	Modified ITT	DB2114634 7.13	Summary of On-treatment Non-Fatal Serious Adverse Events		SAC
3.18.	3.18	Modified ITT	DB2114634 7.14	Summary of Post-treatment Non- Fatal Serious Adverse Events		SAC
3.19.	3.19	Screen and Run-in Failure	DB2114634 7.15	Summary of Pre-treatment Adverse Events Leading to Withdrawal from the Study		SAC

Safety : Tables						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.20.	3.20	Modified ITT	DB2114634 7.16	Summary of On-treatment Adverse Events Leading to Discontinuation of Study Treatment or Withdrawal from the Study		SAC
3.21.	3.21	Modified ITT	DB2114634 7.17	Summary of On-treatment Adverse Events of Special Interest		SAC[1]
3.22.	3.22	Modified ITT	DB2114634 7.18	Summary of Fatal Serious Adverse Events of Special Interest		SAC
3.23.	3.23	Modified ITT	DB2114634 7.19	Summary of On-treatment Non-Fatal Serious Adverse Events of Special Interest		SAC
3.24.	3.24	Modified ITT	DB2114634 7.20	Summary of Fatal Drug Related Serious Adverse Events		SAC
3.25.	3.25	Modified ITT	DB2114634 7.21	Summary of On-treatment Non-Fatal Drug Related Serious Adverse Events		SAC
3.26.	3.26	Modified ITT	DB2114634 7.22	Summary of Chemistry Data		SAC
3.27.	3.27	Modified ITT	DB2114634 7.23	Summary of Change from Baseline in Chemistry Data		SAC
3.28.	3.28	Modified ITT	DB2114634 7.24	Summary of Chemistry Data Outside the Normal Range		SAC
3.29.	3.29	Modified ITT	DB2114634 7.25	Summary of Chemistry Changes from Baseline Relative to the Normal Range		SAC
3.30.	3.30	Modified ITT	DB2114634 7.26	Summary of Haematology Data		SAC

Safety : Tables						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.31.	3.31	Modified ITT	DB2114634 7.27	Summary of Change from Baseline in Haematology Data		SAC
3.32.	3.32	Modified ITT	DB2114634 7.28	Summary of Haematology Data Outside the Normal Range		SAC
3.33.	3.33	Modified ITT	DB2114634 7.29	Summary of Haematology Changes from Baseline Relative to the Normal Range		SAC
3.34.	3.34	Modified ITT	HZC113684 7.27	Summary of Urinalysis Data		SAC
3.35.	3.35	Modified ITT	DB2114634 7.30	Summary of Vital Signs		SAC
3.36.	3.36	Modified ITT	DB2114634 7.31	Summary of Change from Baseline in Vital Signs		SAC
3.37.	3.37	Modified ITT	DB2114634 7.32	Statistical Analysis of Pulse Rate (bpm)		SAC
3.38.	3.38	Modified ITT	DB2114634 7.33	Statistical Analysis of Systolic Blood Pressure (mmHg)		SAC
3.39.	3.39	Modified ITT	DB2114634 7.34	Statistical Analysis of Diastolic Blood Pressure (mmHg)		SAC
3.40.	3.40	Modified ITT	DB2114634 7.35	Summary of ECG Values		SAC
3.41.	3.41	Modified ITT	DB2114634 7.36	Summary of Change from Baseline in ECG Values		SAC

Safety : Tables						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.42.	3.42	Modified ITT	DB2114634 7.37	Summary of QTc(F) (msec) Categories		SAC
3.43.	3.43	Modified ITT	DB2114634 7.38	Summary of Change From Baseline in QTc(F) (msec) Categories		SAC
3.44.	3.44	Modified ITT	DB2114634 7.39	Statistical Analysis of QTc(F) (msec)		SAC
3.45.	3.45	Modified ITT	DB2114634 7.40	Statistical Analysis of PR Interval (msec)		SAC
3.46.	3.46	Modified ITT	DB2114634 7.41	Statistical Analysis of ECG Heart Rate (bpm)		SAC
3.47.	3.47	Modified ITT	DB2114634 7.42	Summary of ECG Result Interpretations		SAC
3.48.	3.48	Modified ITT	DB2114634 7.44	Summary of All ECG Abnormalities		SAC

10.14.9. Safety Figures

Safety : Figures						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.1.	3.1	Modified ITT	DB2114634 7.01	Scatter Plots of Maximum Post Baseline versus Baseline for Chemistry Parameters with an Upper Limit of Normal Range		SAC
3.2.	3.2	Modified ITT	DB2114634 7.02	Box Plots of Change from Baseline to Maximum Post-baseline for Chemistry Parameters with an Upper Limit of Normal Range		SAC
3.3.	3.3	Modified ITT	DB2114634 7.03	Scatter Plots of Minimum Post Baseline versus Baseline for Chemistry Parameters with a Lower Limit of Normal Range		SAC
3.4.	3.4	Modified ITT	DB2114634 7.04	Box Plots of Change from Baseline to Minimum Post-baseline for Chemistry Parameters with a Lower Limit of Normal Range		SAC
3.5.	3.5	Modified ITT	DB2114634 7.05	Scatter Plots of Maximum Post Baseline versus Baseline for Haematology Parameters with an Upper Limit of Normal Range		SAC
3.6.	3.6	Modified ITT	DB2114634 7.06	Box Plots of Change from Baseline to Maximum Post-baseline for Haematology Parameters with an Upper Limit of Normal Range		SAC
3.7.	3.7	Modified ITT	DB2114634 7.07	Scatter Plots of Minimum Post Baseline versus Baseline for Haematology Parameters with a Lower Limit of Normal Range		SAC
3.8.	3.8	Modified ITT	DB2114634 7.08	Box Plots of Change from Baseline to Minimum Post-baseline for Haematology Parameters with A Lower Limit of Normal Range		SAC
3.9.	3.9	Modified ITT	DB2114634 7.09	Trellis Display of Maximum Post-baseline versus Baseline for Liver Function Test Parameters		SAC
3.10.	3.10	Modified ITT	DB2114634 7.10	Least Squares Means Change from Baseline (95% CI) in Pre-dose Pulse Rate (bpm)		SAC

Safety : Figures						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.11.	3.11	Modified ITT	DB2114634 7.11	Least Squares Means Change from Baseline (95% CI) in Pre-dose Systolic Blood Pressure (mmHg)		SAC
3.12.	3.12	Modified ITT	DB2114634 7.12	Least Squares Means Change from Baseline (95% CI) in Pre-dose Diastolic Blood Pressure (mmHg)		SAC
3.13.	3.13	Modified ITT	DB2114634 7.13	Empirical Distribution Function Plot of Maximum Post-baseline QTc(F) (msec)		SAC
3.14.	3.14	Modified ITT	DB2114634 7.14	Empirical Distribution Function Plot of Change from Baseline in Maximum Post-baseline QTc(F) (msec)		SAC
3.15.	3.15	Modified ITT	DB2114634 7.15	Least Squares Means Change from Baseline (95% CI) in Pre-dose QTc(F) (msec)		SAC
3.16.	3.16	Modified ITT	DB2114634 7.16	Least Squares Means Change from Baseline (95% CI) in Pre-dose PR Interval (msec)		SAC
3.17.	3.17	Modified ITT	DB2114634 7.17	Least Squares Means Change from Baseline (95% CI) in Pre-dose Heart Rate (bpm)		SAC

10.14.10. ICH Listings

ICH : Listings						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population						
1.	1.	Screen and Run in Failure	ES7	Listing of Reasons for Screen Failure / Run-in Failure		SAC
2.	2.	Modified ITT	DB2114634 5.01	Listing of Reasons for Withdrawal		SAC
3.	3.	Modified ITT	DB2114634 5.02	Listing of Planned and Actual Treatments		SAC
4.	4.	Modified ITT	DV2	Listing of Important Protocol Deviations		SAC
5.	5.	Modified ITT	DV2	Listing of Participants Excluded from PP population		SAC
6.	6.	Modified ITT	DB2114634 5.03	Listing of Inclusion, Exclusion or Randomisation Criteria Deviations		SAC
7.	7.	Modified ITT	DB2114634 5.04	Listing of Date of and Reason for Breaking Treatment Blind During the Study		SAC
8.	8.	Modified ITT	DB2114634 5.05	Listing of Demographic Characteristics	Birth date will be presented as 'YYYY'	SAC
9.	9.	Modified ITT	DB2114634 5.06	Listing of Race		SAC
10.	10.	Modified ITT	DB2114634 5.17	Listing of COPD Concomitant Medications		SAC

ICH : Listings						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
11.	11.	Modified ITT	DB2114634 5.18	Listing of Non-COPD Concomitant Medications		SAC
12.	12.	Modified ITT	DB2114634 5.07	Listing of Screening Lung Function Test Results		SAC
Efficacy						
13.	13.	Modified ITT	DB2114634 6.01	Listing of Raw FEV1 (L) and FVC (L)		SAC
Safety						
14.	14.	Modified ITT	DB2114634 7.01	Listing of Exposure		SAC
15.	15.	All Subjects Enrolled	DB2114634 7.02	Listing of Subject Numbers for Individual Adverse Events		SAC
16.	16.	All Subjects Enrolled	DB2114634 7.03	Listing of All Adverse Events		SAC
17.	17.	All Subjects Enrolled	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		SAC
18.	18.	All Subjects Enrolled	DB2114634 7.04	Listing of Non-fatal Serious Adverse Events		SAC
19.	19.	All Subjects Enrolled	DB2114634 7.05	Listing of Fatal Adverse Events		SAC
20.	20.	All Subjects Enrolled	DB2114634 7.06	Listing of On-Treatment Drug Related SAEs		SAC

ICH : Listings						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
21.	21.	Modified ITT	DB2114634 7.07	Listing of Subject Numbers for On-treatment Adverse Events of Special Interest		SAC
22.	22.	All Subjects Enrolled	DB2114634 7.08	Listing of Adverse Events leading to Discontinuation of Study Treatment or Withdrawal from the Study		SAC
23.	23.	Modified ITT	DB2114634 7.09	Listing of Potential Investigational Product Inhaler Malfunctions Reported by Subjects		SAC
24.	24.	Modified ITT	DB2114634 7.10	Listing of Chemistry Values for Subjects with at Least One Value outside the Normal Range		SAC
25.	25.	Modified ITT	DB2114634 7.11	Listing of Haematology Values for Subjects with at Least One Value outside the Normal Range		SAC

10.14.11. Non-ICH Listings

Non-ICH : Listings						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population						
26.	26.	All Subjects Enrolled	DB2114634 5.08	Listing of Reasons for Withdrawal- Subjects Randomised but Not in the Modified Intent-to-Treat Population		SAC
27.	27.	All Subjects Enrolled	DB2114634 5.10	Listing of Treatment Misallocations		SAC
28.	28.	Modified ITT	DB2114634 5.11	Listing of Medical Conditions		SAC
29.	29.	Modified ITT	DB2114634 5.12	Listing of Past Cholecystectomies		SAC
30.	30.	Modified ITT	DB2114634 5.13	Listing of Family History of Cardiovascular Risk Factors		SAC
31.	31.	Modified ITT	DB2114634 5.14	Listing of COPD History		SAC
32.	32.	Modified ITT	DB2114634 5.15	Listing of Smoking History and Smoking Status		SAC
33.	33.	Modified ITT	DB2114634 5.16	Listing of mMRC Dyspnoea Scale		SAC
34.	34.	Modified ITT	DB2114634 5.19	Relationship between ATC Level 1, Ingredient and Verbatim Text		SAC
35.	35.	Modified ITT	DB2114634 5.20	Listing of Treatment Compliance Data		SAC

Non-ICH : Listings						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
36.	36.	All Subjects Enrolled	DB2114634 5.21	Listing of All Protocol Deviations		SAC
Efficacy						
37.	37.	Modified ITT	DB2114634 6.02	Listing of Derived FEV1 Endpoints		SAC
38.	38.	Modified ITT	DB2114634 6.03	Listing of Derived FVC Endpoints		SAC
39.	39.	Modified ITT	DB2114634 6.04	Listing of BDI/TDI		SAC
40.	40.	Modified ITT	DB2114634 6.05	Listing of SGRQ Scores		SAC
41.	41.	Modified ITT	DB2114634 6.06	Listing of Derived Rescue Endpoints		SAC
42.	42.	Modified ITT	DB2114634 6.07	Listing of CAT Scores		SAC
43.	43.	Modified ITT	DB2114634 6.08	Listing of COPD Exacerbations		SAC
44.	44.	Modified ITT	Non-Standard EFF_L1	Listing of Healthcare Resource Utilisation		SAC
Safety						
45.	45.	Modified ITT	DB2114634 7.12	Listing of Immunology Data for subjects with at least one Reactive Result		SAC

Non-ICH : Listings						
IMCT No.	**China Subgroup No.**	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
46.	46.	Modified ITT	DB2114634 7.13	Listing of Virology Data		SAC
47.	47.	Modified ITT	DB2114634 7.14	Listing of Urinalysis Data		SAC
48.	48.	Modified ITT	DB2114634 7.15	Listing of Vital Signs		SAC
49.	49.	Modified ITT	DB2114634 7.18	Listing of ECG Values for Subjects with Any Abnormal ECG Interpretation		SAC
50.	50.	Modified ITT	DB2114634 7.19	Listing of ECG Findings for Subjects with Any Abnormal ECG Interpretation		SAC
51.	51.	Modified ITT	DB2114634 7.20	Listing of Liver Event Results and Time of Event Relative to Treatment		SAC
52.	52.	Modified ITT	DB2114634 7.21	Listing of Liver Event Information for RUCAM Score		SAC
53.	53.	Modified ITT	DB2114634 7.22	Listing of Liver Biopsy Details		SAC
54.	54.	Modified ITT	DB2114634 7.23	Listing of Liver Imaging Details		SAC

10.15. Appendix 15: Example Mock Shells for Data Displays

Example : EFF_L1
Protocol : AC4117410
Population : ITT

Listing 41
Listing of Healthcare Resource Utilisation

Investigator at Centre/ Subject	Date of Contact	Number of office/practice visits	Number of urgent care/outpatient Visits	Number of emergency room visits	Number of days in intensive care	Number of days in general ward	Was this contact due to an exacerbation
PPD	21May2013	0	1	0	0	0	N
	01MAY2013	1	0	0	0	11	Y