Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan

Title	:	Reporting and Analysis Plan for 201749: A 24-week treatment, multi-center, randomized, double-blind, double-dummy, parallel group study to compare Umeclidinium/Vilanterol, Umeclidimium, and Salmeterol in subjects with chronic obstructive pulmonary disease (COPD)
Compound Number	:	GSK2592356 (GSK573719+GW642444)
Effective Date	:	18-JUL-2018

Description:

- The purpose of this reporting and analysis plan (RAP) is to describe the planned analyses and output to be included in the main Clinical Study Report for Protocol 201749.

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol:

Revision Chronology:		
GlaxoSmithKline Document Number	**Date**	**Version**
2016N277425_00	2016-SEP-13	Original
2016N277425_01	2017-FEB-07	Amendment No. 1
This protocol amendment was created to make the following changes: Regulatory Agency Identifying Number(s): A typographical error in the EudraCT no. corrected. IND no. added Section 4.1 and Section 4.4: Typographical errors and inconsistencies corrected Inconsistencies between Section 4.4, Section 7.3.1.5 and Section 7.1 revised Section 7.1 Time and Events table: Un-intentional deletion of the ("x") were added to confirm that concomitant medications should be reviewed at every clinic visit was corrected. Increased the visit window Typographical error and inconsistencies corrected as described in Appendix 9, Section 12.9. Section 7.2.2 Critical procedures performed at Screening (Visit 1): To clarify that height and weight are collected at V1 **"**Height and weight" added Section 7.3.2 Spirometry: "At Screening, before the morning dose of usual COPD medication(s)" added. Section 7.3.7: Physical activity monitor (study subset) Inconsistency between Section 1, Section 4.1 and Section 7.3.7 revised		
2016N277425_02	2017-FEB-21	Amendment No. 2 Canada ONLY
This protocol amendment was created to comply with Health Canada guidelines. They require pharmaceutical manufacturers to expeditiously report domestic cases of unusual failure in efficacy (UFIE) for new drugs to the Marketed Health Products Directorate (MHPD) within 15 days of first notification. Changes were made to Section 7.4.1 and Appendix 4.		

Revision Chronology:		
GlaxoSmithKline Document Number	**Date**	**Version**
2016N277425_03	2017-APR-18	Amendment No. 3
This protocol amendment was created to make the following changes: • Clarifications concerning study design, stratification, permitted and prohibited COPD medications, stopping criteria, visit windows, chest x-rays performed in the context of the protocol and site professional expertise • Rate of COPD exacerbations from tertiary endpoints to exploratory endpoints • Addition of an inclusion criterion specific to France • Integration of Canadian Amendment 2 • Correction of typographical errors and inconsistencies		

Note there is a separate RAP to cover the required analyses for the German Federal Joint Committee (G-BA).

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
	• An additional population has been defined, the Activity Monitoring (AM) Population, which will comprise all subjects in the ITT population who provide data from at least one activity monitoring session.	• Population needed for subset of subjects participating in Activity Monitoring.
	• All other Endpoints promoted to secondary endpoints	• Study aims have developed since protocol and thus previous endpoints classed as 'other' have further importance
	• An analysis by Maintenance Naive (MN) and Non-Maintenance Naive subgroups have been included.	• To investigate prospectively the 1st line use of LAMA/LABA in all symptomatic subjects (no existing data I the literature to our knowledge)
	• An analysis of ratio of trough FEV1 to baseline trough FEV1	• To investigate trough FEV1 ratio change from baseline
• Intent-to-treat ICS free (ITT ICS free)	• Population excluded.	• G-BA analysis to be conducted on the ITT population due to a change in G-BA guidance.
• To compare albuterol/salbutamol use captured in the eDiary with the electronic metered dose inhaler (eMDI) Device as data allow	• Not included in this RAP.	• Will be included in a supplementary RAP if deemed necessary.

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• To compare physical activity levels, ER-S, rescue medication use, hospital exacerbations and mortality in subjects with and without a CID	• To compare ER-S, rescue medication use, hospital exacerbations and mortality in subjects with and without a CID	• Physical activity levels will not be assessed via CID due to a smaller subset of subjects.

There were changes to the originally planned populations specified in the protocol (Dated: 13-SEP-2016) and Table 1.

2.2. Study Objectives and Endpoints

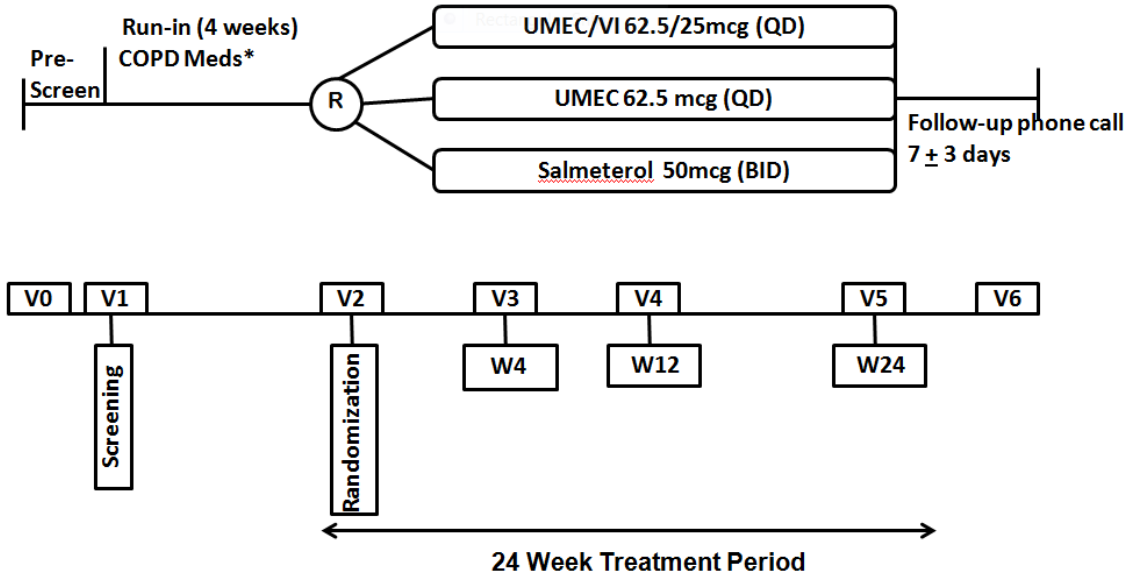
Objectives	Endpoints
Primary	**Primary**
• To compare the effect of UMEC/VI (62.5/25 mcg once daily) with UMEC (62.5 mcg once daily) on lung function	• Change from baseline in trough Forced Expiratory Volume in One Second (FEV_1) at week 24
Secondary	**Secondary**
• To compare UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on patient reported outcomes (PROs)	• Change from baseline in self administered computerised (SAC) transient dyspnea index (TDI) • Percentage of TDI responders according to SAC TDI score. A responder is defined as a ≥1 unit improvement in SAC TDI score • Assessment of respiratory daily symptoms over 24 weeks using Evaluating Respiratory Symptoms- COPD (E-RS) and its subscales (breathlessness, cough and sputum and chest symptoms) • Percentage of E-RS responders according to E-RS score (defined as reduction in E-RS score of ≥2 or ≥3.35 units) from baseline • Change from baseline in St George's Respiratory Questionnaire (SGRQ-C) • Percentage of responders according to SGRQ-C total score (defined as a 4 point or greater reduction from baseline) • Change from baseline in COPD assessment test (CAT) • Percentage of responders according to CAT

Objectives	Endpoints
	(defined as a ≥2 unit improvement in score from baseline)
• To compare UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on other COPD efficacy measures	• Ratio to baseline of trough Forced Expiratory Volume in One Second (FEV1) • Time to first mild, moderate or severe exacerbation • Time to first moderate or severe exacerbation • Time to first severe exacerbations • Time to first clinically important deterioration (CID) composite endpoint • Time to first clinically important deterioration composite endpoint excluding FEV_1 (Exacerbation, SGRQ, TDI, CAT) • Rescue albuterol/salbutamol use, (percentage of rescue-free days and mean number of Inhalations/day) captured by the electronic diary (eDiary) over 24 weeks • Inspiratory capacity (IC) • Forced Vital capacity (FVC) • Change from baseline in trough FEV_1 • Change from baseline in global impression of disease severity

Objectives	Endpoints
Safety	**Safety**
• To evaluate safety and tolerability of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5mcg once daily) and salmeterol 50mcg twice daily)	• Incidence of adverse events
Exploratory	**Exploratory**
• To explore the effect of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on rate of COPD exacerbation	• Rate of mild, moderate or severe exacerbations • Rate of moderate or severe exacerbation
• To explore the effect of UMEC/VI (62.5/25 mcg once daily), UMEC (62.5 mcg once daily) with salmeterol (50 mcg twice daily) on physical activity	• Change from baseline in physical activity
• To investigate the CID composite endpoint ability to predict short term outcomes	• To compare ER-S, rescue medication use, hospital exacerbations and mortality in subjects with and without a CID

2.3. Study Design

Overview of Study Design and Key Features



Overview of Key Study Design Features	
Design Features:	• Multi-centre, randomized, double blind, double dummy, 3-arm parallel group study to compare Umeclidinium/Vilanterol, Umeclidimium, and Salmeterol in subjects with chronic obstructive pulmonary disease (COPD). • Approximately 3232 subjects will be screened, such that 2424 subjects will be randomized and approximately 2181 evaluable subjects complete the study. • Eligible subjects will be stratified by country, long-acting bronchodilator usage during the run-in (none or one long-acting bronchodilator per day) and activity subset (activity subset or no activity subset), and randomized in a ratio of 1:1:1 to UMEC/VI inhalation powder (62.5/25 mcg once daily) administered via the ELLIPTA inhaler, or UMEC (62.5 mcg once daily) administered via the ELLIPTA or salmeterol (50 mcg BID) administered via the DISKUS. Note the activity subset was only included as a randomisation stratification group for logistical purposes. • A subset of subjects up to 150 per treatment arm will undergo assessment of their physical activity measured through a physical activity monitor (Actigraph GT9X) worn for 7 days from Screening (Visit 1), for 7 days from Randomisation (Visit 2), 7 days from Visit 3, and for 7 days prior to last clinic Visit (Visit 5). • The total duration of subject participation in the study will be approximately 29 to 35 weeks consisting of 6 weeks pre-screening if necessary, 4 weeks run-in, 24 week treatment and one week Follow-Up.
Dosing :	• The following study medications will be used in this study: - UMEC/VI 62.5/ 25mcg administered via ELLIPTA - UMEC 62.5 mcg administered via ELLIPTA - Salmeterol 50 mcg administered via DISKUS - Placebo via ELLIPTA - Placebo via DISKUS Subjects will be instructed to take one dose of medication each morning from the ELLIPTA (one inhalation equals one dose), and one dose in the morning and one in the evening from the DISKUS. The ELLIPTA will provide a total of 30 doses and the DISKUS will provide a total of 60 doses.

Overview of Key Study Design Features	
Treatment Assignment:	• Subjects will be randomly assigned to one of the blinded study treatment regimens in equal proportion (ratio of 1:1:1): - UMEC/VI 62.5/25 mcg once daily via ELLIPTA + placebo twice daily via DISKUS - UMEC 62.5 mcg once daily via ELLIPTA + placebo twice daily via DISKUS - Salmeterol 50 mcg twice daily via DISKUS + placebo once daily via ELLIPTA • GSK RandAll NG used to generate randomisation schedules. • Centralised randomisation within country using GSK RAMOS NG for treatment allocation. • Stratified by long-acting bronchodilator usage during run-in (none or one **long-acting bronchodilator** per day), country and activity subset (activity subset or no activity subset). Note the activity subset was only included as a randomisation stratification group for logistical purposes.
Interim Analysis	• No interim analysis will be performed.

2.4. Statistical Hypotheses

The primary purpose of this study is to demonstrate improvements in lung function for subjects treated with UMEC/VI compared with UMEC for 24 weeks.

The primary endpoint is change from baseline in trough FEV_1 at Week 24.
The null hypothesis is no difference between treatment groups (H0: $\mu T - \mu S = 0$), with the alternative hypothesis that there is a difference between treatment groups (H1: $\mu T - \mu S \neq 0$), where μT is the mean change from baseline for UMEC/VI and μS is the mean change from baseline for UMEC.

In order to account for multiplicity across treatment comparisons and endpoints, a step-down closed testing procedure will be applied whereby inference for secondary endpoints or treatment comparisons are dependent upon statistical significance having been achieved for the primary comparison. If the primary comparison is significant i.e. the associated p-value for UMEC/VI versus UMEC for change from baseline in trough FEV1 at Week 24 is below 0.05, this will allow inference of treatment comparisons (UMEC/VI versus UMEC on all secondary endpoints, and UMEC/VI versus Salmeterol and UMEC versus Salmeterol on all primary and secondary endpoints), which will be declared statistically significant if the associated p-value is below 0.05.

3. PLANNED ANALYSES

3.1. Final Analyses

The final planned analyses of the study will be performed after the completion of the following sequential steps (for this Clinical Data Interchange Standards Consortium [CDISC] study):

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final System Independent (SI) database release has been declared by Data Management (DM).
3. SI data to SDTM data conversion has completed by Conversion Service and quality control of unblinded SDTM has completed by DM.
4. All criteria for unblinding the randomization codes have been met.
5. Randomization codes have been distributed according to [RandAll NG].
6. Database freeze on SDTM datasets has been declared by DM

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Subjects Enrolled (ASE)	• All subjects for whom a record exists in the study database, including 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.	• Subject Disposition • Reasons for withdrawal prior to randomisation • Inclusion, exclusion and randomisation criteria deviations • SAEs for non-randomised subjects
Intent-to-treat (ITT)	• All randomized subjects (excluding those who were randomized in error) who received at least one dose of study medication. A subject who is recorded as a screen or run-in failure and also randomized will be considered to be randomized in error. Any other subject who receives a randomization number will be considered to have been randomized. • Displays will be based on the treatment to which the subject was randomized	• Study Population • Efficacy • Safety
Activity Monitoring (AM)	• All subjects in the ITT population who provide data from at least one activity monitoring session. • Displays will be based on the treatment to which the subject was randomized	• Activity Monitoring

1. **NOTE :**

- Please refer to Section 10.8 Appendix 8: List of Data Displays which details the population to be used for each display being generated.

4.1. Protocol Deviations

- Protocol deviations (PDs) will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (PDMP).
- Data will be reviewed by SDL prior to SDTM DBF to ensure all important deviations are captured and categorized on the protocol deviations dataset (except for the PD of taking incorrect treatment).
- Subjects who received an incorrect container will be captured as an important protocol deviation. Whether or not the incorrect container contains incorrect treatment will be identified following DBF in the Analysis Data Model (ADaM) dataset.
- Important protocol deviations (as identified in the PDMP) will be summarized and listed.
- 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 electronic case report form (eCRF).

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TFL
1	UMEC/VI 62.5/25 mcg once daily via ELLIPTA + placebo twice daily via DISKUS	UMEC/VI 62.5/25	1
2	UMEC 62.5 mcg once daily via ELLIPTA + placebo twice daily via DISKUS	UMEC 62.5	2
3	Salmeterol 50 mcg twice daily via DISKUS + placebo once daily via ELLIPTA	SAL 50	3

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Endpoint	Baseline derivation
Trough FEV_1, FVC and IC	The mean of the values measured at 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

Endpoint	Baseline derivation
	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.
TDI	BDI assessment taken prior to dosing on Day 1. The baseline dyspnea index (BDI) focal score will be calculated as the sum of the ratings recorded for each of the three individual scales (Functional Impairment, Magnitude of Task, 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.
E-RS and subscale scores	Average of measurements from day -28 to day -1 inclusive; at least 16 days must be non-missing.
Physical activity	Average of measurements prior to randomisation; at least 3 days must be non-missing.
Rescue Use - Mean Number of Puffs of Rescue Medication Per Day and Percentage of Rescue-free Days Over Weeks 1-24 captured using e-diary	The total puffs of rescue for each day will be calculated as number of salbutamol puffs. If the number of puffs is missing then the total puffs will be set to missing for that day. The baseline number of inhalations is calculated using the mean number of total inhalations and the baseline percentage rescue use is calculated from the percentage of rescue free days as the average of measurements from day -28 to day -1 inclusive; at least 14 days must be non-missing.
Rescue Use - Mean Number of Occurrences of Rescue Medication Per Day and Percentage of Rescue-free Days Over Weeks 1-24 captured using e-MDI	The total occurrences, defined as =>1 puff within a 2 minute time window, of rescue for each day will be calculated. The baseline is calculated using the mean number of occurrences and the baseline percentage rescue use is calculated from the percentage of rescue free days as the average of measurements from the first date of sensor sync to the last date of sensor sync (per sensor subject combination) up until the day prior to first dose.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.3. Multicentre Studies

- This study will be randomized centrally within country.
- It is likely that many centres will enrol a very small number of subjects and so rather than adjusting for centre in the statistical analyses, a geographical region will be used. This will consist of all centres within a similar geographical region.
- Country is determined by the location of the centre, as entered into GSK systems by the site monitor. The CENTREID variable will be used to identify and group centres.
- Geographical Region will be used wherever geographical region is included and defined as follows:

South America	North America	EU	Other
Argentina	Canada	France	Australia
Mexico	US	Germany	South Africa
		Italy	
		Netherlands	
		Spain	
		Sweden	

5.4. Examination of Covariates and Other Strata

5.4.1. Covariates and Other Strata

- Randomization is stratified by **long-acting bronchodilator** usage during the run-in (none or one **long-acting bronchodilator** per day) and long-acting bronchodilator usage will be included as a covariate in all statistical models. The no. of bronchodilators per day during run-in be re-derived and used for analysis. The randomized stratum from RAMOS and reported on the eCRF will be listed only.

- Other covariates will be included for specific analyses as detailed in model specifications in Section 7 and Section 8.

5.5. Multiple Comparisons and Multiplicity

See Section 2.4 for details on inferences that can be drawn on primary, secondary and 'other' endpoints.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
10.2	Appendix 2: Assessment Windows
10.3	Appendix 3: Study Phases and Treatment Emergent Adverse Events
10.4	Appendix 4: Data Display Standards & Handling Conventions
10.5	Appendix 5: Derived and Transformed Data
10.6	Appendix 6: Reporting Standards for Missing Data

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the ITT population, unless otherwise specified.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 8: List of Data Displays

6.1.1. Disposition

The study population summary will show the number of subjects overall who were enrolled, the number of pre-screen failures, the number of screen failures and the number with each reason for screen failure, the number of run-in failures each reason the number with each reason for run-in failure and the number of subjects in each treatment group and overall who were randomized, in the ITT population. Of those in the ITT population the number and percentage of subjects in the AM population will be presented by treatment and overall.

The end of study record summary shows the number of subjects who completed the study as well as the number who withdrew early from the study along with reasons for early withdrawal.

The summary of study treatment status shows the number of subjects who completed study treatment as well as the number who stopped study treatment prior to the end of the study, along with the reasons for discontinuation.

6.1.2. Medical Conditions

The number and percentage of subjects reporting each current medical condition will be presented by randomized treatment group and overall. All medical conditions must be summarised on this table regardless of frequency.

This will be repeated for past medical conditions.

6.1.3. Concomitant Medications

Medications that have been stopped prior to Screening will be listed and not be included in any summary tables.

Medications not taken for an exacerbation will be summarised by Anatomical-Therapeutic-Chemical (ATC) level 1 and ingredient. COPD medications given for an exacerbation will be summarised by Respiratory Medication Class (RMC).

Medications taken for an exacerbation and those not taken for an exacerbation will be listed separately. Both listings will indicate in which study phases each medication was taken (pre-treatment and/or on- treatment and/or post-treatment)

6.1.4. Screening Lung Function Tests

Pre- and post-salbutamol FEV_1, FVC and FEV_1/FVC ratio, post-salbutamol FEV_1 as a percentage of predicted normal and FEV_1 reversibility to salbutamol (expressed in mL and as a percentage) at Screening will be summarised by treatment group and overall.

6.1.5. GOLD Grade/Categories, Reversibility and long-acting bronchodilator usage Stratum

The number and percentage of subjects in each GOLD Grade 1-4 and GOLD Category A-D using CAT, the number and percentage of subjects classified as Reversible/Non-reversible to salbutamol at Screening and the number and percentage of subjects in each stratum (none or one long-acting bronchodilators per day) based on the long-acting bronchodilator usage during run-in (all defined in Section 10.5.2) will be presented by treatment group and overall.

6.1.6. Maintenance Naive

Summary Maintenance Naive and Non-Maintenance Naive status will be presented by treatment group and overall.

7. PRIMARY STATISTICAL ANALYSES

7.1. Primary Efficacy Analyses

7.1.1. Endpoint / Variables

Trough FEV_1 at Week 24

7.1.2. Summary Measure

Mean change from baseline

7.1.3. Population of Interest

The primary efficacy analyses will be based on the ITT population,.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

An intercurrent event considered to have an impact on the estimand for the ITT population analysis is:

- Discontinuation of randomised treatment

- The primary treatment effect to be estimated for the ITT population will be the hypothetical effect if all subjects had stayed on their randomised treatment.

7.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 8: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.1.5.1. Statistical Methodology Specification

Primary Statistical Analysis
Endpoint
• Change from Baseline in trough FEV_1 at Week 24 (results for trough FEV_1 at all other time points and other treatment comparisons will be obtained from the same analysis even though those are not the primary endpoint)
Model Specification
• Trough FEV_1 at Week 24 will be analysed for the ITT population using a mixed model repeated measures (MMRM) including data recorded at each of Week 4, Week 12 and Week 24. • The following covariates will be included in the model: baseline FEV_1, geographical region, stratum (no. of bronchodilators per day during run-in), visit, treatment, visit by baseline and visit by treatment interactions, where visit is nominal. • Two models will be fitted; one with a response variable of trough FEV_1, and one with a response variable of change from baseline in trough FEV_1. • While missing data are not explicitly imputed in the primary MMRM analyses, there is an underlying assumption that the data are missing at random. • 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. • An unstructured covariance structure for the R matrix will be used by specifying 'type='UN' on the REPEATED line. • Results for all time points where data are scheduled to be collected and all treatment comparisons will be included in the analysis and presented in the displays.
Model Checking & Diagnostics
• Model assumptions will be applied but appropriate adjustments may be made based on the data.

Primary Statistical Analysis

- Normality 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.
- If there are any departures from the distributional assumptions, alternative models will be explored using appropriately transformed data.

Model Results Presentation

- Least squares (LS) mean and LS mean changes from baseline with their corresponding standard errors (SEs) will be presented for each treatment by visit, together with estimated treatment differences (UMEC/VI 62.5/25 vs. UMEC 62.5, UMEC/VI 62.5/25 vs Salmeterol and UMEC 62.5 vs Salmeterol), corresponding 95% CIs and p-values.
- A plot of LS mean changes from baseline and 95% CIs for each treatment by visit will be generated.
- A plot of LS mean treatment differences and 95% CIs between the treatment groups by visit will also be generated.
- The type III tests of fixed effects and the covariance parameter estimates from the model will be presented in two tables.

Summary Results Presentation

- Summary of baseline FEV_1 will be presented by treatment for all subjects.
- A box plot and an empirical distribution function plot of change from baseline in trough FEV_1 at Week 24 will be produced.
- Summary statistics for raw and change from baseline in trough FEV_1 at each visit and for each treatment will be presented on the same table.

Sensitivity and Support Statistical Analysis

- An assessment of whether the effect of treatment is modified by the interaction with
  o Baseline FEV_1
  o Geographical Region
  o Stratum (no. of bronchodilators per day during run-in)
  will be made (for primary endpoint only for the ITT population only) by fitting separate MMRM models including an additional term for treatment by each covariate. The interaction term will be tested at the 10% significance level.
- For factors with two levels or continuous factors i.e. Baseline FEV_1 and Stratum, interactions with treatment will be investigated by fitting a model with the same terms as the main model, and adding in treatment by factor by Visit interaction. Contrast statements will be used to obtain the p-value for the treatment by factor interaction at Week 24. If that p-value is >=0.10 the interaction will be considered not significant. If the p-value is <0.10, further investigation will be performed, for example running analysis by each level of the factor, or for subgroups

above and below the median.

- For factors with more than 2 levels i.e. Geographical Region, the overall interaction of factor by treatment will be investigated by fitting a model with the same terms as the main model, and adding in treatment by factor interaction. The p-value for the overall treatment by factor interaction will be obtained. If that p-value is >=0.10 the interaction will be considered not significant. If the p-value is <0.10 then the analysis will be repeated including the treatment by factor by visit interaction and the p-value for the interaction on Week 24 obtained. If that p-value is >=0.10 the interaction will be considered not significant. If the p-value is <0.10 then the factor will be dichotomised – for example US vs. non-US and EU vs. non-EU for geographical region interactions (several different dichotomies may be explored). A model will be fitted with the same terms as the main model, and adding in treatment by dichotomized factor by Visit interaction, and contrast statements will be used to obtain the p-value for the treatment by dichotomized factor interaction on Week 24. If that p-value is >=0.10 the interaction will be considered not significant. If the p-value is <0.10, further investigation will be performed, for example running analysis by each level of the factor.

7.2. Secondary Efficacy Analyses

7.2.1. Endpoint / Variables

1) SAC TDI focal score
2) Assessment of respiratory daily symptoms using E-RS and its subscales
3) Change from baseline in SGRQ
4) Change from baseline in CAT
5) Proportion of responders according to SAC TDI focal score
6) Proportion of responders according to E-RS total and subscale scores
7) Proportion of responders according to SGRQ total score
8) Proportion of responders according to CAT score
9) Time to first on-treatment mild/moderate/severe COPD exacerbation
10) Time to first on-treatment moderate/severe COPD exacerbation
11) Time to first on-treatment severe COPD exacerbation
12) Time to CID composite endpoint (including individual components)
13) Time to CID composite endpoint excluding FEV1 (including individual components)
14) Mean number of inhalations of rescue use per day (using eDiary)
15) Percentage of rescue-free days (using eDiary)
16) Trough FEV1 ratio to baseline
17) Trough FVC
18) Trough IC
19) Subject global rating of change in COPD severity

7.2.2. Summary Measure

1) Mean change from BDI score
2) Mean change from baseline
3) Mean change from baseline
4) Mean change from baseline
5) Odds ratio
6) Odds ratio
7) Odds ratio
8) Odds ratio
9) Hazard ratio
10) Hazard ratio
11) Hazard ratio
12) Hazard ratio
13) Hazard ratio
14) Mean change from baseline
15) Mean change from baseline
16) Ratio of trough FEV1 to baseline FEV1
17) Mean change from baseline
18) Mean change from baseline
19) Odds ratio

7.2.3. Population of Interest

The secondary efficacy analyses will be based on the ITT population, unless otherwise specified.

7.2.4. Strategy for Intercurrent (Post-Randomization) Events

All endpoints will use the same strategy for intercurrent events as defined in Section 7.1.4.

7.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 8: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.2.5.1. Statistical Methodology Specification

TDI, E-RS, SGRQ-C and CAT Scores

Secondary Statistical Analysis
Endpoints
• SAC TDI focal score • Assessment of respiratory daily symptoms using E-RS and its subscales • Change from baseline in SGRQ • Change from baseline in CAT
Model Specification, Checking and Results Presentation
• Similar to trough FEV1 in Section 7.1.5.1. • For TDI one model will be fitted with a dependent variable of TDI and BDI in place of baseline. • For E-RS and subscales, all 4-weekly mean scores will be included in the analysis.

Responders according to TDI, E-RS, SGRQ-C and CAT Scores

Secondary Statistical Analysis
Endpoints
• Proportion of responders according to TDI focal score • Proportion of responders according to E-RS total score • Proportion of responders according to E-RS Breathlessness score • Proportion of responders according to E-RS Cough & Sputum score • Proportion of responders according to E-RS Chest Symptoms score • Proportion of responders according to SGRQ total score • Proportion of responders according to CAT score
Model Specification
• The proportion of responders will be analyzed using a generalized linear mixed model with treatment as an explanatory variable and visit, baseline score, stratum (no. of bronchodilators per day during run-in), geographical region, visit by baseline score and visit by treatment interactions included as covariates. • Model using proc glimmax with; random visit / subject=subject*period residual type=un statement to account for repeated visit; • For TDI the model will use BDI in place of baseline score. • For E-RS the model will use 4 weekly period in place of visit. • This analysis will include all subjects with a non-missing baseline assessment. See Section 10.6.2.3 for details on how to handle missing data.
Model Checking & Diagnostics
• UMEC will be used as the reference level for treatment for the comparison between UMEC/VI vs. UMEC. Salmeterol will be used as the reference level for treatment for the comparison between UMEC/VI vs. Salmeterol and UMEC vs Salmeterol.

Secondary Statistical Analysis
• Pearson residuals will be plotted by using PLOTS=RESIDUALPANEL option for the model statement in SAS.
Model Results Presentation
• The odds ratio, 95% CI and p-value will be presented for UMEC/VI versus UMEC, UMEC/VI versus Salmeterol and UMEC versus Salmeterol.
Summary Results Presentation
• The number and percentage of responders and non-responders at each visit will be summarized on the same table as the analysis results details above.
Sensitivity and Supportive Statistical Analyses
• If the model fails to converge then the analyses will be carried out separately for each visit or 4 weekly period instead.

COPD Exacerbation

Secondary Statistical Analysis
Endpoints
• Time to first on-treatment mild/moderate/severe COPD exacerbation • Time to first on-treatment moderate/severe COPD exacerbation • Time to first on-treatment severe COPD exacerbation
Model Specification
• Cox's proportional hazards model, Terms in the model: Dependent variable: time to first on-treatment mild/moderate/severe exacerbation or moderate/severe exacerbation or severe exacerbation Categorical: treatment group, stratum (no. of bronchodilators per day during run-in) and geographical region. • 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
• 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. • If model fails to converge, model will be investigated excluding the geographical region covariate.

Secondary Statistical Analysis
Model Results Presentation
• The Hazard ratio, 95% CI and p-value will be presented for comparison between UMEC/VI versus UMEC, UMEC/VI versus Salmeterol and UMEC versus Salmeterol.

Secondary Statistical Analysis
Endpoints
• Time to first on-treatment mild/moderate/severe COPD exacerbation • Time to first on-treatment moderate/severe COPD exacerbation • Time to first on-treatment severe COPD exacerbation
Model Specification
• A Kaplan-Meier analysis will also be performed for figure showing Kaplan-Meier survivor functions of the proportion of subjects with a first exacerbation over time for each treatment group separately plotted on the same figure.
Model Results Presentation
• Probability of having an event, 95% CI and first quartile time to exacerbation (estimate of the time at which 25% of subjects in each treatment group would have had an exacerbation) • Figure showing Kaplan-Meier survivor functions of the proportion of subjects with a first exacerbation over time for each treatment group separately plotted on the same figure.

CID

Secondary Statistical Analysis
Endpoints
• Time to first deterioration of each of the individual components i.e. Trough FEV1, SGRQ total score, CAT score, TDI focal score • Time to first CID composite endpoint (SGRQ, FEV1, EXAC (mod/sev)) • Time to first CID composite endpoint (CAT, FEV1, EXAC (mod/sev)) • Time to first CID composite endpoint (CAT, SGRQ, TDI, EXAC (mod/sev))
Model Specification
• Cox's proportional hazards model, Terms in the model: Dependent variable: time to endpoint of interest Categorical: treatment group, stratum (no. of bronchodilators per day during run-in) and geographical region and respective baselines (i.e. endpoint includes CAT and SGRQ then include baselines for these 2 variables) . • 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
• 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

Secondary Statistical Analysis
not violated. If these curves cross each other or diverge greatly from the assumption of parallel lines, then the assumption is not met.
Model Results Presentation
• The Hazard ratio, 95% CI and p-value will be presented for comparison between UMEC/VI versus UMEC, UMEC/VI versus Salmeterol and UMEC versus Salmeterol.
Summary Results Presentation
• The total number of deteriorations (Yes/No) for each of the composite and the individual components for each treatment will be summarised. This will be produced for three the composite endpoint definitions.

Secondary Statistical Analysis
Endpoints
• Time to first CID composite endpoint (SGRQ, FEV1, EXAC (mod/sev)) • Time to first CID composite endpoint (CAT, FEV1, EXAC (mod/sev)) • Time to first CID composite endpoint (CAT, SGRQ, TDI, EXAC (mod/sev))
Model Specification
• Kaplan-Meier survivor functions of the proportion of subjects with deterioration (composite and individual components) over time will be obtained for each treatment group separately and will be plotted on the same figure.
Model Results Presentation
• Probability of having an event, 95% CI and first quartile time to CID composite endpoint (estimate of the time at which 25% of subjects in each treatment group would have had a deterioration) • Figure showing Kaplan-Meier survivor functions of the proportion of subjects with a first deterioration over time for each treatment group separately plotted on the same figure.
Summary Results Presentation
• The first quartile time to first deterioration (taken from the Kaplan Meier analysis) will also be presented in a summary table.

Rescue Medication

Secondary Statistical Analysis
Endpoints
• Mean number of inhalations of rescue use per day (using eDiary) • Percentage of rescue-free days (using eDiary)
Model Specification, Checking and Results Presentation
• Similar to trough FEV1 in Section 7.1.5.1 where Visit is replaced with 4-weekly period. • The model will use all available values: • Periods defined as Weeks 1-4, 5-8, 9-12, and up to Weeks 21-24 • Baseline is defined in Section 5.2 • Model will include the period by baseline and period by treatment interaction. • Overall treatment effect from the same model using overall main effect on Lsmean statement.
Sensitivity and Supportive Statistical Analyses
• If the assumption of normality for the percentage of rescue-free days is not satisfied, a non-

Secondary Statistical Analysis
parametric analysis of percentage of rescue-free days will be carried out. Hodges Lehman estimates for the median treatment difference and 95% CI based upon a Wilcoxon rank sum test will be used. The p-value will be based on Van Elteren test, an extension to the Wilcoxon rank sum test for two group comparison, stratified by geographical region.

Trough FEV1, FVC and IC

Secondary Statistical Analysis
Endpoints
• Ratio of trough FEV1 to baseline FEV1 • Trough FVC • Trough IC
Model Specification
• Ratio of trough FEV1 to baseline FEV1 at Week 24 will be analysed for the ITT population using a mixed model repeated measures (MMRM) including data recorded at each of Week 4, Week 12 and Week 24. The model will have a response of log (Trough FEV1/Baseline FEV1) with covariates of log (baseline FEV1), geographical region, stratum (no. of bronchodilators per day during run-in), visit, treatment, visit by log (baseline FEV1) and visit by treatment interactions, where visit is nominal. Results will be back transformed to provide point estimates for the ratios. • Trough FVC and Trough IC endpoints above will be analyzed using the same methodology as the primary analysis of trough FEV1 (detailed in Section 7.1) using all available FVC or IC data recorded at Weeks 4, 12 and 24 and with relevant baseline. Baseline defined in Section 5.2. The following will apply for all the endpoints FEV1, FVC and IC: • 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. • An unstructured covariance structure for the R matrix will be used by specifying 'type='UN' on the REPEATED line.
Model Checking & Diagnostics
• Model assumptions will be applied but appropriate adjustments may be made based on the data. • Normality 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. • If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data.
Model Results Presentation
• Least squares (LS) mean and LS mean changes from baseline with their corresponding

Secondary Statistical Analysis
standard errors (SEs) will be presented for each treatment by visit, together with estimated treatment differences (UMEC/VI 62.5/25 vs. UMEC 62.5, UMEC/VI 62.5/25 vs Salmeterol and UMEC 62.5 vs Salmeterol), corresponding 95% CIs and p-values. • A plot of LS mean changes from baseline and 95% CIs for each treatment by visit will be generated. • A plot of LS mean treatment differences and 95% CIs between the treatment groups by visit will also be generated.
Summary Results Presentation
• Summary of baseline FVC will be presented by treatment for all subjects. • Summary statistics for raw and change from baseline in trough FVC at each visit and for each treatment will be presented on the same table. • Summary of baseline IC will be presented by treatment for all subjects. • Summary statistics for raw and change from baseline in trough IC at each visit and for each treatment will be presented on the same table.

Subject Global Ratings of Change

Secondary Statistical Analysis
Endpoints
• Subject global rating of COPD severity • Subject global rating of change in COPD Severity
Model Specification
• Change of Severity will be analyzed using a generalized linear mixed model with treatment as an explanatory variable and visit, stratum (no. of bronchodilators per day during run-in), geographical region, visit by treatment interactions included as covariates.
Model Checking
• Pearson residuals will be plotted by using PLOTS=RESIDUALPANEL option for the model statement in SAS..
Model Results Presentation
• Number and percentage of subjects reporting each category of change at each visit • P-value for comparison between UMEC/VI 62.5/25 vs. UMEC 62.5, UMEC/VI 62.5/25 vs Salmeterol and UMEC 62.5 vs Salmeterol for change. • UMEC will be used as the reference level for treatment for the comparison between UMEC/VI vs. UMEC. Salmeterol will be used as the reference level for treatment for the comparison between UMEC/VI vs. Salmeterol and UMEC vs Salmeterol.

7.3. Exploratory Efficacy Analyses

7.3.1. Endpoint / Variables

1) Annual rate of on-treatment mild/moderate/severe exacerbations
2) Annual rate of on-treatment moderate/severe exacerbations
3) Mean number of inhalations of rescue use per day (using eMDI)
4) Percentage of rescue-free days (using eMDI)
5) To compare physical activity levels, ER-S, rescue medication use, exacerbations and mortality in subjects with and without a CID
6) Physical activity

7.3.2. Summary Measure

1) Rate ratio
2) Rate ratio
3) Mean change from baseline
4) Mean change from baseline
5) Mean change from baseline
6) Mean change from baseline

7.3.3. Population of Interest

The exploratory analyses will be based on the ITT population apart from the physical activity endpoint and deterioration status at 24 weeks to predict the outcome of physical activity levels, which will be based on the AM population.

7.3.4. Strategy for Intercurrent (Post-Randomization) Events

- All Endpoints will use the same strategy for intercurrent events as defined in Section 7.1.4.

7.3.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 8: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.3.5.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.3.5.1. Statistical Methodology Specification

Exploratory Statistical Analyses
Endpoints
• Annual rate of on-treatment mild/moderate/severe exacerbations • Annual rate of on-treatment moderate/severe exacerbations
Model Specification
• Generalized linear model assuming a negative binomial distribution,

Exploratory Statistical Analyses
Terms in the model: Response: number of on-treatment mild/moderate/severe exacerbations or moderate/severe exacerbations per subject Categorical: treatment group, exacerbation history ($\leq 1, \geq 2$ of severity endpoint), stratum (no. of bronchodilators per day during run-in) and geographical region. Offset: logarithm of time on treatment
Model Checking & Diagnostics
• The fit of the regression models will be examined using "Q-Q" plots of the standardized residuals. Interpretation of these plots will be aided by the addition of simulated envelopes as proposed by Atkinson (Atkinson, 1985). Should the model not fit with all specified covariates (fixed effects with very large estimates/variances) then geographical region will be dropped from the model. • If there are concerns over model fit then an over dispersed poisson model will be investigated.
Model Results Presentation
• Treatment group mean annual exacerbation rates, treatment rate ratio and associated 95% CI will be presented and p-values will be presented. Analysis is limited by number of moderate and severe exacerbations possible before withdrawal to the study and due the assumption they continue at this rate post withdrawal. Output to be appropriately footnoted.

Exploratory Efficacy Statistical Analyses
Endpoints
• Mean number of occurrences of rescue use per day (using eMDI) • Percentage of rescue-free days (using eMDI)
Model Specification, Checking and Results Presentation
• Similar to trough FEV1 in Section 7.1.5.1 excluding visit from the model   • Baseline is defined in Section 5.2

Exploratory Statistical Analyses
Endpoints

• Deterioration Status at Day 30 to predict short term outcomes:
  ○ ER-S
  ○ Rescue medication use (Mean number of inhalations of rescue use per day (using eDiary))
  ○ Mortality
  ○ Hospitalised Exacerbations

Model Specification
• Change in E-RS and mean number of inhalations of rescue use per day will be compared between subjects who have and have not experienced deterioration up to and including day 30, using a MMRM model.The following covariates will be included in the model: treatment,

Exploratory Statistical Analyses
deterioration status at day 30 , baseline, geographical region, stratum (no. of bronchodilators per day during run-in), 4-weekly period, deterioration status at day 30 weeks by 4 weekly period, and 4-weekly period by baseline interactions. Data will only be included post visit 3. • The time to first hospitalized exacerbation after day 30 and time to mortality after day 30 will be presented for subjects with and without deterioration at day 30. The actual time to post day 30 hospitalised exacerbation and mortality will be analysed using a Cox's proportional hazards models, with covariates treatment group, stratum (no. of bronchodilators per day during run-in) and geographical region. and deterioration at day 30.
Model Checking & Diagnostics
• 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.
Model Results Presentation
• For E-RS and mean number of inhalations of rescue use per day the adjusted means, pairwise differences, p-values and 95% confidence limits for the deterioration status differences will be summarised at visit 4 and visit 5 only. • For mortality and hospitalized exacerbations, the Hazard ratio, 95% CI and p-value will be presented for the comparison between deterioration status.
Summary Results Presentation
• A summary of subjects who have and have not experienced a first deterioration at day 30 will be presented.

Exploratory Statistical Analyses
Endpoints
Physical activity • Change from baseline in step count • Change from baseline in light activity duration • Change from baseline in moderate to vigorous physical activity duration • Change from baseline in total energy expenditure
Model Specification
• The dataset containing the mean value for each subject-visit will be used to look at differences between baseline, Week 1, Week 4 and Week 24. • MMRM will be used to model each activity variable against the treatment group variable including data recorded at each of baseline, Week 1, Week 4 and Week 24.

• Other covariates included will be the mean of the activity monitor variable at baseline and smoking status.
Model Checking
• The physical activity endpoints will be plotted in histograms to view their distributions and enable possible sensitivity analyses.
Model Results Presentation
• Estimated mean change from baseline for each treatment group will be calculated from the model and displayed with their associated standard errors. The estimated treatment difference will also be presented together with 95% confidence intervals (CIs) for the difference and p-value.
Summary Results Presentation
• Summaries will include the means and standard deviations of the activity monitor variables at the four time points by treatment group.
Sensitivity and Supportive Statistical Analyses
• If the histogram for change in step count or light activity duration or moderate to vigorous physical activity duration or total energy expenditure is not normally distributed, a transformation of the variable may be considered. If the MMRM analysis shows that the model is ill-fitting then a Mann-Whitney test (non-parametric t-test) will be used to look at the change in activity monitor outputs between each treatment group at Week 1, Week 4 and Week 24.

7.4. Subgroup Analyses

Subgroup Analysis
Endpoints
Repeat specified analyses/displays for: • Study Population • Efficacy • Safety Output for subgroup analysis indicated in Section 10.8.8
Model Specification
• Analysis will be performed 'by' each subgroup separately. Please refer to main endpoint model for model specification.
Model Checking & Diagnostics
• As per main endpoint
Model Results Presentation
• As per main endpoint

8. SAFETY ANALYSES

The safety analyses will be based on the ITT population, unless otherwise specified. Data collected after completion or withdrawal of study treatment will be considered post-treatment and included in relevant displays.

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 8: List of Data Displays.

The 10 most frequent on-treatment adverse events in each treatment will be summarised. In case of ties in frequency all AEs for that frequency will be displayed. On-treatment AEs experienced by 3 % (without rounding) or more of subjects in any treatment group will also be displayed.
The most common on-treatment serious drug-related and most common on-treatment non-serious drug-related adverse events will be based on events experienced by 3% (without rounding) or more of subjects in any treatment group.

Classification of an AE as pre-, on- or post-treatment is provided in Section 10.3.2. All listings of AEs/SAEs will include an identification of the treatment phase (see Section 10.3.2).

8.2. Adverse Events of Special Interest Analyses

Adverse events (AEs) of special interest (AESI) have been defined as AEs which have specified areas of interest for UMEC, VI or for the COPD population. A list of Standardized Medical Dictionary for Regulatory Affairs (MedDRA) Queries (SMQs) and other groupings for AESI is provided in Section 10.5.4.

Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting. The details of the planned displays are provided in Appendix 8: List of Data Displays.

8.3. Clinical Laboratory Analyses

Laboratory evaluations for liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 8: List of Data Displays.

9. REFERENCES

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10. APPENDICES

10.1. Appendix 1: Schedule of Activities

10.1.1. Protocol Defined Schedule of Events

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-10 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**-70 to -28**	**-28**	**1**	**28**	**84**	**168**		**7 days after V5 or EW Visit**
Window	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**		**±3 days**
Screen/Baseline								
Informed consent	X							
Demography	X							
Medical/COPD history		X						
Smoking history/status		X						
Smoking cessation counselling		X						
Concomitant medication assessment	X	X	X	X	X	X	X	X
Height and weight		X						
Cardiovascular History/family history of premature CV disease])		X						
Screening spirometry (including post bronchodilator testing)[3]		X						
CAT questionnaire		X	X					
Verify Inclusion/Exclusion Criteria		X						
Training on use of inhalers		X	X					
Training on use of eDiary and eMDI		X	X					
Verify randomization Criteria			X					

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-10 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**-70 to -28**	**-28**	**1**	**28**	**84**	**168**		**7 days after V5 or EW Visit**
Window	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**		**±3 days**
Register Visit in InForm	X	X	X	X	X	X	X	X
Register Visit in RAMOS NG	X	X	X	X	X	X	X	X
Efficacy/HRQoL assessments								
Spirometry, including pre-dose FEV_1, trough FEV_1 and inspiratory capacity			X	X	X	X		
SAC BDI questionnaire [4]			X					
SAC TDI questionnaire [4]				X	X	X		
SGRQ-C questionnaire [4]			X	X	X	X		
CAT questionnaire [4]		X	X	X	X	X		
EXACT/ER-S: COPD [5]		→	→	→	→	→		
Patient Global Rating of COPD severity			X	X	X	X		
Patient Global Rating of Change in COPD				X	X	X		
Safety assessments								
Adverse events/Serious adverse events [6]	X	X	X	X	X	X	X	X
COPD exacerbation assessment	X	X	X	X	X	X	X	X
12-Lead ECG		X						
Urine pregnancy test [7]		X	X			X	X	
Pharmacogenetic sample[8]			←	←	X	→	→	
Medication/Supplies								
Dispense rescue albuterol/slabutamol. Dispense MDI[9]		X	X	X	X	X		
Assess COPD medication compliance[10] during run-in			X					
Dispense eDiary		X						
Assess compliance with eDiary during run-in			X					
Collect rescue albuterol/slabutamol.			X	X	X	X	X	

			Blinded Treatment					
Visit	**Pre-screen[1] 0**	**Screen/ Run-in 1**	**Rando-mization 2**	**3**	**4**	**5**	**EW Visit [2]**	**Telephone Follow up contact 6**
Week	**-10 to -4**	**-4**	**0**	**4**	**12**	**24**		
Day	**-70 to -28**	**-28**	**1**	**28**	**84**	**168**		**7 days after V5 or EW Visit**
Window	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**	**-7/+2 days**		**±3 days**
Collect eDiary						X	X	
Dispense study treatment[11]			X	X	X			
Collect study treatment				X	X	X	X	
Assess study treatment compliance during treatment[10]				X	X	X	X	
Study sub-set								
Physical activity monitor[12]		X	X	X		X		
Collect Physical activity monitor						X	X	

1. Pre-screen Visit 0 must be completed prior to Screening Visit1. It can be completed 6 weeks prior or on the same day of V1, if no wash out of exclusionary medications is required.
2. Early Withdrawal Visit: Subjects that withdraw should return to the clinic as soon as possible to complete the Early Withdrawal Visit procedures.
3. Spirometry at screening should be performed as described in (Section 7.2.2.1 in the protocol).
4. SAC BDI, SAC TDI, SGRQ-C, CAT questionnaires will be completed at clinic visits and in the eDiary
5. EXACT/ER-S: COPD is completed daily in the eDiary approximately 2 hours before bed-time, starting on Day 1 of the run-in period.
6. For the start date of collecting AEs and SAEs see (Appendix 4)
7. Pregnancy test: for females for child bearing potential only.
8. Pharmacogenetic sample may be drawn at visit 2 or any visit after.
9. Rescue medication use to be recorded in the eDiary daily **and** in some sites in the eDiary and the eMDI
10. Sites are requested to call subjects every 2 weeks to remind them to take study treatment regularly and to record the time of the morning and evening dose in the eDiary.
11. In order to ensure subjects have sufficient doses of study treatment, they must return to clinic within 30 days from V2 and within 60 days from V3 respectively.
12. The Actigraph GT9X should be worn for 7 days from Visit 1, for 7 days from Visit 2, for 7 days from Visit 3 and for 7 days prior to Visit 5.

10.2. Appendix 2: Assessment Windows

10.2.1. Definitions of Assessment Windows for Analyses

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 (Day 28) visit that were actually made on the 21st day of treatment, they will be presented as Week 4 (Day 28) values in the summary tables.

10.3. Appendix 3: Study Phases and Treatment Emergent Adverse Events

10.3.1. Study Phases for Concomitant Medication

The following rules will be used to classify a concomitant medication as being taken during one or more study treatment phases (pre-treatment, on-treatment and post-treatment):

Study Phase	Definition		
	Pre-Treatment	On-Treatment	Post-Treatment
Subject did not take study treatment (e.g, screen failures) and conmed stop date > date of Screening or variable that asks if conmed is on-going (refer hereafter as goingmed) is "yes"	Y		
(Conmed start date<treatment start date or variable that asks if medication taken prior to study is" yes" (refer hereafter as priormed)) and date of Screening < conmed stop date < treatment start date	Y		
(Conmed start date<treatment start date or priormed is yes) and treatment start date ≤ conmed stop date ≤ treatment stop date	Y	Y	
(Conmed start date<treatment start date or priormed is yes) and (conmed stop date>treatment stop date or goingmed is "yes")	Y	Y	Y
(Treatment start date ≤ conmed start date<treatment stop date and treatment start date ≤ conmed stop date ≤ treatment stop date) or (Treatment start date=conmed start date=conmed stop date=treatment stop date)		Y	
([Treatment start date ≤ conmed start date<treatment stop date] or [Treatment start date=conmed start date=treatment stop date]) and (conmed stop date>treatment stop date or goingmed is Yes)		Y	Y
Conmed start ≥ treatment stop date and treatment start date ≠ treatment stop date			Y

1. **NOTES:**

- The duration of a single concomitant medication can extend over multiple study phases
- Please refer to Appendix 6: Reporting Standards for Missing Data for handling of partial dates for concomitant medication.
- Note: If priormed or goingmed flags are missing or inconsistent, then medications will be assigned to all applicable phases.

10.3.2. Study Phases for Adverse Events and All Other Data Recorded in Logs (excluding Concomitant Medications)

Study Phase	Definition
Pre-Treatment	Date < Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ Date ≤ Study Treatment Stop Date + 1
Post-Treatment	Date > Study Treatment Stop Date + 1

10.3.3. Treatment Emergent Flag for Adverse Events and Exacerbations

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date & on or before treatment stop date plus one day. • Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 1.

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

10.4. Appendix 4: Data Display Standards & Handling Conventions

10.4.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Compound	: gsk573719_gw642444/mid201749/final
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.0 or higher]. • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files will be generated for all tables in the final reporting effort for use in writing the CSR.	

10.4.2. Reporting Standards

General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx): 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 randomised treatment the subject received unless otherwise stated. • 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, unless otherwise stated. • 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. • FEV_1, FVC and IC will have a min and max to 2dp and then follow IDSL standards to reporting other summary statistics • SGRQ and TDI will have a min and max to 1dp and then follow IDSL standards to reporting other summary statistics • CAT will have a min and max to 0dp and then follow IDSL standards to reporting other summary statistics • Odds Ratios and Hazard Ratios will be reported to 2dp

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. Actual time will be used for calculation of times to events and Kaplan-Meier plots.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• 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 only be included in summary tables as part of 'minimum/maximum post baseline' and 'minimum/maximum change from baseline' summary. • 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.	

10.5. Appendix 5: Derived and Transformed Data

10.5.1. General

Study Day

• Calculated as the number of days from randomisation date :
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < treatment start date → Study Day = Ref Date – treatment start date
  • Ref Date ≥ treatment start date → Study Day = Ref Date – (treatment start date) + 1

Completer
• A study completer will be defined as a subject who completes the visit 5 trough FEV1 assessment.

10.5.2. Study Population

Demographics
Age
• Since the eCRF only collects the year of birth, GSK standard IDSL algorithms will be used for calculating age where date and month will be imputed as '30th June'. • Birth date will be presented in listings as 'YYYY'. • Age will be calculated based on the Pre-screening visit date.
Age Category

• Age categories are based on age at Pre-screening and are defined as:
  • ≤64 years
  • 65-74 years
  • 75-84 years
  • ≥85 years

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

Smoking Status
• Smoking status at Screening is determined directly from the eCRF.

Maintenance Naive/Non Maintenance Naive
• Maintenance naive (MN) is defined as subjects with no COPD maintenance medication apart from short-acting bronchodilators recorded in the 30 days prior to screening (evaluation period 30 days prior to screening until 1st study treatment).

Reversibility and GOLD Classifications

Reversibility

- 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 FEV_1 and their post-salbutamol assessment of FEV_1 as follows:
  - Reversible, if they had a difference in FEV1 of ≥ 12 % and ≥ 200 mL, or
  - 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.

GOLD Grade 1-4

Based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2018), Subjects will be classified into GOLD Grades 1-4 using the post-salbutamol percent predicted FEV_1 assessment at Screening (Visit 1):

- GOLD Grade 1 (Mild): Percent Predicted FEV_1 ≥ 80%
- GOLD Grade 2 (Moderate): 50% ≤ Percent Predicted FEV_1 < 80%
- GOLD Grade 3 (Severe): 30% ≤ Percent Predicted FEV_1 < 50%
- GOLD Grade 4 (Very Severe): Percent Predicted FEV_1 < 30%

GOLD Category A-D (Using CAT)

GOLD (CAT) Category A-D definitions as follows:

A. Low risk, less symptoms: CAT < 10; ≤1 moderate exacerbation; and no hospitalizations for exacerbations, prior year.
B. Low risk, more symptoms: CAT ≥ 10; ≤1 moderate exacerbation and no hospitalizations for exacerbations, prior year
C. High risk, less symptoms: CAT < 10; ≥ 2 moderate exacerbations, prior year OR >=1 leading to COPD hospitalization, prior year
D. High risk, more symptoms: CAT ≥ 10; ≥ 2 moderate exacerbations, prior year OR >=1 leading COPD hospitalization, prior year

Long-acting Bronchodilator Usage During the Run-in (Randomisation Stratum)

Randomization stratum, long-acting bronchodilator usage during the run-in, will be derived based on the RMC classification and will be grouped into the following 2 categories:

- None
- One long-acting bronchodilator per day

Long-acting bronchodilator is defined as any COPD medication in Respiratory Medication Class (MRC) under 'Long-acting beta-2 agonist – Group 2' or 'Long-acting beta-2 agonist – Group 3' or 'Long-acting anticholinergic'.

Randomisation stratum is also collected at randomization in RAMOS NG and on eCRF. All randomisation stratum (RANDALL NG, eCRF and derived) will be listed.

Compliance

ELLIPTA DPI 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:

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

- If any dose counter stop is missing then the treatment compliance will be set to missing for that subject.
- If the dose counter start=dose counter stop then it will be assumed that no doses were taken from that container.

DISKUS 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 60. If all dose counter stop counts are non-missing then the percentage compliance will be calculated as:

$$\text{Compliance} = \frac{\text{sum of all (capsules dispensed –capsules returned)} \times 100}{\text{2 x (exposure stop date – exposure start date +1)}}$$

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

Overall Compliance

- The average of the compliance with the ELLIPTA DPI and compliance with the DISKUS. If the compliance with any of the two inhalers is missing then the overall compliance for that subject will be considered missing.
- Overall compliance and compliance with each type of inhaler 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 randomized treatment during the study, the compliance will still be calculated using data from all containers received and overall exposure start and stop dates.

Cardiovascular Risk Factors

- Subjects with at least one of the following current or past medical conditions at Screening will be classed as having a cardiovascular (CV) risk factor. The number of CV risk factors at Screening (0, 1, or >=2) will be derived.

Cardiovascular Risk Factors
• Coronary artery disease • Myocardial infarction • Arrhythmia • Congestive heart failure • Hypertension • Cerebrovascular accident • Diabetes mellitus • Hypercholesterolemia

Concomitant Medications and COPD Exacerbation History
COPD Concomitant medications
COPD concomitant medications given for an exacerbation will be grouped into the following RMCs based on pre-defined code lists derived from ATC classifications: • Androgens and Estrogens • Anti-IgE, Anti-IL5 • Anticholinergic • Antiinfectives (antibiotics, antiseptics) • Antimycotics • Antivirals • Short-acting anticholinergic • Short-acting beta-2 agonist • Long-acting anticholinergic • Long-acting beta-2 agonist • Xanthine • PDE4 Inhibitors • Corticosteroid - inhaled • Corticosteroid - depot • Corticosteroid - systemic oral parenteral and intra-articular • Corticosteroid - other • Leukotriene receptor antagonist • Nedocromil or cromolyn sodium • Mucolytics • Oxygen • Other medication given for exacerbation • Other COPD medication
COPD Exacerbation History
• Number of COPD exacerbations reported in the past year prior to Screening will be summarised (0, 1, =>2) according to the following categories: mild COPD exacerbation, moderate COPD exacerbation, severe COPD exacerbation, mild/moderate/severe COPD exacerbation, moderate/severe COPD exacerbation and severe COPD exacerbation. • Moderate COPD exacerbations are defined as exacerbation that required treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalisation). • Severe COPD exacerbations are defined as exacerbations that required in-patient hospitalisation.

Concomitant Medications and COPD Exacerbation History
• Total number of mild/moderate/severe COPD exacerbations are defined as total numbers of mild, moderate and severe COPD exacerbation for each subject. • Total number of moderate/severe COPD exacerbations are defined as total numbers of moderate and severe COPD exacerbation for each subject.

10.5.3. Efficacy

Spirometry
Predicted FEV_1, Absolute and Percent Reversibility in FEV_1, Percent Predicted FEV_1 and Pre-salbutamol and Post-salbutamol FEV_1/FVC Ratio
• These derived items will be delivered in a dataset from the vendor for central spirometry, except for post-salbutamol FEV_1/FVC ratio, and no recalculation will be performed. Post-salbutamol FEV_1/FVC ratio will be calculated as the ratio of post-salbutamol FEV_1 and FVC values.
Trough
• The trough value for FEV_1, FVC and IC at each of Weeks 4, 12 and 24 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 for FEV_1, FVC and IC will not be used in the calculation of trough. • 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
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

SGRQ-C
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

CAT
CAT Score
• 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. The score can have values ranging from 0 to 40. • If one item is missing, then the score for that item is set as the average of the non-missing items. If more than one item is missing, then the CAT score will be set to missing. • If the language of the CAT conducted at a post-baseline visit is different to the language used at baseline, the CAT score for that visit and all subsequent visits will be set to missing.
CAT Responder
• A subject will be considered a 'responder' according to CAT at each visit if their CAT score has decreased at least 2 units from baseline CAT score. • A subject will be considered a 'non-responder' if their CAT score has decreased by less than 2 units, has not changed or has increased compared to baseline. • Missing data will be handled as detailed in Section 10.6.2.

COPD Exacerbations
General
• The duration of the exacerbation will be calculated as (exacerbation resolution date or date of death - exacerbation onset date + 1). • The time to the first on-treatment exacerbation will be calculated as (exacerbation onset date of first on-treatment exacerbation – date of start of treatment + 1). • For summaries/analyses, subjects will be represented from their Day 1 date to the start date of their first event up to and including their treatment stop date+1 day. • Subjects that have not withdrawn from study treatment or experienced the event are censored

COPD Exacerbations

at their treatment stop date+1 day.

- The event rate for exacerbations will be lovemocalculated as the total number of events divided by the total annual subject exposure during the time-period of interest

Severity

- Each COPD exacerbation will be categorized based on severity as follows:
  - Mild: no treatment with oral/systemic corticosteroids and/or antibiotics and no hospitalisation
  - Moderate: required treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalisation).
  - Severe: required in-patient hospitalization or emergency room
- Certain displays will include only moderate/severe exacerbations.

Calculation of Daily eDiary Endpoints

General

Subjects were instructed to complete the daily eDiary in the evening (typically at bedtime). The parameters collected include rescue use and EXACT-PRO scores.

The table below shows which daily eDiary records are used to calculate the daily eDiary parameters for each period. Any diary data collected in the post-treatment phase of the study will not be slotted.

Daily Record		Analysis Time Period
Beginning Timepoint (day)	Ending Timepoint (day)	
-28	-1	Week -1 (Baseline)
1	28	Weeks 1 – 4
29	56	Weeks 5 – 8
57	84	Weeks 9 – 12
85	112	Weeks 13 – 16
113	140	Weeks 17 – 20
141	168	Weeks 21 – 24
1	168	Weeks 1 – 24

Note: There is no Day 0. Any records with actual day>168 will not be assigned to a time period.
Note: Daily eDiary records that were not assigned to a time period will not be used in calculation of daily eDiary endpoints.

- For use of rescue medication endpoint, for a subject to be counted in a time period (except for baseline where at least 14 days non-missing entries required) they must have at least one diary entry recorded for that endpoint during that time period.
- For E-RS endpoint, for a subject to be counted in a time period they must have at least 16 days non-missing diary entries recorded for that endpoint during that time period.
- Any daily diary data that were collected post-study treatment discontinuation will be excluded from any analyses, including 4-weekly interval data summaries.

Calculation of Daily eDiary Endpoints
Use of Rescue Medication via E-diary
• The mean number of inhalations of rescue use per day and percentage of rescue-free days will be calculated during the 4-weekly interval intervals defined above.
EXACT PRO
EXACT Respiratory Symptoms
• The 4-weekly mean scores for E-RS, and the subscales RS-Breathlessness, RS-Cough and Sputum, and RS-Chest Symptoms will be calculated as the mean of the daily scores in the 4-weekly intervals defined above.
EXACT–RS and Subscale Scores Responder
For each four weekly period; • A subject will be considered as a responder according to E-RS total score if their 4- weekly mean change from baseline EXACT–RS ≤ -2.0. • A subject will be considered as a non-responder according to E-RS total score if their 4-weekly mean change from baseline EXACT–RS >-2.0. • A subject will be considered as a responder according to RS-Breathlessness score if their 4-weekly mean change from baseline RS-Breathlessness ≤ -1.0. • A subject will be considered as a non-responder according to RS-Breathlessness score if their 4-weekly mean change from baseline RS-Breathlessness >-1.0. • A subject will be considered as a responder according to RS-Cough & Sputum score if their 4-weekly mean change from baseline RS-Cough & Sputum ≤ -0.70. • A subject will be considered as a non-responder according to RS-Cough & Sputum score if their 4-weekly mean change from baseline RS-Cough & Sputum >-0.70. • A subject will be considered as a responder according to RS-Chest Symptoms score if their 4-weekly mean change from baseline RS-Chest Symptoms ≤ -0.70. • A subject will be considered as a non-responder according to RS-Chest Symptoms score if their 4-weekly mean change from baseline RS-Chest Symptoms >-0.70. • Missing data will be handled as outlined in Section 10.6.2.

Rescue use for EMDI

- Will be analysed over Weeks 1 – 24 only
- The Medication Sensor Observation Period for each subject will be defined by the first date of sensor sync and the last date of sensor sync recorded in the database. Since a recorded rescue inhaler usage event in the database is also considered a sync event, if no first sync date is recorded, the date of the first rescue inhaler usage event will be used as the start date of observation. If no last sync date is recorded, the date of the last rescue inhaler usage event will be used as the end date of observation.
- A rescue occasion is defined as an inhaler usage event(s) in which one or more puffs occur within 2 minutes of each other, starting with the first reported puff.
- Days within the Medication Sensor Observation Period with no recorded rescue inhaler usage by the sensor will be assigned a rescue inhaler usage of 0.

Deterioration

- A Clinically Important Deterioration (CID) will be defined by a composite endpoint. A subject is considered to have deteriorated if, in the period from start of treatment to treatment stop + 1 day, one or more of the following occurs (definition dependent);
- A decrease from baseline of ≥100mL in Trough pre-bronchodilator FEV1
- An increase from baseline of ≥4 units in SGRQ total score
- An exacerbation
- An increase from baseline of ≥2 units in CAT Score
- A TDI score of ≤-1 unit

- Subjects who are withdrawn from the study or have missing data will be included in analyses wherever possible. No imputation for missing data will be made.
- A subject [who had not met the deterioration definition at another timepoint] will be classed as not deteriorated and will be censored at their treatment stop date+1 day.
- To be evaluable for deterioration assessment you must have at least 1 post baseline assessment (not including exacerbations) for at least one of the individual components or had an exacerbation.
- For day 30 status assessment a subject will be classed as deteriorated if they had not met the deterioration definition by Day 30. To be evaluable for Day 30 deterioration status assessment you must have at least 1 post baseline assessment (not including exacerbations) for at least one of the individual components or had an exacerbation prior or on Day 30.

Physical Activity Monitoring

- The data for Actigraph is generated as minute by minute for the amount of time worn on the body. The device generates the summary of each subject's daily total with the times the device was not worn excluded (WEAR - DAY TIME) and time not worn included (TOTAL - DAY TIME). The time that the device is worn is algorithmically detected. For analysis, we will only consider the daily summary data where the device was worn (WEAR - DAY TIME).

- For the physical activity monitoring analysis, a day will only be considered valid if the activity monitor is worn for at least 23 hours[1]. A minimum of 3 days[2] for each visit, visit 1 (baseline), visit 2 (randomization, week 1), visit 3 (week 4) and visit 5 (week 24), are needed in the analysis in order to have an accurate view of subjects' activity for each week. Only valid days within the 7 days after visit 1, after visit 2, after visit 3 and 7 days before visit 5 will be used in the primary analysis. Additional days may be used for further exploration of the data if deemed useful.

- To get a single observation per subject per visit, the mean of the daily values will be calculated for the week (no less than 3 days and no more than 7 days).
- Table 2.1 shows examples of acceptable and unacceptable weeks after visit 1 to use in the analysis. The boxes with an 'x' indicate days with valid activity monitor data. The day of the study visit will not be used since the activity may be out of the ordinary or not meet the minimum requirement of 23 hours. For instance, if a subject had visit 1 on January 1st, 2016, the acceptable days for use would be January 2nd to January 8th (Day 2 through 8) for a total of 7 days. Data from January 9th would not be used as it is out of scope of the week-long observation criteria. Examples of selection of days for visit 2, visit 3 and visit 5 are shown in Table 2.2, Table 2.3 and Table 2.4 respectively.

Table 2.1 Examples of Visit 1 Day Selection for Activity Monitor Analysis

	Days With Valid Activity Monitoring Data									
Day of Activity Monitoring	1	2	3	4	5	6	7	8	9	**Use/Do Not Use**
Target Study Day	Visit 1	Study Day -27	Study Day -26	Study Day -25	Study Day -24	Study Day - 23	Study Day - 22	Study Day - 21	Study Day - 20	
Subject PPD	x	x	x	x	x	x	x	x	x	Use Days 2-8
Subject	x			x	x	x	x			Use Days 4-8
Subject		x	x	x	x	x	x	x	x	Use Days 2-8
Subject	x	x				x		x	x	Use Days 2, 6, and 8
Subject	x	x			x					Do Not Use
Subject	x			x		x			x	Do Not Use

Table 2.2 Examples of Visit 2 Day Selection for Activity Monitor Analysis

	Days With Valid Activity Monitoring Data									
Day of Activity Monitoring	1	2	3	4	5	6	7	8	9	**Use/Do Not Use**
Target Study Day	Visit 2	Study Day 2	Study Day 3	Study Day 4	Study Day 5	Study Day 6	Study Day 7	Study Day 8	Study Day 9	
Subject PPD	x	x	x	x	x	x	x	x	x	Use Days 2-8
Subject	x			x	x	x	x			Use Days 4-8
Subject		x	x	x	x	x	x	x	x	Use Days 2-8
Subject	x	x				x		x	x	Use Days 2, 6, and 8
Subject	x	x			x					Do Not Use
Subject	x			x		x			x	Do Not Use

Table 2.3 Examples of Visit 3 Day Selection for Activity Monitor Analysis

	Days With Valid Activity Monitoring Data									
Day of Activity Monitoring	1	2	3	4	5	6	7	8	9	**Use/Do Not Use**
Target Study Day	Visit 3	Study Day 29	Study Day 30	Study Day 31	Study Day 32	Study Day 33	Study Day 34	Study Day 35	Study Day 36	
Subject PPD	x	x	x	x	x	x	x	x	x	Use Days 2-8
Subject	x			x	x	x	x			Use Days 4-8
Subject		x	x	x	x	x	x	x	x	Use Days 2-8
Subject	x	x				x		x	x	Use Days 2, 6, and 8
Subject	x	x			x					Do Not Use
Subject	x			x		x			x	Do Not Use

Table 2.4 Examples of Visit 5 Day Selection for Activity Monitor Analysis

	Days With Valid Activity Monitoring Data									
Day of Activity Monitoring	1	2	3	4	5	6	7	8	9	**Use/Do Not Use**
Target Study Day	Study Day 160	Study Day 161	Study Day 162	Study Day 163	Study Day 164	Study Day 165	Study Day 166	Study Day 167	Visit 5	
Subject PPD	x	x	x	x	x	x	x	x	x	Use Days 2-8
Subject	x			x	x	x	x			Use Days 4-8
Subject		x	x	x	x	x	x	x	x	Use Days 2-8
Subject	x	x				x		x	x	Use Days 2, 6, and 8
Subject	x	x			x					Do Not Use
Subject	x			x		x			x	Do Not Use

10.5.4. Safety

Adverse Events
AE's OF Special Interest
• AE groups of special interest have been defined as AEs which have specified areas of interest for UMEC or VI or the overall COPD population. Groups which are not SMQs are made up of a selection of preferred terms (PTs) defined by GSK. The complete list, including the preferred terms which contribute to each of the groups will be provided by Global Clinical Safety and Pharmacovigilance (GCSP) using the MedDRA version at the time of reporting. This will be finalised prior to unblinding.

Special Interest AE Group	Subgroup	Sub-SMQ	SMQ Group
Anticholinergic syndrome			Anticholinergic syndrome (SMQ)
Asthma/bronchospasm			Asthma/bronchospasm (SMQ)
Paradoxical bronchospasm			
Cardiovascular effects	Cardiac Arrhythmia	Arrhythmia related investigations, signs and symptoms (SMQ)	Arrhythmia related investigations, signs and symptoms (SMQ)
Cardiovascular effects	Cardiac Arrhythmia	Bradyarrhythmia terms, nonspecific (SMQ)	Bradyarrhythmia terms, nonspecific (SMQ)
Cardiovascular effects	Cardiac Arrhythmia	Conduction defects (SMQ)	Conduction defects (SMQ)
Cardiovascular effects	Cardiac Arrhythmia	Disorders of sinus node function (SMQ)	Disorders of sinus node function (SMQ)
Cardiovascular effects	Cardiac Arrhythmia	Cardiac arrhythmia terms, nonspecific (SMQ)	Cardiac arrhythmia terms, nonspecific (SMQ)
Cardiovascular effects	Cardiac Arrhythmia	Supraventricular tachyarrhythmias (SMQ)	Supraventricular tachyarrhythmias (SMQ)
Cardiovascular effects	Cardiac Arrhythmia	Tachyarrhythmia terms,	Tachyarrhythmia terms, nonspecific (SMQ)

Special Interest AE Group	Subgroup	Sub-SMQ	SMQ Group
		nonspecific (SMQ)	
Cardiovascular effects	Cardiac Arrhythmia	Ventricular tachyarrhythmias (SMQ)	Ventricular tachyarrhythmias (SMQ)
Cardiovascular effects	Cardiac Failure		Cardiac failure (SMQ)
Cardiovascular effects	Cardiac Ischaemia		Ischaemic heart disease (SMQ)
Cardiovascular effects	Hypertension		Hypertension (SMQ)
Cardiovascular effects	Stroke		Central nervous system haemorrhages and cerebrovascular conditions (SMQ)
Pneumonia			Infective pneumonia (SMQ)
LRTI excluding infective pneumonia			
Ocular effects (antimuscarinic)			Glaucoma (SMQ)
Effects on glucose			Hyperglycaemia/new onset diabetes mellitus (SMQ)
Effects on potassium			
Gastrointestinal obstruction			Gastrointestinal obstruction (SMQ)
Hypersensitivity			
Tremor			
Urinary retention			

Exposure
Exposure Duration
• Number of days of exposure to study drug will be calculated based on the formula: Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1 • If a subject's overall exposure stop date is missing it will be assumed to be the latest recorded exposure start or stop date in the database. • If a subject's overall exposure start date is missing then it will be assumed to be their Day 1 visit date (Visit 2). • If a subject received a treatment other than the randomized treatment during the study, the exposure will still be calculated based on overall exposure start and stop dates. • If the dose counter start=dose counter stop then it will be assumed that no doses were taken from that container.
Exposure Categories
The following exposure categories will be derived: 1-84 days, 85-168 days, >168 days

10.6. Appendix 6: Reporting Standards for Missing Data

10.6.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as receiving treatment at the final on-treatment clinic visit (Visit 5) and completion of the follow-up contact (Visit 6). • Withdrawn subjects will not be replaced in the study. • With the exception of the responder analyses, the minimum data required will be a baseline evaluation and at least one post-baseline evaluation. Note that this is not the case for the responder definition, see Section 10.6.2.3 for details. • 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.

10.6.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a "blank" in subject listing displays unless all data for a specific visit are missing in which case the visit is not displayed in the listing. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such. ○ No imputation will be made for any missing numerical data. Missing data will generally not be considered in the calculation of percentages (i.e., the denominator will not include subjects who have missing data at a given time point).

10.6.2.1. Handling of Missing Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4: Treatment States. ○ Missing Stop Day: Last day of the month will be used, unless this is after the

Element	Reporting Detail
	stop date of study treatment; in this case the study treatment stop date will be used. • 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.

10.6.2.2. 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. o 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. o The AE will then be considered to start on-treatment (worst case). 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.

10.6.2.3. Handling of Missing Data for Statistical Analysis

Element	Reporting Detail
Responder	• Subjects with a missing baseline will have responder status as missing • Subjects with missing post-baseline data at a time point and a subsequent non-missing assessment will not be considered a responder or non-responder but will be left as missing at that time point • Subjects with a missing post-baseline assessment with no subsequent non-missing assessments will be considered a non-responder for that and all subsequent time points. • Subjects with a baseline but all missing post-baseline data will be considered a non-responder at all time points.

10.7. Appendix 7: Abbreviations & Trade Marks

10.7.1. Abbreviations

Abbreviation	Description
A&R	Analysis and Reporting
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
ASE	All Subjects Enrolled
ATC	Anatomical-Therapeutic-Chemical
BDI	Baseline Dyspnea Index
CAT	COPD Assessment Test
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CSR	Clinical Study Report
CV	Cardiovascular
DBF	Database Freeze
DM	Data Management
DPI	Dry Powder Inhaler
eCRF	Electronic Case Record Form
EXACT	Exacerbations of Chronic Pulmonary Disease Tool
FEV_1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
GCSP	Global Clinical Safety and Pharmacovigilance
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
GUI	Guidance
IA	Interim Analysis
ICS	Inhaled Corticosteroid
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
KR	Kenwood Roger
LRTI	Lower Respiratory Tract Infection
LS	Least-square
mcg	Microgram
MMRM	Mixed Model Repeated Measures
PD	Protocol Deviation
PDMP	Protocol Deviation Management Plan
PRO	Patient Reported Outcomes
QD	Once Daily
QoL	Quality of Life

Abbreviation	Description
RAMOS	Randomization & Medication Ordering System
RAP	Reporting & Analysis Plan
RMC	Respiratory Medication Classification
RTF	Rich Text Format
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SAL	Salmeterol
SDL	Source Data Lock
SDTM	Study Data Tabulation Model
SE	Standard Error
SGRQ	St. George Respiratory Questionnaire
SGRQ-C	SGRQ for COPD patients
SI	System Independent
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SOP	Standard Operation Procedure
TDI	Transition Dyspnea Index
TFL	Tables, Figures & Listings
UMEC	Umeclidinium Bromide (GSK573719)
VI	Vilanterol Trifenatate

10.7.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
DISKUS
ELLIPTA

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10.8. Appendix 8: List of Data Displays

10.8.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.n	1.1 to 1.n
Efficacy	2.1 to 2.n	2.1 to 2.n
Safety	3.1 to 3.n	3.1 to 3.n
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	y to z	

10.8.2. Deliverables

Delivery	Description
SAC	Final Statistical Analysis Complete.

10.8.3. Study Population Tables

Study Population Tables				
No.	**Popu-lation**	**Title**	**Programming Note**	**Deliverable**
Subject Disposition				
1.1	ASE	Summary of Study Populations		SAC
1.2	ASE	Summary of Screen Failures and Run-in failures		SAC
1.3	ITT	Summary of Attendance/Telephone Contact at Each Visit		SAC
1.4	ITT	Summary of Completion and Premature Discontinuation of Study Treatment		SAC
1.5	ITT	Summary of Study Completion and Withdrawal		SAC
1.6	ITT	Summary of Number of Subjects by Geographical Region, Country and Center		SAC
1.7	ASE	Summary of Inclusion/ Exclusion/ Randomization Criteria Deviations for Screen or Run-in failures		SAC
1.8	ITT	Summary of Inclusion/ Exclusion/ Randomization Criteria Deviations		SAC
1.9	ITT	Summary of Important Protocol Deviations		SAC
Demography				
1.10	ITT	Summary of Demographic Characteristics		SAC
1.11	ITT	Summary of Race and Racial Combinations		SAC
1.12	ITT	Summary of Race and Racial Combination Details		SAC
Medical Condition & Concomitant Medications				
1.13	ITT	Summary of Current Medical Conditions		SAC
1.14	ITT	Summary of Past Medical Conditions		SAC
1.15	ITT	Summary of Cardiovascular Risk Factors		SAC
1.16	ITT	Summary of Family History of Cardiovascular Risk Factors		SAC
1.17	ITT	Summary of COPD History at Screening	Include Duration of COPD and COPD type	SAC
1.18	ITT	Summary of COPD Exacerbation History at Screening		SAC

Study Population Tables				
No.	**Popu-lation**	**Title**	**Programming Note**	**Deliverable**
1.19	ITT	Summary of Smoking Status and History at Screening		SAC
1.20	ITT	Summary of Long-acting Bronchodilator Usage during the Run-in (Randomization Strata)		
1.21	ITT	Summary of Concomitant Medications Not Given for a COPD Exacerbation Taken Pre-Treatment		SAC
1.22	ITT	Summary of Concomitant Medications Not Given for a COPD Exacerbation Taken On-treatment		SAC
1.23	ITT	Summary of Concomitant Medications Not Given for a COPD Exacerbation Taken Post-treatment		
1.24	ITT	Summary of Concomitant Medications Given for a COPD Exacerbation Taken Pre-treatment		SAC
1.25	ITT	Summary of Concomitant Medications Given for a COPD Exacerbation Taken On-treatment		SAC
1.26	ITT	Summary of Concomitant Medications Given for a COPD Exacerbation Taken Post-treatment		SAC
Baseline Severity				
1.27	ITT	Summary of Screening Lung Function Test Results		SAC
1.28	ITT	Summary of GOLD Grade 1-4, GOLD CAT Category A-D and Reversibility at Screening		SAC
1.29	ITT	Summary of GOLD Grade 1-4, GOLD CAT Category A-D and Reversibility at Screening by Country		SAC
1.30	ITT	Summary of CAT Score at Screening		SAC
Compliance				
1.31	ITT	Summary of Device and Overall Percentage Treatment Compliance		SAC

10.8.4. Efficacy Tables

Efficacy: Tables				
No.	**Population**	**Title**	**Programming Note**	**Deliverable**
2.01	ITT	Summary of Baseline FEV1 (L)		SAC
2.02	ITT	Summary of Trough FEV1 (L)		SAC
2.03	ITT	Analysis of Trough FEV1 (L)		SAC
2.04	ITT	Covariance Parameter Estimates for Repeated Measures Analysis of Trough FEV1 (L)		SAC
2.05	ITT	Type III Tests of Fixed Effects for Repeated Measures Analysis of Trough FEV1 (L)		SAC
2.06	ITT	Significance Levels for Interactions of Treatment with Baseline FEV1, Geographical Region and Stratum for Trough FEV1 (L)		SAC
2.07	ITT	Analysis of Ratio (Trough FEV1/Baseline FEV1)		SAC
2.08	ITT	Summary of Baseline FVC (L)		SAC
2.09	ITT	Summary of Trough FVC (L)		SAC
2.10	ITT	Analysis of Trough FVC (L)		SAC
2.11	ITT	Summary of Baseline IC (L)		SAC
2.12	ITT	Summary of Trough IC (L)		SAC
2.13	ITT	Analysis of Trough IC (L)		SAC
BDI/TDI				
2.14	ITT	Summary of BDI Focal Score		SAC
2.15	ITT	Summary of TDI Focal Score		SAC
2.16	ITT	Analysis of TDI Focal Score		SAC
2.17	ITT	Summary and Analysis of Proportion of Responders According to TDI Focal Score		SAC
E-RS				
2.18	ITT	Summary of Four-Weekly Mean E-RS Total Score		SAC
2.19	ITT	Summary of Four-Weekly Mean E-RS Breathlessness Score		SAC

Efficacy: Tables				
No.	**Population**	**Title**	**Programming Note**	**Deliverable**
2.20	ITT	Summary of Four-Weekly Mean E-RS Cough and Sputum Score		SAC
2.21	ITT	Summary of Four-Weekly Mean E-RS Chest Score		SAC
2.22	ITT	Analysis of Four-Weekly Mean E-RS Total Score		SAC
2.23	ITT	Analysis of Four-Weekly Mean E-RS Breathlessness Score		SAC
2.24	ITT	Analysis of Four-Weekly Mean E-RS Cough and Sputum Score		SAC
2.25	ITT	Analysis of Four-Weekly Mean E-RS Chest Score		SAC
2.26	ITT	Summary and Analysis of Proportion of Responders According To E-RS Total Score		SAC
2.27	ITT	Summary and Analysis of Proportion of Responders According To E-RS Breathlessness Score		SAC
2.28	ITT	Summary and Analysis of Proportion of Responders According To E-RS Cough and Sputum Score		SAC
2.29	ITT	Summary and Analysis of Proportion of Responders According To E-RS Chest Score		SAC
SGRQ-C				
2.30	ITT	Summary of Baseline SGRQ Scores		SAC
2.31	ITT	Summary of SGRQ Total Score		SAC
2.32	ITT	Summary of SGRQ Symptoms Score		SAC
2.33	ITT	Summary of SGRQ Activity Score		SAC
2.34	ITT	Summary of SGRQ Impacts Score		SAC
2.35	ITT	Analysis of SGRQ Total Score		SAC
2.36	ITT	Summary and Analysis of Proportion of Responders According To SGRQ Total Score		SAC
CAT				
2.37	ITT	Summary of CAT Score	Include Baseline	SAC
2.38	ITT	Analysis of CAT Score		SAC
2.39	ITT	Summary and Analysis of Proportion of Responders According To CAT Score		SAC

Efficacy: Tables				
No.	**Population**	**Title**	**Programming Note**	**Deliverable**
COPD Exacerbations				
2.40	ITT	Summary of On-Treatment COPD Exacerbations		SAC
2.41	ITT	Summary of Post-Treatment COPD Exacerbations		SAC
2.42	ITT	Summary and Analysis of Time to First On-Treatment Mild/Moderate/Severe COPD Exacerbation		SAC
2.43	ITT	Summary and Analysis of Time to First On-Treatment Moderate/Severe COPD Exacerbation		SAC
2.44	ITT	Summary and Analysis of Time to First On-Treatment Severe COPD Exacerbation		SAC
2.45	ITT	Annual rate of on-treatment mild/moderate/severe exacerbations		SAC
2.46	ITT	Annual rate of on-treatment moderate/severe exacerbations		SAC
CID				
2.47	ITT	Summary of Deterioration and Individual Components	Include all composites	SAC
2.48	ITT	Summary and Analysis of Time to First Decrease from Baseline of >=100ml in Trough FEV1		SAC
2.49	ITT	Summary and Analysis of Time to First Increase from Baseline of >=4 units in SGRQ Total Score		SAC
2.50	ITT	Summary and Analysis of Time to First Increase from Baseline of >=2 units in CAT Score		SAC
2.51	ITT	Summary and Analysis of Time to First Decrease of >=1 units in TDI		SAC
2.52	ITT	Summary and Analysis of Time to First Deterioration (SGRQ, FEV1, EXAC (mod/sev))		SAC
2.53	ITT	Summary and Analysis of Time to First Deterioration (CAT, FEV1, EXAC (mod/sev))		SAC
2.54	ITT	Summary and Analysis of Time to First Deterioration (CAT, SGRQ, TDI, EXAC (mod/sev))		SAC
2.55	ITT	Summary of Deterioration Status at Day 30		SAC
2.56	ITT	Analysis of Four-Weekly Mean E-RS Total Score by Day 30 Deterioration Status		SAC

Efficacy: Tables				
No.	**Population**	**Title**	**Programming Note**	**Deliverable**
2.57	ITT	Analysis of Mean Number of Inhalations of Rescue use per Day using e-Diary Day 30 Deterioration Status		SAC
2.58	ITT	Summary and Analysis of Time to First On-Treatment Moderate/Severe Exacerbation leading to hospitalisation by Day 30 Deterioration Status		SAC
2.59	ITT	Summary and Analysis of Time to Mortality by Day 30 Deterioration Status		SAC
Rescue Use				
2.60	ITT	Summary of Mean Number of Inhalations of Rescue Medication per Day using e-Diary		SAC
2.61	ITT	Analysis of Mean Number of Inhalations of Rescue Medication per Day over Weeks 1-24 using e-Diary		SAC
2.62	ITT	Summary of Percentage of Rescue-Free Days using e-Diary		SAC
2.63	ITT	Analysis of Percentage of Rescue-Free Days over Weeks 1-24 using e-Diary		SAC
2.64	ITT	Summary of Mean Number of Occurrences of Rescue Medication per Day using eMDI.		SAC
2.65	ITT	Analysis of Mean Number of Occurrences of Rescue Medication per Day over Weeks 1-24 using eMDI		SAC
2.66	ITT	Summary of Percentage of Rescue-Free Days using eMDI		SAC
2.67	ITT	Analysis of Percentage of Rescue-Free Days over Weeks 1-24 using eMDI		SAC
Subject Global Ratings				
2.68	ITT	Summary of Subject Global Rating of COPD Severity		SAC
2.69	ITT	Summary and Analysis of Subject Global Rating of Change in COPD Severity	Use gsk2834425/ctt116853 as reference	SAC
Physical Activity Monitor				
2.70	AM	Summary of Weekly Mean Step Count		SAC

Efficacy: Tables				
No.	**Population**	**Title**	**Programming Note**	**Deliverable**
2.71	AM	Analysis of Weekly Mean Step Count		SAC
2.72	AM	Summary of Weekly Mean Duration of Light Physical Activity (Hours)		SAC
2.73	AM	Analysis of Weekly Mean Duration of Light Physical Activity (Hours)		SAC
2.74	AM	Summary of Weekly Mean Duration of Moderate to Vigorous Physical Activity (Hours)		SAC
2.75	AM	Analysis of Weekly Mean Duration of Moderate to Vigorous Physical Activity (Hours)		SAC
2.76	AM	Summary of Weekly Mean Total Energy Expenditure (kCal)		SAC
2.77	AM	Analysis of Weekly Mean Total Energy Expenditure (kCal)		SAC

10.8.5. Efficacy Figures

Efficacy: Figures				
	Popu-lation	**Title**	**Programming Note**	**Deliverable**
Spirometry				
2.01	ITT	Box Plot of Change from Baseline in Trough FEV1 (L) at Week 24		SAC
2.02	ITT	Empirical Distribution Function Plot of Change from Baseline in Trough FEV1 (L) at Week 24		SAC
2.03	ITT	Least Squares Mean (95% CI) Change from Baseline in Trough FEV1 (L)		SAC
2.04	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Trough FEV1 (L)		SAC
2.05	ITT	Least Squares Mean (95% CI) Change from Baseline in Trough FVC (L)		SAC
2.06	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Trough FVC (L)		SAC
2.07	ITT	Least Squares Mean Change from Baseline (95% CI) in Trough IC (L)		SAC

Efficacy: Figures				
	Popu-lation	**Title**	**Programming Note**	**Deliverable**
2.08	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Trough IC (L)		SAC
BDI/TDI				
2.09	ITT	Least Squares Means (95% CI) TDI Focal Score		SAC
2.10	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in TDI Focal Score		SAC
E-RS				
2.11	ITT	Least Squares Mean Change from Baseline (95% CI) in Four-Weekly Mean E-RS Total Score		SAC
2.12	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Four-Weekly Mean E-RS Total Score		SAC
2.13	ITT	Least Squares Mean Change from Baseline (95% CI) in Four-Weekly Mean E-RS Breathlessness Score		SAC
2.14	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Four-Weekly Mean E-RS Breathlessness Score		SAC
2.15	ITT	Least Squares Mean Change from Baseline (95% CI) in Four-Weekly Mean E-RS Cough and Sputum Score		SAC
2.16	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline) in Four-Weekly Mean E-RS Cough and Sputum Score		SAC
2.17	ITT	Least Squares Mean Change from Baseline (95% CI) in Four-Weekly Mean E-RS Chest Score		SAC
2.18	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Four-Weekly Mean E-RS Chest Score		SAC
SGRQ				
2.19	ITT	Least Squares Mean (95% CI) Change from Baseline in SGRQ Total Score		SAC
2.20	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in SGRQ Total Score		SAC

Efficacy: Figures				
	Popu-lation	Title	Programming Note	Deliverable
CAT				
2.21	ITT	Least Squares Mean Change from Baseline (95% CI) in CAT Score		SAC
2.22	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline) in CAT Score		SAC
COPD Exacerbations				
2.23	ITT	Kaplan-Meier Plot of Time to First On-Treatment Mild/Moderate/Severe COPD Exacerbation (Days)		SAC
2.24	ITT	Kaplan-Meier Plot of Time to First On-Treatment Moderate/Severe COPD Exacerbation (Days)		SAC
2.25	ITT	Kaplan-Meier Plot of Time to First On-Treatment Severe COPD Exacerbation (Days)		SAC
CID				
2.26	ITT	Kaplan-Meier Plot of Time to First Decrease from Baseline of >=100ml in Trough FEV1		SAC
2.27	ITT	Kaplan-Meier Plot of Time to First Increase from Baseline of >=4 units in SGRQ Total Score		SAC
2.28	ITT	Kaplan-Meier Plot of Time to First Increase from Baseline of >=2 units in CAT Score		SAC
2.29	ITT	Kaplan-Meier Plot of Time to First Decrease of >=1 units in TDI		SAC
2.30	ITT	Kaplan-Meier Plot of Time to First Deterioration (SGRQ, FEV1, EXAC (mod/sev)) (Days)		SAC
2.31	ITT	Kaplan-Meier Plot of Time to First Deterioration (CAT, FEV1, EXAC (mod/sev)) (Days)		SAC
2.32	ITT	Kaplan-Meier Plot of Time to First Deterioration (CAT, SGRQ, TDI, EXAC (mod/sev)) (Days)		SAC
2.33	ITT	Kaplan-Meier Plot of Time to First On-Treatment Moderate/Severe Exacerbation Leading to Hospitalisation by Day 30 Deterioration Status		SAC
2.35	ITT	Kaplan-Meier Plot of Time to Mortality by Day 30 Deterioration Status		SAC
Rescue Use				
2.36	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Mean Number of Inhalations of Rescue Medication per Day over Weeks 1-24 using e-Diary		SAC

Efficacy: Figures				
	Popu-lation	**Title**	**Programming Note**	**Deliverable**
2.37	ITT	Least Squares Mean (95% CI) Change from Baseline in Percentage of Rescue-Free Days over Weeks 1-24 using e-Diary		SAC
2.38	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Mean Number of Occurrences of Rescue Medication per Day over Weeks 1-24 using eMDI		SAC
2.39	ITT	Least Squares Mean (95% CI) Change from Baseline in Percentage of Rescue-Free Days over Weeks 1-24 using eMDI		SAC
Physical Activity Monitor				
2.40	ITT	Histograms of Change from Baseline in Weekly Mean Step Count at Week 1, Week 4 and Week 24 by Treatment Group		SAC
2.41	ITT	Histograms of Change from Baseline in Weekly Mean Duration of Light Physical Activity (Hours) at Week 1, Week 4 and Week 24 by Treatment Group		SAC
2.42	ITT	Histograms of Change from Baseline in Weekly Mean Duration of Moderate to Vigorous Physical Activity (Hours) at Week 1, Week 4 and Week 24 by Treatment Group		SAC
2.43	ITT	Histograms of Change from Baseline in Weekly Mean Total Energy Expenditure (kCal) at Week 1, Week 4 and Week 24 by Treatment Group		SAC
2.44	ITT	Least Squares Mean (95% CI) Change from Baseline in Weekly Mean Step Count		SAC
2.45	ITT	Least Squares Mean (95% CI) Change from Baseline in Weekly Mean Duration of Light Physical Activity (Hours)		SAC
2.46	ITT	Least Squares Mean (95% CI) Change from Baseline in Weekly Mean Duration of Moderate to Vigorous Physical Activity (Hours)		SAC
2.47	ITT	Least Squares Mean (95% CI) Change from Baseline in Weekly Mean Total Energy Expenditure (kCal)		SAC

10.8.6. Safety Tables

Safety Tables				
No.	**Population**	**Title**	**Programming Note**	**Deliverable**
Exposure				
3.01	ITT	Summary of Exposure		SAC
Adverse Events				
3.02	ITT	Overview of Adverse Events		SAC
3.03	ITT	Summary of On-treatment Adverse Events by System Organ Class and Preferred Term		SAC
3.04	ITT	Summary of Post-treatment Adverse Events by System Organ Class and Preferred Term		SAC
3.05	ITT	Summary of On-treatment Drug-Related Adverse Events by System Organ Class and Preferred Term		SAC
3.06	ITT	Summary of Pre-treatment Serious Adverse Events by System Organ Class and Preferred Term		SAC
3.07	ITT	Summary of On-treatment Serious Adverse Events by System Organ Class and Preferred Term		SAC
3.08	ITT	Summary of On-treatment Fatal Serious Adverse Events by System Organ Class and Preferred Term		SAC

Safety Tables				
No.	**Popu-lation**	**Title**	**Programming Note**	**Deliverable**
3.09	ITT	Summary of On-treatment Serious Adverse Events (Serious, Drug-Related Serious and Fatal) by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
3.10	ASE	Summary of Pre-treatment Adverse Events Leading Withdrawal from the Study by System Organ Class and Preferred Term		SAC
3.11	ITT	Summary of On-treatment Drug-related Serious Adverse Events by System Organ Class and Preferred Term		SAC
3.12	ITT	Summary of On-treatment Drug-related Fatal Serious Adverse Events by System Organ Class and Preferred Term		SAC
3.13	ITT	Summary of On-treatment Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from the Study by System Organ Class and Preferred Term		SAC
3.14	ITT	Summary of On-treatment Adverse Events of Special Interest		SAC
3.15	ITT	Summary of On-treatment Serious Adverse Events of Special Interest		SAC
3.16	ASE	Relationship between Adverse Event System Organ Class, Preferred Term and Verbatim Text		SAC
3.17	ITT	Summary of Common (>=3%) On-treatment Non-Serious Drug-related Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC

Safety Tables				
No.	**Popu-lation**	**Title**	**Programming Note**	**Deliverable**
3.18	ITT	Summary of Common (>=3%) On-treatment Serious Adverse Events by Overall Frequency		SAC
3.19	ITT	Summary of Common (>=3%) On-treatment Serious Drug-related Adverse Events by Overall Frequency		SAC
3.20	ITT	Summary of the 10 Most Frequent On-treatment Adverse Events in Each Treatment Group		SAC
3.21	ITT	Summary of On-treatment Adverse Events by System Organ Class, Preferred Term and Age Subgroup		SAC
3.22	ITT	Summary of On-treatment Adverse Events by System Organ Class and Preferred Term and Maximum Intensity		SAC
3.33	ITT	Summary of On-treatment Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity		SAC

10.8.7. Safety Figures

Safety: Figures				
	Popu-lation	**Title**	**Programming Note**	**Deliverable**
3.01	ITT	Adverse Event Incidence Rates and Relative Risks		SAC

10.8.8. ICH Listings

ICH : Listings				
No.	**Popu-lation**	**Title**	**Programming Note**	**Deliverable**
Study Population				
1.	ITT	Listing of Subjects who Discontinued Study Treatment		SAC
2.	ITT	Listing of Reasons for Withdrawal		SAC
3.	ASE	Listings of Reasons for Withdrawal – Subjects Randomised but not in the Intent-to-Treat Population		SAC
4.	ITT	Listing of the Follow-up Contact		SAC
5.	ITT	Listing of Important Protocol Deviations		SAC
6.	ITT	Listing of Subjects with Inclusion, Exclusion or Randomisation Criteria Deviations		SAC
7.	ITT	Listing of Subjects for whom the Treatment Blind was Broken		SAC
8.	ITT	Listing of Randomised and Actual Treatments		SAC
9.	ITT	Listing of Overall Treatment Compliance		SAC
10.	ITT	Listing of Demographic Characteristics		SAC
11.	ITT	Listing of Race		SAC
12.	ITT	Listing of Medical Conditions		SAC

ICH : Listings				
No.	**Popu-lation**	**Title**	**Programming Note**	**Deliverable**
13.	ITT	Listing of Cardiovascular Risk Factors		SAC
14.	ITT	Listing of Family History of Cardiovascular Risk Factors		SAC
15.	ITT	Listing of Concomitant Medications Given for a COPD Exacerbation		SAC
16.	ITT	Listing of Concomitant Medications Not Given for a COPD Exacerbation		SAC
17.	ITT	Relationship between ATC Level 1, ingredient and verbatim text Non-COPD medications		SAC
18.	ITT	Listing of COPD History	Include COPD duration and COPD type	SAC
19.	ITT	Listing of Smoking History and Smoking Status		SAC
Study Population				
20.	ITT	Listing of Screening Lung Function Test Results		SAC
21.	ITT	Listing of GOLD Grade/Categories, Reversibility and long-acting bronchodilator usage stratum at Screening		SAC
22.	ITT	Listing of Derived FEV1 (L) Endpoints		SAC
23.	ITT	Listing of Derived FVC (L) Endpoints		SAC
24.	ITT	Listing of Derived IC (L) Endpoints		SAC

ICH : Listings				
No.	**Popu-lation**	**Title**	**Programming Note**	**Deliverable**
25.	ITT	Listing of Derived Rescue Use Endpoints (eDiary)		SAC
26.	ITT	Listing of Derived Rescue Use Endpoints (eMDI)		SAC
27.	ITT	Listing of Derived E-RS Scores		SAC
28.	ITT	Listing of CAT Scores	Include Screening	SAC
29.	ITT	Listing of SGRQ Scores		SAC
30.	ITT	Listing of TDI Scores		SAC
Exposure				
31.	ITT	Listing of Exposure		SAC
Adverse Events				
32.	ITT	Listing of Subject Numbers for Individual Adverse Events		SAC
33.	ITT	Listing of All Adverse Events		SAC
34.	ITT	Listing of Non-fatal Serious Adverse Events		SAC
35.	ITT	Listing of Fatal Serious Adverse Events		SAC
36.	ITT	Listing of Adverse Events Leading to Discontinuation of Study Treatment or Withdrawal from the Study		SAC

ICH : Listings				
No.	**Popu-lation**	**Title**	**Programming Note**	**Deliverable**
37.	ITT	Listing of On-treatment Drug-Related Adverse Events		SAC
38.	ITT	Listing of Reasons for Considering as a Serious Adverse Event		
Inhaler Malfunctions				
39.	ITT	Listing of Potential DPI Inhaler Malfunctions		SAC
COPD Exacerbations				
40.	ITT	Listing of COPD Exacerbations		SAC
Pneumonia and Chest X-ray				
41.	ITT	Listing of Chest X-ray Data		SAC
42.	ITT	Listing of All Pneumonia Data		SAC
Liver Events: Note only produced if there is a Liver Event				
43.	ITT	Listing of Liver Events		SAC
44.	ITT	Listing of Liver Event Information for RUCAM Score		SAC
45.	ITT	Listing of Liver Biopsy		SAC
46.	ITT	Listing of Liver Imaging Details		SAC

ICH : Listings				
No.	**Popu-lation**	**Title**	**Programming Note**	**Deliverable**
Cardiovascular Events: Note only produced if there is a Cardiovascular Event				
47.	ITT	Listing of Myocardial Infarction/Unstable Angina	Include under patient profiles in HARP	SAC
48.	ITT	Listing of Congestive Heart Failure	Include under patient profiles in HARP	SAC
49.	ITT	Listing of Arrhythmias	Include under patient profiles in HARP	SAC
50.	ITT	Listing of Valvulopathy	Include under patient profiles in HARP	SAC
51.	ITT	Listing of Pulmonary Hypertension	Include under patient profiles in HARP	SAC
52.	ITT	Listing of Cerebrovascular Events/Stroke and Transient Ischemic Attack	Include under patient profiles in HARP	SAC

ICH : Listings				
No.	**Popu-lation**	**Title**	**Programming Note**	**Deliverable**
53.	ITT	Listing of Peripheral Arterial Thromboembolism	Include under patient profiles in HARP	SAC
54.	ITT	Listing of Deep Venous Thrombosis/Pulmonary Embolism	Include under patient profiles in HARP	SAC
55.	ITT	Listing of Revascularisation	Include under patient profiles in HARP	SAC
56.	ITT	Listing of All cause deaths	Include under patient profiles in HARP	SAC

10.8.9. Non-ICH Listings

Non-ICH : Listings				
No.	**Popu-lation**	**Title**	**Programming Note**	**Deliverable**
Study Population				
57.	ITT	Listing of Treatment Misallocations		SAC
58.	ITT	Listing of Raw FEV1 (L) and FVC (L) Data		SAC
59.	ITT	Listing of Raw IC (L) Data		SAC
60.	ITT	Listing of Adverse Event of Special Interest Group, Subgroup, Sub-SMQ and Preferred Term		SAC
61.	AM	Listing of Physical Activity Monitoring Data		SAC

10.8.10. Maintenance Naive

10.8.1. Study Population Tables

Study Population Tables				
No.	**Popu-lation**	**Title**	**Programming Note**	**Deliverable**
Subject Disposition				
1.33	ITT	Summary of Study Completion and Withdrawal		SAC

Study Population Tables				
No.	**Popu-lation**	**Title**	**Programming Note**	**Deliverable**
Demography				
1.34	ITT	Summary of Demographic Characteristics		SAC
1.35	ITT	Summary of Maintenance Naive Status		SAC
Medical Condition & Concomitant Medications				
1.36	ITT	Summary of Current Medical Conditions		SAC
1.37	ITT	Summary of Cardiovascular Risk Factors		SAC
1.38	ITT	Summary of COPD History at Screening	Include Duration of COPD and COPD type	SAC
1.39	ITT	Summary of COPD Exacerbation History at Screening		SAC
1.40	ITT	Summary of Smoking Status and History at Screening		SAC
Baseline Severity				
1.41	ITT	Summary of Screening Lung Function Test Results		SAC
1.42	ITT	Summary of GOLD Grade 1-4, GOLD CAT Category A-D and Reversibility at Screening		SAC
1.43	ITT	Summary of CAT Score at Screening		SAC
Compliance				
1.44	ITT	Summary of Device and Overall Percentage Treatment Compliance		SAC

10.8.2. Efficacy Tables

Efficacy: Tables				
No.	**Population**	**Title**	**Programming Note**	**Deliverable**
2.78	ITT	Summary of Baseline FEV1 (L)		SAC
2.79	ITT	Summary of Trough FEV1 (L)		SAC
2.80	ITT	Analysis of Trough FEV1 (L)		SAC
2.81	ITT	Analysis of Ratio (Trough FEV1/Baseline FEV1)		SAC
2.82	ITT	Summary of Baseline FVC (L)		SAC
2.83	ITT	Summary of Trough FVC (L)		SAC
2.84	ITT	Analysis of Trough FVC (L)		SAC
2.85	ITT	Summary of Baseline IC (L)		SAC
2.86	ITT	Summary of Trough IC (L)		SAC
2.87	ITT	Analysis of Trough IC (L)		SAC
BDI/TDI				
2.88	ITT	Summary of BDI Focal Score		SAC
2.89	ITT	Summary of TDI Focal Score		SAC

Efficacy: Tables				
No.	**Population**	**Title**	**Programming Note**	**Deliverable**
2.90	ITT	Analysis of TDI Focal Score		SAC
2.91	ITT	Summary and Analysis of Proportion of Responders According to TDI Focal Score		SAC
E-RS				
2.92	ITT	Summary of Four-Weekly Mean E-RS Total Score		SAC
2.93	ITT	Analysis of Four-Weekly Mean E-RS Total Score		SAC
2.94	ITT	Summary and Analysis of Proportion of Responders According To E-RS Total Score		SAC
SGRQ-C				
2.95	ITT	Summary of Baseline SGRQ Scores		SAC
2.96	ITT	Summary of SGRQ Total Score		SAC
2.97	ITT	Analysis of SGRQ Total Score		SAC
2.98	ITT	Summary and Analysis of Proportion of Responders According To SGRQ Total Score		SAC
CAT				
2.99	ITT	Summary of CAT Score	Include Baseline	SAC
2.100	ITT	Analysis of CAT Score		SAC

Efficacy: Tables				
No.	**Population**	**Title**	**Programming Note**	**Deliverable**
2.101	ITT	Summary and Analysis of Proportion of Responders According To CAT Score		SAC
COPD Exacerbations				
2.102	ITT	Summary of On-Treatment COPD Exacerbations		SAC
2.103	ITT	Summary of Post-Treatment COPD Exacerbations		SAC
2.104	ITT	Summary and Analysis of Time to First On-Treatment Mild/Moderate/Severe COPD Exacerbation		SAC
2.105	ITT	Summary and Analysis of Time to First On-Treatment Moderate/Severe COPD Exacerbation		SAC
2.106	ITT	Summary and Analysis of Time to First On-Treatment Severe COPD Exacerbation		SAC
2.107	ITT	Annual rate of on-treatment moderate/severe exacerbations		SAC
CID				
2.108	ITT	Summary of Deterioration and Individual Components	Include all composites	SAC
2.109	ITT	Summary and Analysis of Time to First Decrease from Baseline of >=100ml in Trough FEV1		SAC
2.110	ITT	Summary and Analysis of Time to First Increase from Baseline of >=4 units in SGRQ Total Score		SAC
2.111	ITT	Summary and Analysis of Time to First Increase from Baseline of >=2 units in CAT Score		SAC
2.112	ITT	Summary and Analysis of Time to First Decrease of >=1 units in TDI		SAC

Efficacy: Tables				
No.	**Population**	**Title**	**Programming Note**	**Deliverable**
2.113	ITT	Summary and Analysis of Time to First Deterioration (SGRQ, FEV1, EXAC (mod/sev))		SAC
2.114	ITT	Summary and Analysis of Time to First Deterioration (CAT, FEV1, EXAC (mod/sev))		SAC
2.115	ITT	Summary and Analysis of Time to First Deterioration (CAT, SGRQ, TDI, EXAC (mod/sev))		SAC
Rescue Use				
2.116	ITT	Summary of Mean Number of Inhalations of Rescue Medication per Day using e-Diary		SAC
2.117	ITT	Analysis of Mean Number of Inhalations of Rescue Medication per Day over Weeks 1-24 using e-Diary		SAC
2.118	ITT	Summary of Percentage of Rescue-Free Days using e-Diary		SAC
2.119	ITT	Analysis of Percentage of Rescue-Free Days over Weeks 1-24 using e-Diary		SAC
2.120	ITT	Summary of Mean Number of Occurrences of Rescue Medication per Day using eMDI		SAC
2.121	ITT	Analysis of Mean Number of Occurrences of Rescue Medication per Day over Weeks 1-24 using eMDI		SAC
2.122	ITT	Summary of Percentage of Rescue-Free Days using eMDI		SAC
2.123	ITT	Analysis of Percentage of Rescue-Free Days over Weeks 1-24 using eMDI		SAC

Efficacy: Tables				
No.	**Population**	**Title**	**Programming Note**	**Deliverable**
Subject Global Ratings				
2.124	ITT	Summary of Subject Global Rating of COPD Severity		SAC
2.125	ITT	Summary and Analysis of Subject Global Rating of Change in COPD Severity	Use gsk2834425/ctt116853 as reference	SAC
Physical Activity Monitor				
2.126	ITT	Summary of Weekly Mean Step Count		SAC
2.127	ITT	Analysis of Weekly Mean Step Count		SAC
2.128	ITT	Summary of Weekly Mean Duration of Light Physical Activity (Hours)		SAC
2.129	ITT	Analysis of Weekly Mean Duration of Light Physical Activity (Hours)		SAC
2.130	ITT	Summary of Weekly Mean Duration of Moderate to Vigorous Physical Activity (Hours)		SAC
2.131	ITT	Analysis of Weekly Mean Duration of Moderate to Vigorous Physical Activity (Hours)		SAC
2.132	ITT	Summary of Weekly Mean Total Energy Expenditure (kCal)		SAC
2.133	ITT	Analysis of Weekly Mean Total Energy Expenditure (kCal)		SAC

10.8.3. Efficacy Figures

Efficacy: Figures				
	Popu-lation	Title	Programming Note	Deliverable
Spirometry				
2.48	ITT	Least Squares Mean (95% CI) Change from Baseline in Trough FEV1 (L)		SAC
2.49	ITT	Least Squares Mean Change from Baseline (95% CI) in Trough FVC (L)		SAC
2.50	ITT	Least Squares Mean Change from Baseline (95% CI) in Trough IC (L)		SAC
BDI/TDI				
2.51	ITT	Least Squares Means (95% CI) TDI Focal Score		SAC
E-RS				
2.52	ITT	Least Squares Mean Change from Baseline (95% CI) in Four-Weekly Mean E-RS Total Score		SAC
SGRQ				
2.53	ITT	Least Squares Mean (95% CI) Change from Baseline in SGRQ Total Score		SAC
CAT				
2.54	ITT	Least Squares Mean Change from Baseline (95% CI) in CAT Score		SAC
COPD Exacerbations				
2.55	ITT	Kaplan-Meier Plot of Time to First On-Treatment Mild/Moderate/Severe COPD Exacerbation (Days)		SAC
2.56	ITT	Kaplan-Meier Plot of Time to First On-Treatment Moderate/Severe COPD Exacerbation (Days)		SAC
2.57	ITT	Kaplan-Meier Plot of Time to First On-Treatment Severe COPD Exacerbation (Days)		SAC

Efficacy: Figures				
	Popu-lation	Title	Programming Note	Deliverable
CID				
2.58	ITT	Kaplan-Meier Plot of Time to First Decrease from Baseline of >=100ml in Trough FEV1		SAC
2.59	ITT	Kaplan-Meier Plot of Time to First Increase from Baseline of >=4 units in SGRQ Total Score		SAC
2.60	ITT	Kaplan-Meier Plot of Time to First Increase from Baseline of >=2 units in CAT Score		SAC
2.61	ITT	Kaplan-Meier Plot of Time to First Decrease of >=1 units in TDI		SAC
2.62	ITT	Kaplan-Meier Plot of Time to First Deterioration (SGRQ, FEV1, EXAC (mod/sev)) (Days)		SAC
2.63	ITT	Kaplan-Meier Plot of Time to First Deterioration (CAT, FEV1, EXAC (mod/sev)) (Days)		SAC
2.64	ITT	Kaplan-Meier Plot of Time to First Deterioration (CAT, SGRQ, TDI, EXAC (mod/sev)) (Days)		SAC
Rescue Use				
2.65	ITT	Least Squares Mean (95% CI) Change from Baseline in Percentage of Rescue-Free Days over Weeks 1-24 using e-Diary		SAC
2.66	ITT	Least Squares Mean (95% CI) Change from Baseline in Percentage of Rescue-Free Days over Weeks 1-24 using eMDI		SAC
Physical Activity Monitor				
2.67	ITT	Least Squares Mean (95% CI) Change from Baseline in Weekly Mean Step Count		SAC
2.68	ITT	Least Squares Mean (95% CI) Change from Baseline in Weekly Mean Duration of Light Physical Activity Duration(Hours)		SAC

Efficacy: Figures				
	Popu-lation	Title	Programming Note	Deliverable
2.69	ITT	Least Squares Mean (95% CI) Change from Baseline in Weekly Mean Duration of Moderate to Vigorous Physical Activity (Hours)		SAC
2.70	ITT	Least Squares Mean (95% CI) Change from Baseline in Weekly Mean Total Energy Expenditure (kCal)		SAC

10.8.4. Safety Tables

Safety Tables				
No.	Popu-lation	Title	Programming Note	Deliverable
Exposure				
3.34	ITT	Summary of Exposure		SAC
Adverse Events				
3.35	ITT	Overview of Adverse Events		SAC
3.36	ITT	Summary of On-treatment Adverse Events by System Organ Class and Preferred Term		SAC
3.37	ITT	Summary of On-treatment Drug-Related Adverse Events by System Organ Class and Preferred Term		SAC
3.38	ITT	Summary of On-treatment Serious Adverse Events by System Organ Class and Preferred Term		SAC

Safety Tables				
No.	**Popu-lation**	**Title**	**Programming Note**	**Deliverable**
3.39	ITT	Summary of On-treatment Fatal Serious Adverse Events by System Organ Class and Preferred Term		SAC
3.40	ITT	Summary of Common (>=3%) On-treatment Non-serious Drug-related Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
3.41	ITT	Summary of Common (>=3%) On-treatment Serious Adverse Events by Overall Frequency		SAC
3.42	ITT	Summary of Common (>=3%) On-treatment Serious Drug-related Adverse Events by Overall Frequency		SAC