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

Title	:	Reporting and Analysis Plan for A Randomized, Open-Label, 8-Week Cross-Over Study to Compare Umeclidinium/Vilanterol with Tiotropium/Olodaterol Once-Daily in Subjects with Chronic Obstructive Pulmonary Disease (COPD)
Compound Number	:	GSK2592356 (GSK573719 + GW642444)
Effective Date	:	26-MAY-2017

Description :

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 204990.
- This RAP is intended to describe the planned efficacy and safety analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the final Statistical Analysis Complete (SAC) Deliverable.

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1. REPORTING & ANALYSIS PLAN SYNPOSIS

Overview	Key Elements of the RAP
Purpose	• This RAP details all planned analyses and outputs required for the final Clinical Study Report (CSR) of study 204990.
Protocol	• This RAP is based on the original protocol (Dated: 29-Mar-2016) for study 204990 [GlaxoSmithKline Document Number 2015N256437_00] and eCRF Version 1.2.
Primary Objective	• To compare the effect of UMEC/VI 62.5/25mcg with TIO/OLO 5/5mcg once daily on lung function in subjects with moderate COPD over 8 weeks of treatment.
Primary Endpoint	• Trough FEV_1 at Week 8
Study Design	• Multicentre, randomized, open-label, 2 period cross-over, complete block design study to evaluate the efficacy and safety of UMEC/VI 62.5/25mcg with TIO/OLO 5/5mcg when used in subjects with moderate COPD. • Eligible subjects will be randomized to receive a sequence consisting of UMEC/VI 62.5/25 mcg once-daily administered as 1 inhalation once-daily from the Ellipta Inhaler and TIO/OLO 5/5mcg inhalation spray administered as inhalation of 2 puffs once-daily from the Respimat inhaler. Each treatment period will be 8 weeks. • A study with 168 evaluable subjects for the primary analysis on the per-protocol (PP) population will have 90% power to detect non-inferiority of UMEC/VI 62.5/25mcg to TIO/OLO 5/5mcg based on trough FEV_1 at Week 8, when the margin of non-inferiority is -50mL and the true mean treatment difference is assumed to be 0mL. Based on 15% withdrawal rate and 10% exclusion rate from the PP population 220 subjects will be randomized.
Planned Analyses	• No interim analyses are planned. • All decisions regarding final analysis, as defined in this RAP document, will be made prior to Database Freeze (unblinding) of the study data.
Analysis Populations	• The **All Subjects Enrolled** Population will comprise all subjects for whom a record exists on the study database, including screen failures and any subject who was not screened but experienced a serious adverse event (SAE) between the date of informed consent and the planned date of the Screening Visit. This population will be used for reporting subject disposition, reasons for withdrawal prior to randomization, and inclusion, exclusion and randomization criteria deviations and SAEs for non-randomized subjects. • The **Intent-to-treat** (ITT) Population will comprise 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

Overview	Key Elements of the RAP
	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. This population will be the used for all efficacy and safety displays unless specified otherwise. • The **Per Protocol** (PP) Population will comprise all subjects in the ITT Population who do not have a full protocol deviation considered to impact efficacy. Receipt of a study treatment other than the randomized treatment will be considered a full protocol deviation. Subjects with partial protocol deviations considered to impact efficacy will be included in the PP Population but will have their data excluded from PP analyses from the time of deviation onwards. Subjects with time-point specific or period specific protocol deviations will be included in the PP population but will have the data affected excluded from PP analyses. This population will be used for the primary comparison between the treatments to determine NI. It will also be used for the primary comparison between treatments to assess superiority, assuming that the primary analysis on the PP population supports the conclusion of NI. • The **Inhaler Naive** (IN) population definition will comprise of all subjects in the ITT population who have not used either Ellipta or Respimat for 6 months prior to inhaler evaluation (Visit 2 or Visit 5). This population will be used for all Inhaler assessment displays unless stated otherwise.
Hypothesis	• The null hypothesis is that the difference in trough FEV_1 between treatment groups is less than or equal to a pre-specified non-inferiority margin Δ: H_0: $T_1 - T_2 \leq \Delta$ The alternative hypothesis is that the difference between treatment groups is greater than the margin. H_1: $T_1 - T_2 > \Delta$ where T_1 and T_2 are the treatment means for UMEC/VI 62.5/25 mcg and TIO/OLO 5/5 mcg, respectively. • The non-inferiority margin has been set at -50mL, which is consistent with the non-inferiority margins used for trough FEV_1 or 0 to 24 hour weighted mean FEV_1 in previous studies comparing long-acting bronchodilators or long-acting bronchodilator/ICS combinations [Ichinose M, 2010; Vogelmeier C, 2010; Agustí A, 2014]. • If the lower bound of the two-sided 95% confidence interval around the (UMEC/VI 62.5/25 mcg vs. TIO/OLO 5/5 mcg) treatment difference is above -50mL then UMEC/VI 62.5/25 mcg will be considered non-inferior to TIO/OLO 5/5

Overview	Key Elements of the RAP
	mcg. • If the lower bound of the two-sided 95% confidence interval around the (UMEC/VI 62.5/25 mcg vs. TIO/OLO 5/5 mcg) treatment difference is above 0 then UMEC/VI 62.5/25 mcg will be considered superior to TIO/OLO 5/5 mcg.
Primary Analyses	• The primary endpoint of trough FEV_1 at week 8 will be analysed using a repeated measures model including data recorded at each of Week 4 and Week 8 for the PP population. Treatment group (categorical) will be fitted as the explanatory variable, with period baseline, mean baseline, period, and visit fitted as covariates. Visit (nominal) will be fitted as a categorical variable and visit by period baseline, visit by mean baseline and visit by treatment interaction terms will be included. Treatment effects will be estimated at each visit separately. The variance-covariance matrix will be assumed unstructured. Missing data are not imputed in this analysis; however, all non-missing data will be used within the analysis to estimate the treatment effect at Week 8. The MMRM analysis of the primary endpoint will be repeated for the ITT Population testing for superiority in order to ensure consistent results with those from the PP population. These analyses will include data from protocol deviators. In addition, a tipping point analysis will be carried out as a sensitivity analysis for the primary endpoint of trough FEV1 at Week 8 on the PP and ITT population in order to assess the impact of missing data on conclusions of non-inferiority and superiority.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Any changes from the originally planned statistical analysis specified in the protocol GlaxoSmithKline Document Number 2015N256437_00 are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

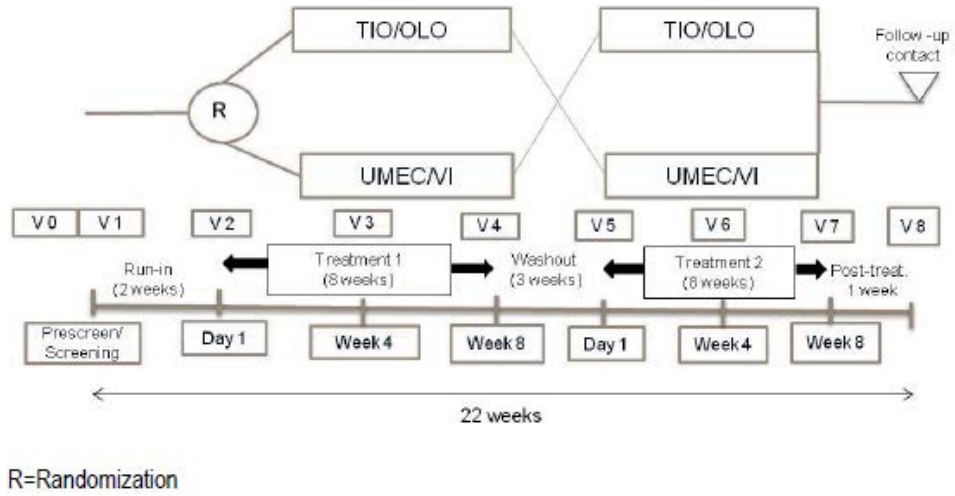
Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• Time to clinically important deterioration composite endpoint	• Time to clinically important deterioration composite endpoint will not be analysed	• Study deemed too short to assess and SGRQ is not collected.
• Proportion of responders according to CAT (defined as a ≥1 unit improvement in score from baseline) at Weeks 4 and 8	• Proportion of responders according to CAT (defined as a ≥2 unit improvement in score from baseline) at Weeks 4 and 8	• Typographical error
• ITT population definition • All randomized subjects, excluding those who were randomized in error. 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.	• ITT population definition now includes – received at least one dose of study medication. • All randomized subjects, excluding those who were randomized in error and 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.	• For consistency with prior GSK573719 + GW642444 studies
• No Inhaler Naive population	• Inhaler Naive population definition • All subjects in the ITT population who have not used either Ellipta or Respimat for 6 months prior to inhaler evaluation (Visit 2	• Population for Inhaler summaries and analysis

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
	or Visit 5). • This population will be used for all Inhaler assessment displays unless stated otherwise.	

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoint**
• To compare the effect of UMEC/VI 62.5/25 mcg with TIO/OLO 5/5mcg once daily on lung function in subjects with moderate COPD over 8 weeks of treatment.	• Trough FEV_1 at Week 8
Other Efficacy Objectives	**Other Efficacy Endpoints**
• To compare the effect of UMEC/VI 62.5/25 mcg with TIO/OLO 5 /5mcg on other measures of efficacy and measures of health-related quality of life	• Proportion of responders according to FEV1 (a responder is defined as a ≥100mL change in Trough FEV_1 from baseline) at Week 8 • Rescue albuterol/salbutamol use (percentage of rescue-free days and mean number of Inhalations/day) captured in e diary • Trough FEV_1 at Week 4 • Trough FVC at Weeks 4 and 8 • Trough IC at Weeks 4 and 8 • COPD Assessment Test (CAT) score at Weeks 4 and 8 • Proportion of responders according to CAT (defined as a ≥2 unit improvement in score from baseline) at Weeks 4 and 8 • Inhaler ease of use • Inhaler errors • Assessment of respiratory daily symptoms over Weeks 1-8 using Evaluating Respiratory Symptoms - COPD (E-RS) and its subscales (breathlessness, cough and sputum and chest symptoms)
Exploratory Objectives	**Exploratory Endpoints**
• To compare the effect of UMEC/VI 62.5/25 mcg with TIO/OLO 5 /5mcg on other measures of efficacy and measures of health-related quality of life	• Rescue albuterol/salbutamol use (percentage of rescue-free days and mean number of Inhalations/day) over Weeks 1-8 might using eMDI
Safety	**Safety Endpoints**
• To evaluate safety and tolerability of UMEC/VI 62.5/25 mcg and TIO/OLO 5/5mcg	• Incidence of adverse events (AEs) • Incidence of COPD exacerbations

2.3. Study Design

Overview of Study Design and Key Features	
 R=Randomization	
Design Features	• Multicenter, randomized, open-label, 2 period complete block design cross-over study.
Dosing	• Subjects will be instructed to take one dose of medication each morning from either the ELLIPTA (one inhalation to equal one dose) or the Respimat (inhalation of two puffs to equal one dose.), for 8 weeks in each treatment period.
Treatment Assignment	• 220 subjects equally randomized to two treatment sequences containing the two treatments UMEC/VI 62.5/25mcg and TIO/OLO 5/5 mcg. • GSK RandAll NG used to generate randomization schedules. • Centralised randomization using GSK RAMOS for treatment allocation.
Interim Analysis	• No interim analysis is planned.

2.4. Statistical Hypotheses

The null hypothesis is that the difference in trough FEV_1 between treatment groups is less than or equal to a pre-specified non-inferiority margin Δ:

H_0: $T_1 - T_2 \leq \Delta$

The alternative hypothesis is that the difference between treatment groups is greater than the margin.

H_1: $T_1 - T_2 > \Delta$

where T_1 and T_2 are the treatment means for UMEC/VI 62.5/25 mcg and TIO/OLO 5/5 mcg, respectively.

The non-inferiority margin has been set at -50mL, which is consistent with the non-inferiority margins used for trough FEV_1 or 0 to 24 hour weighted mean FEV_1 in previous studies comparing long-acting bronchodilators or long-acting bronchodilator/ICS combinations [Ichinose M, 2010; Vogelmeier C, 2010; Agustí A, 2014].

If the lower bound of the two-sided 95% confidence interval around the (UMEC/VI 62.5/25 mcg vs. TIO/OLO 5/5 mcg) treatment difference is above -50mL then UMEC/VI 62.5/25 mcg will be considered non-inferior to TIO/OLO 5/5 mcg.

If the lower bound of the two-sided 95% confidence interval around the (UMEC/VI 62.5/25 mcg vs. TIO/OLO 5/5 mcg) treatment difference is above 0 then UMEC/VI 62.5/25 mcg will be considered superior to TIO/OLO 5/5 mcg.

P-values will be displayed in the analysis outputs in this study. Inference to be drawn from these p-values will be as follows:

- If the treatment comparison on the primary endpoint has a lower confidence limit below the non-inferiority margin, non-inferiority is not demonstrated. No inference will be drawn from p-values for treatment comparisons on any other endpoints.
- If the treatment comparison on the primary endpoint has a lower confidence limit above the non-inferiority margin but below 0, non-inferiority is established but the p-value cannot be used to give an indication of the strength of that non-inferiority. Note the p-value is for a test of superiority and not associated with a test for non-inferiority.
  Inference will be drawn from p-values for treatment comparisons on non lung-function related endpoints (see below), which will be called statistically significant if <0.05. If the treatment comparison on the primary endpoint has a lower confidence limit above 0, superiority is established and the p-value can be used to give an indication of the strength of that superiority. Inference will be drawn from p-values for treatment comparisons on all other endpoints, which will be called statistically significant if <0.05.

The primary endpoint of trough FEV_1 is considered independent of non lung function 'other' endpoints, defined as rescue medication use, CAT score, inhaler ease of use, inhaler errors, respiratory daily symptoms endpoints. All other endpoints are lung function endpoints and are not considered to be independent from the primary endpoint of trough FEV_1.

3. PLANNED ANALYSES

3.1. Final Analyses

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

1. All subjects have completed the study as defined in the protocol.

2. All required database cleaning activities have been completed and final database release has been declared by Data Management.
3. All decisions on exclusion of data from PP analyses based on the PDMP will be agreed prior to releasing the randomization codes (See Section 10.1 for details).
4. All criteria for releasing the randomization codes have been met.
5. Randomization codes have been distributed according to RandAll NG procedures.
6. Database freeze has been declared by Data Management.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Subjects Enrolled (ASE)	• All subjects for whom a record exists on the study database, including screen failures and any subject who was not screened but experienced a serious adverse event (SAE) between the date of informed consent and the planned date of the Screening Visit. • Displays for this population will not be split by treatment.	• Subject disposition • Reasons for withdrawal prior to randomization • Inclusion/exclusion/randomization criteria deviations for non-randomized subjects • SAEs for screen and run-in failures and randomized 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 • Primary efficacy • Other efficacy • Safety
Per-Protocol (PP)	• All subjects in the ITT Population who were not identified as full protocol deviators. • Subjects with partial protocol deviations considered to impact efficacy will be included in the PP Population but will have their data excluded from the PP analysis from the time of deviation onwards. • Subjects with time-point specific or period specific protocol deviations will be included in the PP population but will have the data affected excluded from the PP analysis. • Protocol deviations that would exclude subjects from the PP population or subject data from PP analysis are defined in Appendix 1 (Protocol Deviation Management and Definition for Per-Protocol Population). • The decision to exclude a subject from the PP	• Primary efficacy

Population	Definition / Criteria	Analyses Evaluated
	population will be made prior to releasing the randomization codes. • Displays will be based on the treatment to which the subject was randomized.	
Inhaler Naive (IN)	• All subjects in the ITT population who have not used either Ellipta or Respimat for 6 months prior to inhaler evaluation (Visit 2 or Visit 5). • This population will be used for all Inhaler assessment displays.	

NOTES :

- Please refer to Appendix 13: List of Data Displays which details the population to be used for each displays being generated.

4.1. Protocol Deviations

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

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 2 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 2 Overview of Appendices

Section	Component
10.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
10.2	Appendix 2: Time & Events
10.3	Appendix 3: Assessment Windows
10.4	Appendix 4: Treatment States and Phases
10.5	Appendix 5: Data Display Standards & Handling Conventions
10.6	Appendix 6: Derived and Transformed Data
10.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
10.8	Appendix 8: Multicenter Studies
10.9	Appendix 9: Examination of Covariates, Subgroups & Other Strata
10.10	Appendix 10: Multiple Comparisons & Multiplicity
10.11	Appendix 11: Model Checking and Diagnostics for Statistical Analyses.

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

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

Table 3 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 13: List of Data Displays.

Table 3 Overview of Planned Study Population Analyses

Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Study Populations and Reasons for Screen Failures (ASE)	Y		
Attendance at Each Clinic Visit	Y		
End of Study Record	Y		Y
Treatment Completion	Y		
Reasons for Subject Withdrawal from the Study During Each Period	Y		
Reasons for Discontinuation of Treatment During Each Period	Y		
Number of Subjects by Country and Centre	Y		
Follow-up Contact			Y
Treatment			
Randomized and Actual Treatments			Y
Overall Percentage Treatment Compliance	Y		Y
Subjects Who Discontinued Study Treatment			Y
Protocol Deviations			
Important Protocol Deviations	Y		Y
Exclusions from Per Protocol Analyses	Y		Y
Inclusion/Exclusion/Randomization Criteria Deviations, ASE and ITT	Y		Y
Treatment Misallocations (ASE)			Y
Demography			
Demographic Characteristics, ITT and PP (Note the listing will only be produced for ITT)	Y		Y
Race and Racial Combinations	Y		
Race and Racial Combinations Details	Y		Y
Age group breakdown for the trial (ASE)	Y		
Subject Number per Country (ASE)	Y		
Medical Conditions and Concomitant Medications			
Current/Past Medical Conditions	Y		Y
Family History of Cardiovascular Risk Factors	Y		Y
COPD Concomitant Medications Not Given for an Exacerbation (Pre-Run-in, During Run-in or Washout, On-treatment, Post-treatment) (Only one listing required for all COPD medications)	Y		Y

Display Type	Data Displays Generated		
	Table	Figure	Listing
COPD Concomitant Medications Given for an Exacerbation (On-treatment, During Washout, Post-treatment)	Y		Y
Non-COPD Concomitant Medications (On-treatment, Post-treatment) (Only one listing required for all non-COPD medications)	Y		Y
Relationship Between Anatomical Therapeutic Classification (ATC) Level 1, Ingredient and Verbatim Text Non-COPD Concomitant Medications Only			Y
Disease and Background Characteristics			
COPD History and COPD Exacerbation History (only one listing required)	Y		Y
Smoking History and Status	Y		Y
Screening Lung Function Test Results (listed as part of the Listing of FEV1)	Y		Y
GOLD Categories and Reversibility at Screening	Y		Y
Screening IC Results (listed as part of the Listing of IC)	Y		Y
mMRC Dyspnoea Scale at Screening	Y		Y

NOTES :

- Y = Yes display generated.

6.1.1. Subject Disposition

The number of subjects in the ASE population, the number and percentage of subjects who were pre-screen failures, who had exacerbations during the pre-screening period, who attended the screening visit and of those the number and percentage of subjects who were screen failures with the reasons for failing or run-in failures with reasons for failing will be presented. The number of subjects randomized and the number of subjects who were in the ITT population will be presented by treatment and overall. Of those in the ITT population the number and percentage of subjects who discontinued treatment and the number and percentage of subjects in the PP Population will be presented by treatment and overall.

The number and percentage of subjects who completed the study as planned as well subjects who stopped investigational product prematurely will be presented, along with the number and percentage of subjects who reported each primary and sub-reason for discontinuation of treatment.

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.

A summary of the number and percentage of subjects who entered, discontinued treatment and completed each period of the study will be displayed.

A summary of reasons for withdrawal during each period (period 1, washout and period 2) will be presented for each treatment. A summary of reasons for discontinuation of treatment during each period will also be produced.

6.1.2. Medical Conditions and Concomitant Medications

The number and percentage of subjects reporting each current medical condition will be presented for the overall population. This table will include a category of 'Any Cardiovascular Risk Factor' and will present all medical conditions regardless of frequency. The table will be repeated for past medical conditions.

Non-COPD medications will be summarised by Anatomical-Therapeutic-Chemical (ATC) level 1 and ingredient. Multi-ingredient medications will be presented according to their combination ATC classification rather than the classifications of the ingredients.

Respiratory Medication Class (RMC) will be provided by Data Management for each COPD concomitant medication. COPD medications not given for an exacerbation, and medications given for an exacerbation, will be summarised by Respiratory Medication Class (RMC).

COPD and non-COPD medications will be listed separately. The COPD medications listing will indicate whether each medication was taken for an exacerbation. Both listings will indicate in which treatment state each medication was taken (Pre-Run-in, During Run-in, On-treatment, During Washout, Post-treatment).

A listing of the relationship between ATC Level 1, ingredient and verbatim text will be produced for non-COPD medications only.

6.1.3. Disease and Background Characteristics

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 and overall.

The number and percentage of subjects in each GOLD Grade 1-4, GOLD Category A-D using mMRC and GOLD Category A-D using CAT, and the number and percentage of subjects classified as Reversible/Non-reversible to salbutamol at Screening (defined in Section 10.6.2) will also be summarised by treatment and overall.

History of disease, along with smoking status and family history of cardiovascular disease will also be summarised by treatment and overall.

7. PRIMARY STATISTICAL ANALYSES

7.1. Efficacy Analyses

7.1.1. Overview of Planned Efficacy Analyses

The primary efficacy analyses for the primary endpoint will be on the PP population. All outputs produced for the primary endpoint will be repeated on the ITT population. Further investigation will be done if the results from the PP analysis are not consistent with the results from the ITT analysis for the primary endpoint. In addition, a tipping point analysis will be carried out as a sensitivity analysis for the primary endpoint of trough FEV_1 at Week 8 on the PP and ITT population in order to assess the impact of missing data on conclusions of non-inferiority and superiority.

Table 4 provides an overview of the planned efficacy analyses for the primary endpoint, with full details of data displays being presented in Appendix 13: List of Data Displays.

Table 4 Overview of Planned Efficacy Analyses for the Primary Endpoint

Endpoint	Change from Baseline [1]						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Trough FEV_1							
Trough FEV_1 at Week 8 (ITT and PP population)	Y	Y[3]		Y	Y[2]		Y
Tipping point on Trough FEV_1 at Week 8 (ITT and PP population)	Y						

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- [1] Analysis and Summaries to include absolute values too.
- [2] Box plot and empirical distribution function plot for change from baseline.
- [3] Figures include all time points produced for change from baseline only.

7.1.2. Planned Efficacy Statistical Analyses

Primary Statistical Analyses
Endpoint(s)
• Trough FEV_1 at Week 8 (results for trough FEV_1 at Week 4 will be obtained from the same analysis)
Model Specification
• Trough FEV_1 at Week 8 will be analysed for the PP population using a mixed model repeated measures (MMRM) including data recorded at each of Week 4 and Week 8. • The following covariates will be included in the model: period baseline (the difference between a subject's baseline in each treatment period and the mean overall baseline for that subject), mean baseline (the mean of the baselines in each of the two treatment periods), period, treatment, visit, visit by period baseline, visit by mean baseline and visit by treatment interactions, where visit is nominal Subject will be fitted as a random effect. • 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. • An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line. • The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used. If this method does not run, the residual method will be used instead.
Example SAS code
proc mixed data=start; *class subject period treatment visit;* *model endpoint=period treatment visit mean_base period_base visit*period_base visit*mean_base visit*treatment / ddfm=kr;* *random intercept / subject=subject;* *repeated visit / subject=subject*period type=un;* *lsmeans visit*treatment / cl diff e;* *ods output lsmeans=lsmeans;* *ods output diffs=diffs;* *run;*
Model Checking & Diagnostics
• Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses.
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. TIO/OLO 5/5), 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. • 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.

Primary Statistical Analyses

- A box plot and an empirical distribution function plot of change from baseline in trough FEV_1 at Week 8 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 Supportive Statistical Analyses

- The analysis and results presentation will be repeated for the ITT population (with the exception of the box plot and empirical distribution function plot).

- Sensitivity of the results to missing data will be assessed using Tipping Point Analysis for both the PP and ITT population. Analysis of the primary endpoint at Week 8 will be run with missing data imputed under a variety of assumptions for the mean of the missing data. This will be done for both study arms separately. These analyses will allow for determination of the 'tipping point(s)' which is, the mean values for missing data that would cause a change in the conclusion of a)non-inferiority and b)superiority as assessed by the lower limit of the two-sided 95% CI. Multiple- imputation will be used for imputing the Week 8 endpoint of interest for subjects who had missing on-treatment data at Week 8.

  For each imputation, a random draw will be made from a normal distribution with mean equal to the corresponding assumed mean change from baseline and standard deviation taken from the observed change from baseline data for the combined treatment arms at the Week 8 visit. Data for subjects with missing baseline values will not be imputed. Analysis of the complete Week 8 dataset will be carried out using an ANCOVA model with covariates of treatment group and baseline for that particular period (Note: not the period baseline) .

  Initially the same mean change from baseline will be assumed for subjects who withdrew from both treatment arms. The assumed values for the mean change from baseline at Week 8 will vary from -150mL to +150mL in increments of 50mL.

  The analysis will be repeated assuming different mean changes from baseline for subjects who withdrew from each treatment arm. For each value of the assumed mean change from baseline for subjects who withdrew from UMEC/VI, the full range of values for subjects who withdrew from TIO/OLO will be investigated.

  Seeds for multiple imputation analyses will be set using the following SAS code:

```
data seed1;
   number=round(10000*ranuni(0),1);
   output;
run;

proc print;
run;
```

  The seeds generated and assigned to each analysis will be documented separately prior to DBF. A table will be produced displaying the two-sided 95% lower confidence limit of the Week

Sensitivity and Supportive Statistical Analyses
8 treatment differences under the above assumptions for the mean changes from baseline for each of the treatment arms • An assessment of whether the effect of treatment is modified by the interaction of Period Period baseline Mean baseline will be made. Interactions with treatment will be investigated by fitting separate MMRM models 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 8. The interaction term will be tested at the 10% significance level. 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. This will be assessed for the PP population.

8. OTHER STATISTICAL ANALYSES

8.1. Other Efficacy Endpoints

8.1.1. Overview of Planned Efficacy Analyses

The other efficacy summaries and analyses will be based on the ITT population, unless otherwise specified.

Table 5 provides an overview of the planned efficacy analyses, with further details of data displays being presented in Appendix 13: List of Data Displays.

Table 5 Overview of Planned Efficacy Analyses

Endpoint	Change from Baseline[1]						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Responder FEV_1							
Proportion of responders according to FEV_1 (a responder is defined as a ≥100mL change in Trough FEV_1 from baseline) at Week 4 and 8 [2]	Y			Y			Y
Trough FVC and IC							
Trough FVC	Y	Y		Y			Y
Trough IC	Y	Y		Y			Y
Rescue medication							
Mean number of puffs per day of rescue over the study duration (Weeks 1-8) captured using e-diary	Y			Y			Y
Percentage of rescue free days over the study duration (Weeks 1-8) captured using e-diary [2]	Y			Y			Y
Mean number of occurrences per day of rescue over the study duration (Weeks 1-8) captured using e-MDI				Y			Y
Percentage of rescue free days over the study duration (Weeks 1-8) captured using e-MDI [3]				Y			Y
CAT							
CAT score	Y	Y		Y			Y

Endpoint	Change from Baseline[1]						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Proportion of CAT responders [2]	Y			Y			Y
Inhaler assessments							
Inhaler ease of use	Y			Y			Y
Inhaler errors				Y			Y
E-RS							
E-RS	Y	Y		Y			Y
Proportion of E-RS responders [2]	Y			Y			Y

NOTES :

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

1. Analysis and Summaries to include absolute values too for all endpoints with the exception of Responder analysis
2. Summary and analysis will be combined into a single display.
3. Summary only

8.1.2. Planned Efficacy Statistical Analyses for Other Efficacy Endpoints

8.1.2.1. Responder FEV_1

Statistical Analyses for Proportion of Trough FEV_1 Responders
Endpoints
• Proportion of responders according to FEV_1 (a responder is defined as a ≥100mL change in Trough FEV_1 from baseline)
Model Specification
• At each visit, the proportion of subjects achieving a ≥100mL change in Trough FEV_1 from baseline will be analysed using a generalised linear mixed model. • The following covariates will be included in the model: period baseline, mean baseline, period, treatment, visit, visit by period baseline, visit by mean baseline and visit by treatment interactions, where visit is nominal.
Example SAS code
proc glimmix data=start; *class subject period treatment visit;* *model endpoint(descending)=period treatment visit mean_base period_base visit*period_base visit*mean_base visit*treatment / dist=binary link=logit ddfm=kr solution;* *random intercept / subject=subject;* *random visit / subject=subject*period residual type=un;* *lsmeans visit*treatment / diff;* *ods output lsmeans=lsmeans;* *ods output diffs=diffs;* *run;*

Statistical Analyses for Proportion of Trough FEV_1 Responders
• Note: The residual statement turns the random statement into a repeated statement
Model Checking & Diagnostics
• Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• The odds ratio, 95% CI and p-value of UMEC/VI 62.5/25 vs. TIO/OLO 5/5 will be presented.
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 detailed above.

8.1.2.2. Trough FVC and IC

Statistical Analyses
Endpoints
• Trough FVC • Trough IC
Model Specification
• Trough FVC and Trough IC endpoints above will be analyzed using the same methodology as the primary analysis of trough FEV_1 (detailed in Section 8.1.2.1) using all available FVC or IC data recorded at Weeks 4 and 8.
Model Checking & Diagnostics
• Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses.
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. TIO/OLO 5/5), 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.
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.

8.1.2.3. Rescue Medication

Mean number of Puffs/Occurrences of Rescue Medication
Endpoints
• Mean number of puffs per day of rescue medication over the study duration (Weeks1-8) captured using e-diary • Percentage of rescue-free days over the study duration (Weeks 1-8) captured using e-diary

Mean number of Puffs/Occurrences of Rescue Medication

- Mean number of occurences per day of rescue medication over the study duration (Weeks1-8) captured using e-MDI
- Percentage of rescue-free days over the study duration (Weeks 1-8) captured using e-MDI

Model Specification for MMRM Analysis Weeks 1-8

- Each endpoint derived for Weeks 1-2, 3-4, 5-6 and 7-8 will be analysed using a MMRM analysis using all available values recorded during Weeks 1-2, 3-4, 5-6 and 7-8.
- The following covariates will be included in the model: period baseline, mean baseline, period, treatment, two-weekly period, two-weekly period by period baseline interaction and two-weekly period by mean baseline interaction.
- The overall treatment effect will be estimated.
- Two models will be fitted for each endpoint; one with a response variable of mean number of puffs/day or percentage of rescue-free days, and one with a response variable of the change from baseline.
- An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line.
- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.

Example SAS code

```
proc mixed data=start;
  class subject period treatment 2wkperd;
  model endpoint=period treatment 2wkperd mean_base period_base
                    2wkperd*period_base 2wkperd*mean_base /
                    ddfm=kr;
  random intercept / subject=subject;
  repeated 2wkperd / subject=subject*period type=un;
  lsmeans treatment / cl diff e ;
  ods output lsmeans=lsmeans;
  ods output diffs=diffs;
run;
```

Model Checking & Diagnostics

- Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses.

Model Results Presentation

- The LS mean and LS mean change from baseline over Weeks 1-8 with their corresponding SEs will be presented for each treatment, together with the estimated treatment difference (UMEC/VI 62.5/25 vs. TIO/OLO 5/5), corresponding 95% CI and p-value.
- Percentage of rescue-free days will have LS mean with over Weeks 1-8 with their corresponding SEs will be presented for each treatment, together with the estimated treatment difference (UMEC/VI 62.5/25 vs. TIO/OLO 5/5), corresponding 95% CI and p-value.

Summary Results Presentation

- The mean number of puffs of rescue medication per day at baseline, during each two weeks of treatment and over the entire 8-week treatment period will be summarized by treatment. The change from baseline values will also be summarized by treatment, for each two weeks of treatment and the entire 8-week treatment period.
- This will be repeated for percentage of rescue-free days.
- Only the above summaries (not analysis) will be repeated for rescue medication

Mean number of Puffs/Occurrences of Rescue Medication
(albuterol/salbutamol) collected using eMDI.
Non-parametric analysis
• If the assumption of normality is not satisfied (as seen in previous studies with similar design), a non-parametric analysis will be carried out. Hodges Lehman estimates for the median treatment difference and 95% confidence interval 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.

8.1.2.4. CAT

Statistical Analyses for CAT Score
Endpoints
• CAT Score
Model Specification
• CAT will be analyzed using a MMRM including data recorded at each of Week 4 and Week 8. • The following covariates will be included in the model: period baseline, mean baseline, period, treatment, visit, visit by period baseline, visit by mean baseline and visit by treatment interactions, where visit is nominal. Subject will be fitted as a random effect. • Two models will be fitted; one with a response variable of CAT score, and one with a response variable of change from baseline in CAT score.
Example SAS code
proc mixed data=start; *class subject period treatment visit;* *model endpoint=period treatment visit mean_base period_base* *visit*period_base visit*mean_base visit*treatment /* *ddfm=kr;* *random intercept / subject=subject;* *repeated visit / subject=subject*period type=un;* *lsmeans visit*treatment / cl diff e;* *ods output lsmeans=lsmeans;* *ods output diffs=diffs;* *run;*
Model Checking & Diagnostics
• Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses.
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. TIO/OLO 5/5), 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.
Summary Results Presentation
• Summary of baseline CAT score will be presented by treatment for all subjects. • Summary statistics for raw and change from baseline in CAT score at each visit and for each treatment will be presented on the same table.

Statistical Analyses for Proportion of CAT Responders
Endpoints
• Proportion of Responders according to CAT
Model Specification
• At each visit, the proportion of responders will be analysed using a generalised linear mixed model. • Please see Section 10.6.4 for details on responder definition. • The following covariates will be included in the model: period baseline, mean baseline, period, treatment, visit, visit by period baseline, visit by mean baseline and visit by treatment interactions, where visit is nominal. • See Section 10.7.2 for details on how to handle missing data.
Example SAS code
proc glimmix data=start; *class subject period treatment visit;* *model endpoint(descending)=period treatment visit mean_base period_base visit*period_base visit*mean_base visit*treatment / dist=binary link=logit ddfm=kr solution;* *random intercept / subject=subject;* *random visit / subject=subject*period residual type=un;* *lsmeans visit*treatment / diff;* *ods output lsmeans=lsmeans;* *ods output diffs=diffs;* *run;* • Note: The residual statement turns the random statement into a repeated statement
Model Checking & Diagnostics
• Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• The odds ratio, 95% CI and p-value of UMEC/VI 62.5/25 vs. TIO/OLO 5/5 will be presented.
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 detailed above.

8.1.2.5. E-RS

Statistical Analyses for E-RS
Endpoints
• Change from baseline in weekly mean scores for E-RS and its subscales (breathlessness, cough and sputum and chest symptoms)
Model Specification
• E-RS endpoint above will be analyzed using similar methodology as the MMRM analysis of Trough FEV_1 (detailed in Section 7.1.2) using all available data recorded from the EXACT-PRO questionnaire. • For E-RS and subscales, all weekly mean scores will be included in the analysis.
Model Checking & Diagnostics

Statistical Analyses for E-RS
• Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses.
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 weekly treatment period, together with estimated treatment differences (UMEC/VI 62.5/25 vs. TIO/OLO 5/5), corresponding 95% CIs and p-values.
Summary Results Presentation
• The mean score at baseline and during each week of treatment will be summarized by treatment. The change from baseline values will also be summarized by treatment, for each week of treatment.

Statistical Analysis of Proportion of Responders according to E-RS
Endpoints
• Proportion of responders for E-RS and its subscales (breathlessness, cough and sputum and chest symptoms)
Model Specification
• For each mean weekly E-RS total score and subscales, the proportion of responders will be analyzed using similar methodology as the generalized linear mixed model analysis of Trough FEV_1 responder (detailed in Section 8.1.2.1). • Please see Section 10.6.4 for details on responder definitions. • See Section 10.7.2 for details on how to handle missing data.
Model Checking & Diagnostics
• Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• The odds ratio, 95% CI and p-value of UMEC/VI 62.5/25 vs. TIO/OLO 5/5 will be presented
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 detailed above.

8.1.2.6. Inhaler assessment summaries

Inhaler Error Assessment
Endpoint
• Percentage of subjects making at least one critical error • Percentage of subjects making at least overall error • See Section 10.6.4 for error derivation.
Summary of Results Presentation
• Summarized by inhaler, response (at least one error critical and overall) using n and %. Results will be presented by sequence and total. • The number and percent of subjects reporting each error for each individual question will also be presented (separate table for each inhaler).

Statistical Analysis of Inhaler Ease of Use Assessment

Endpoints

- Ease of use' rating for the ELLIPTA DPI compared with the Respimat.

Model Specification

- Each question will be analysed using the Cochran-Mantel-Haenszel test adjusted for country
- The Cochran-Mantel-Haenszel test serves as a stratified approximation to Prescott's test, a variation of a one-sample chi-square test that accounts for study inhaler sequence and difference in ease of use response [Prescott, 1981; Senn, 2002]. Homogeneity among country with respect difference in to ease of use will be assessed using a Breslow-Day test. Results of this test will not be reported on the final data display.
- See Section 10.6.4 for ease of use derivation.

Example SAS code

- SAS code for stratified approximation to Prescott's test for each preference question:

- ods output CMH = cmhi (where = (upcase(AltHypothesis) =: 'ROW MEAN SCORES') keep = AltHypothesis Prob) ;

```
proc freq data = pref_data ;
      tables country * seq * ease_ord / cmh ;
    run ;
```

- SAS code for checking Breslow-Day Test for 2x2

```
proc freq data = pref_data (where = (ease_ord ne 0)) ;
  tables country * seq * ease_ord / cmh ;
```

Model Results Presentation

- P-values will be presented for the comparison between inhalers on the summary table

Summary Results Presentation

- Responses to the Ease of Use questionnaire will be summarised by inhaler, question/item and type of responses for the IN population.
- The percentage preference (rated higher for Ellipta, rated higher for Respimat, rated the same) will be summarized on the same table as the analysis results detailed above. Results will be presented by question, sequence and total.
- An additional summary will be produced based on the difference between the ratings for the two inhalers. The rating are coded as Very Easy=1, Easy=2, Neutral=3, Difficult=4, Very Difficult=5. Therefore, the difference in rating will be ranged from -4 to 4. A difference of -4 indicates a rating of 'Very Easy' for Ellipta and a 'Very Difficult' for Other.

8.2. Safety Analyses

8.2.1. Overview of Planned Analyses

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

Table 6 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 13: List of Data Displays.

Table 6 Overview of Planned Safety Analyses

Endpoint	Absolute			
	Summary		Individual	
	T	F	F	L
Incidence of Adverse Events				
Overview of On-treatment Adverse Events (AEs)	Y			
On-treatment AEs	Y			
Post-treatment AEs	Y			
Drug related On-treatment AEs	Y			
Fatal On-treatment SAEs	Y			
Fatal Post-treatment SAEs	Y			
Fatal Drug related On-treatment SAEs	Y			
Non-fatal On-treatment SAEs	Y			
Non-fatal Post-treatment SAEs	Y			
Non-fatal Drug related On-treatment SAEs	Y			
10 Most Frequent On-treatment AEs on Each Treatment	Y			
On-treatment AEs of Special Interest (AESI) (SOC will not be presented for this display)	Y			
Pre-treatment Fatal SAEs, (ASE, total column only)	Y			
Pre-treatment Non-fatal SAEs, (ASE, total column only)	Y			
Pre-treatment AEs Leading to Withdrawal from the Study, (ASE, total column only)	Y			
On-treatment AEs Leading to Permanent Discontinuation of Study Treatment or Withdrawal from the Study	Y			
Relationship Between Primary System Organ Class, Preferred Term and Verbatim AE Text,	Y			
On-treatment Non-serious AEs reported by 3% or more subjects (before rounding) in any treatment group, EMA Requirement (ITT)	Y			
Summary of Serious Adverse Events by Preferred Term Including Drug-related Status and Fatal Status (ITT) EMA Requirement	Y			
Subject Numbers for Each AE				Y
All AEs				Y
Non-fatal SAEs				Y
Fatal SAEs				Y
AEs Leading to Permanent Discontinuation of Study Treatment or				Y

Endpoint	Absolute			
	Summary		Individual	
	T	F	F	L
Withdrawal from the Study				
On-treatment Drug-related AEs				Y
Pulse Rate, Systolic Blood Pressure and Diastolic Blood Pressure				Y
On- treatment COPD Exacerbations	Y			Y
Post- treatment COPD Exacerbations	Y			Y
Exposure Data	Y			Y
Potential DPI Inhaler Malfunctions				Y
Potential Chest X-ray Data				Y
All Other potential Pneumonia Data				Y
Liver Events				Y
Virology				Y
Myocardial Infarction/Unstable Angina*				Y
Congestive Heart Failure*				Y
Arrhythmias*				Y
Valvulopathy*				Y
Pulmonary Hypertension*				Y
Cerebrovascular Events/Stroke and Transient Ischemic Attack*				Y
Peripheral Arterial Thromboembolism*				Y
Deep Venous Thrombosis/Pulmonary Embolism*				Y
Revascularisation*				Y
All cause deaths				Y
ECG				Y

*collected if cardiovascular event occurs

8.2.2. Adverse Events

AE incidence will be summarised by treatment using the primary System Organ Class (SOC) and preferred term.

The 10 most frequent on-treatment adverse events in each treatment summary will use the counts to determine the most frequent 10 events. In case of ties in frequency all AEs for that frequency will be displayed. On-treatment AEs experienced by 3 % (after rounding) or more of subjects in any treatment group will also be displayed (SOC will not be presented for this display.)

Classification of an AE as pre-, on- or post-treatment is provided in Section 10.4.1. All listings of AEs/SAEs will include an identification of the treatment state.

8.2.2.1. Adverse Events of Special Interest

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 10.6.3.

8.2.3. COPD Exacerbations

On- and post-treatment exacerbations will be summarized separately.

The definition of on- and post-treatment exacerbations is provided in Section 10.4.1.3.

The number and percentage of subjects reporting 0, 1, 2 or >2 COPD exacerbations, the total number of exacerbations, the number and percentage of subjects withdrawn due to an exacerbation and the number and percentage of subjects treated by oral/systemic corticosteroids, antibiotics or hospitalisation will also be presented. The number and percentage of exacerbations with each outcome category and each severity will be presented and the exacerbation duration will be summarised.

8.2.4. Liver Events

Liver event information will be listed for all subjects who report a liver event, to include:

- The time from the start of randomized study treatment to the liver event.
- The information captured on the Liver Event Assessment Form which is used to calculate the Roussel Uclaf Causality Assessment Method score.
- If liver biopsy was performed, the size of the biopsy and the recorded outcomes.
- If liver imaging was performed, the recorded outcomes for the liver imaging assessment.

9. REFERENCES

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10. APPENDICES

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RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
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Section 10.13	Appendix 13: List of Data Displays

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

10.1.1. Exclusions from Per Protocol Analysis

The full list of protocol deviations collected on the eCRF is in the PDMP. This will include those that will also be excluded from the per protocol analyses.

Concomitant medications will be reviewed for deviations from the time of informed consent through to the time of stopping study treatment.

Subjects with partial deviations will be excluded from PP analyses from the onset of the deviation onwards. Subjects with time point specific or period specific deviations will have only the affected time point excluded from PP analyses.

10.2. Appendix 2: Time & Events

10.2.1. Protocol Defined Time & Events

		Screen/Run-in		Treatment 1			Wash-Out	Treatment 2			Post-Treatment	
Visit		**0 Prescreen[1]**	**1 (Screen)**	**2 (Rand)**	**3**	**4**		**5**	**6**	**7**	**EW Visit[2]**	**Follow up Contact[11]**
Treatment Day			**14 ± 3 days prior to Visit 2**	**1 ± 3 days**	**28 ± 3 days**	**56 ± 3 days**	**21 days ± 3 days**	**1 21 ± 3 days after V4**	**28 ± 3 days after V5**	**56 ± 3 days after V5**		**7 ± 3days after V7 or EW Visit**
Week			**-1**	**N/A**	**4**	**8**		**N/A**	**4**	**8**		
Screen / Baseline	Written informed consent	X										
	Demography	X										
	Medical/COPD history		X									
	Smoking history/status		X							X	X	
	Smoking cessation counselling		X							X	X	
	Verify Inclusion/exclusion criteria		X									
	Concomitant medication assessment	X	X	X	X	X	X	X	X	X	X	X
	Verify Randomization criteria			X								
	Physical examination		X							X	X	
	Screening 12-Lead ECG		X									
	Screening spirometry (including post-bronchodilator testing)[3]		X									
	mMRC dyspnea scale		X									
	Training on use of inhalers[13]			X				X				

		Screen/Run-in		Treatment 1			Wash-Out	Treatment 2			Post-Treatment	
Visit		**0 Prescreen[1]**	**1 (Screen)**	**2 (Rand)**	**3**	**4**		**5**	**6**	**7**	**EW Visit[2]**	**Follow up Contact[11]**
Treatment Day			**14 ± 3 days prior to Visit 2**	**1 ± 3 days**	**28 ± 3 days**	**56 ± 3 days**	**21 days ± 3 days**	**1 21 ± 3 days after V4**	**28 ± 3 days after V5**	**56 ± 3 days after V5**		**7 ± 3days after V7 or EW Visit**
Week			**-1**	**N/A**	**4**	**8**		**N/A**	**4**	**8**		
	Training in the use of eDiary and eMDI		X									
	Register visit IVRS	X	X	X	X	X	X	X	X	X	X	X
Efficacy/ Inhaler Evaluations	Pre dose Spirometry (FEV_1, FVC and IC)[4]			X				X				
	Trough Spirometry (FEV_1, FVC and IC)[5]				X	X			X	X		
	CAT[12]		X	X	X	X		X	X	X		
	EXACT-PRO (14 item questionnaire)		→	→	→	→	→	→	→	→		
	Inhaler Ease of use assessment			X				X				
	Inhaler Errors assessment[13]			X				X				
Safety	Adverse event assessment[6]		X	X	X	X	X	X	X	X	X	X
	COPD exacerbation assessment	X	X	X	X	X	X	X	X	X	X	X
	Urine pregnancy test[7]		X	X				X		X	X	
	Observed dose in clinic[14]				X				X			
Medication/ Supplies	Dispense rescue albuterol/salbutamol[8] with eMDI		X	X	X	X		X	X	X		
	Collect rescue albuterol/salbutamol[9] with eMDI			X	X	X		X	X	X	X	

		Screen/Run-in		Treatment 1			Wash-Out	Treatment 2			Post-Treatment	
Visit		**0 Prescreen[1]**	**1 (Screen)**	**2 (Rand)**	**3**	**4**		**5**	**6**	**7**	**EW Visit[2]**	**Follow up Contact[11]**
Treatment Day			**14 ± 3 days prior to Visit 2**	**1 ± 3 days**	**28 ± 3 days**	**56 ± 3 days**	**21 days ± 3 days**	**1 21 ± 3 days after V4**	**28 ± 3 days after V5**	**56 ± 3 days after V5**		**7 ± 3days after V7 or EW Visit**
Week			**-1**	**N/A**	**4**	**8**		**N/A**	**4**	**8**		
	Dispense period 1 study medication			X	X							
	Collect period 1 study medication					X					X	
	Dispense period 2 study medication							X	X			
	Collect period 2 study medication									X	X	
	Assess drug compliance[10]				X	X			X	X	X	
	Dispense eDiary		X									
	Collect eDiary									X	X	

1. Pre-screen Visit must be completed prior to or on the same day as Screening Visit.
2. Early Withdrawal Visit: Subjects that withdraw should return to the clinic as soon as possible for the Early Withdrawal Visit.
3. Spirometry at screening for FEV_1 and FVC assessments to be conducted as follows: pre-bronchodilator testing followed by post-albuterol/salbutamol testing. Post-albuterol/salbutamol testing conducted 10 to 30 minutes after subject self-administration of 4 Inhalations of albuterol/ salbutamol. IC will not be obtained at Screening.
4. Spirometry: On Day 1 of each period (Visits 2 and 5 respectively), pre-dose IC, FEV_1, and FVC measurements should be conducted 30 minutes and 5 minutes prior to dosing.
5. Trough IC, FEV_1, and FVC measurements on Weeks 4 and 8 of each treatment period should be done 23 hours and 24 hours after the previous day's dose of study medication.
6. Adverse events and Serious Adverse Events to be collected from the start of study drug (Visit 2) until the follow-up contact. However, any serious adverse events assessed as related to study participation or related to a GSK concomitant medication will be recorded from the time of consent. Subjects will use eDiary to record any medical problems experienced during the study and any medication taken for those medical problems
7. Pregnancy test: for females for child bearing potential only.
8. After Visit 1, albuterol/salbutamol to be used and dispensed on an as-needed basis. Use in inhalations/day to be recorded daily by subjects using the ePro.
9. Collect albuterol/salbutamol: as required (all rescue medication should be collected at Visit 7 or the Early Withdrawal Visit).

10. Compliance with UMEC/VI will be determined by reviewing the dose counter on the Ellipta inhaler. Compliance with the TIO/OLO will be determined by reviewing the number of inhalations/day (2 inhalations/day to equal one dose) as recorded in the e Diary.
11. The follow-up contact will be by telephone 5 to 10 days after V7 or the Early Withdrawal Visit.
12. CAT will be performed at the site on the eDiary.
13. For first dosing of each treatment period the subject will follow the subject information sheet under the observation of the site staff. Before the subject leaves the clinic the site staff will make sure the subject is shown a training video on the use of the inhaler and they will make sure the inhaler is correctly loaded.
14. Dosing by the subject will be observed in the clinic and corrected if necessary. Retraining by showing the training video to take place if dosing not correct. PI to make sure inhaler loader appropriately loaded before subject leaves the clinic.

EW= Early withdrawal
Rand = Randomization

10.3. Appendix 3: Assessment Windows

10.3.1. 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.

For the 23 and 24 h post-dose trough FEV_1 measurements, a time window of 22.0-25.0 h is allowed for the actual time of an assessment relative to time of dosing on the previous day. Values falling outside of this window will not be used in the PP analysis of the primary endpoint, but will still be included in all ITT analyses.

10.4. Appendix 4: Treatment States and Phases

10.4.1. Treatment States

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

10.4.1.1. Treatment States for Concomitant Medication Data

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):

DATE RULES	PRETRT (Pre treatment)	DURTRT (On treatment)	POSTTRT (Post treatment)
mststdt = .	Y		
mststdt ^=. AND (cmstdt < mststdt OR cmprior = Y) AND cmendt <= mststdt	Y		
mststdt ^=. AND (cmstdt < mststdt OR cmprior = Y) AND mststdt < cmendt <= mstendt	Y	Y	
mststdt ^=. AND (cmstdt < mststdt OR cmprior = Y) AND (cmendt > mstendt OR cmongo = Y)	Y	Y	Y
mststdt ^= . AND mststdt <= cmstdt <= mstendt AND mststdt <= cmendt <= mstendt		Y	
mststdt ^= . AND mststdt <= cmstdt <= mstendt AND (cmendt > mstendt OR cmongo = Y)		Y	Y
mststdt ^= . AND cmstdt>=mstendt			Y

cmstdt=start date of the concomitant medication, cmendt=end date of the concomitant medication, mststdt =start date of the study medication, mstendt =end date of the study medication

The following SAS code will be used:

```
if mststdt=. then do;
 pretrt="Y"; durtrt='';  posttrt='';
end;
if mststdt ne . and (cmstdt2 < mststdt or cmprior='Y') and (cmendt2 <= mststdt) then do;
 pretrt='Y'; durtrt='';  posttrt='';
end;
if mststdt ne . and (cmstdt2 < mststdt or cmprior='Y') and mststdt < cmendt2 <= mstendt then do;
 pretrt='Y'; durtrt='Y'; posttrt='';
end;
if mststdt ne . and (cmstdt2 < mststdt or cmprior='Y') and (cmendt2 > mstendt or cmongo='Y') then do;
 pretrt='Y'; durtrt='Y'; posttrt='Y';
end;
if mststdt ne . and mststdt <= cmstdt2 <= mstendt and mststdt <= cmendt2 <= mstendt then do;
 pretrt='';  durtrt='Y'; posttrt='';
end;
if mststdt ne . and mststdt <= cmstdt2 <= mstendt and (cmendt2 > mstendt or cmongo='Y') then do;
 pretrt='';  durtrt='Y'; posttrt='Y';
end;
if mststdt ne . and cmstdt2 >= mstendt then do;
 pretrt='';  durtrt='';  posttrt='Y';
end;
```

10.4.1.2. Treatment States for AE Data

Classification of an AE as pre-, on- or post-treatment will be made with reference to the study treatment start and stop dates for each period and the AE onset date. If the AE onset date is missing or partial then the AE will be considered on-treatment unless there is evidence to the contrary (e.g. the month of the onset date is present and is less than the month of the first dose of study treatment). AEs with onset on the day after the last day of treatment will be considered on-treatment. Other AEs with onset during the wash-out or follow-up periods, or following IP discontinuation will be considered post-treatment but will be assigned to the treatment received in the previous period. AEs with missing or partial onset dates which are not classified will be included in listings only. AEs reported by subjects who did not receive treatment will be considered pre-treatment.

Treatment State	Definition
Pre-Treatment	AE Onset Date < First Study Treatment Start Date
On-Treatment	If AE onset date is on or after treatment start date & on or before treatment stop date. Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 1 day
Post-Treatment	If AE onset date is after the treatment stop date plus 1 day. AE Start Date > Study Treatment Stop Date + 1 day
Onset Time Since 1st Dose (Days)	If Treatment Start Date > AE Onset Date: = AE Onset Date - Treatment Start Date If Treatment Start Date ≤ AE Onset Date: = AE Onset Date - Treatment Start Date +1 Missing otherwise.
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	If relationship is marked 'YES' on [Inform/CRF OR value is missing].

NOTES:

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

10.4.1.3. Treatment States for COPD Exacerbation Data

Classification of a COPD exacerbation as having onset on- or post-treatment will be made with reference to the study treatment start and stop dates and the exacerbation onset date. If the exacerbation onset date is missing or partial then the exacerbation will be considered on-treatment unless there is evidence to the contrary (e.g. the month of the onset date is present and is less than the month of the first dose of study medication). Exacerbations with onset on the day after the last day of a treatment will be considered on-treatment. Other exacerbations with onset during a washout or follow-up period, or following IP discontinuation will be considered post-treatment but will be assigned to the treatment received in the previous period. Exacerbations which are not considered on- or post-treatment or which are reported by subjects who did not receive treatment will be included in listings only. The duration of the exacerbation will be calculated as (exacerbation resolution date or date of death - exacerbation onset date + 1).

Treatment State	Definition
On-Treatment	If onset date is on or after treatment start date & on or before treatment stop date. Study Treatment Start Date ≤ Start Date ≤ Study Treatment Stop Date + 1 day
Post-Treatment	If AE onset date is after the treatment stop date. Start Date > Study Treatment Stop Date +1 day

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Study Treatment & Sequence Display Descriptors

Treatment Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
3	UMEC/VI 62.5/25 mcg	UMEC/VI 62.5/25	1
4	TIO/OLO 5/5 mcg	TIO/OLO 5/5	2

NOTES:

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

Sequence Descriptions		
Data Displays for Reporting		
Period 1	Period 2	Description
UMEC/VI 62.5/25	TIO/OLO 5/5	UMEC/VI 62.5/25_TIO/OLO 5/5
TIO/OLO 5/5	UMEC/VI 62.5/25	TIO/OLO 5/5_UMEC/VI 62.5/25

10.5.2. Baseline Definition & Derivations

10.5.2.1. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment.

Baseline definitions are applicable to each period.

Parameter	Study Assessments Considered As Baseline	Baseline Used in Data Display
	Day 1 (Pre-Dose)	
FEV_1 and FVC		
Trough FEV_1 and FVC	X	Mean value (30 min and 5 min pre-dose) recorded before dosing on Day 1 of each period. If one of the values is missing then the baseline will be the single remaining value
IC		
Trough IC	X	Mean value (30 min and 5 min pre-dose) recorded before dosing on Day 1 of each period. If one of the values is missing then the baseline will be the single remaining value
Rescue Use		
Mean Number of Puffs of Rescue	X	The total puffs of rescue for each day will be calculated as number of salbutamol puffs. If

Parameter	Study Assessments Considered As Baseline	Baseline Used in Data Display
	Day 1 (Pre-Dose)	
Medication Per Day and Percentage of Rescue-free Days Over Weeks 1-8 captured using e-diary		the number of puffs is missing then the total puffs will be set to missing for that day. Provided at least half the days within the summary period have non-missing values the baseline is calculated over the duration stated below: Period 1: Values recorded between the latest of (7 days prior to Visit 2 and the day of Visit 1) and the Day before Visit 2 Period 2: Values recorded between the latest of (7 days prior to Visit 5 and the day of Visit 4) and the Day before Visit 5.
Mean Number of Occurrences of Rescue Medication Per Day and Percentage of Rescue-free Days Over Weeks 1-8 captured using e-MDI	X	The total occurrences, defined as >1 puff within a 2 minute time window, of rescue for each day will be calculated. Baseline is calculated over the duration stated below: Period 1: Values recorded between the latest of (7 days prior to Visit 2 and the day of Visit 1) and the Day before Visit 2 Period 2: Values recorded between the latest of (7 days prior to Visit 5 and the day of Visit 4) and the Day before Visit 5. Where entries of occurrences are not present the number of occurrences is assumed to be 0.
CAT		
CAT	X	Value recorded before dosing on Day 1 of each period
E-RS		
E-RS	X	Provided at least 4 days are non-missing, the baseline is calculated as the average of measurements over the duration stated below: Period 1: Values recorded between the latest of (7 days prior to Visit 2 and the day of Visit 1) and the Day before Visit 2 Period 2: Values recorded between the latest of (7 days prior to Visit 5 and the day of Visit 4) and the Day before Visit 5.

For FEV_1 and FVC, IC, rescue use, CAT and E-RS analyses:

- Mean (subject level) baseline is defined as the mean of the baselines in each period for each subject.
- Period baseline is defined as the difference between the baseline and mean baseline for each period and each subject.

10.5.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
Percentage Change from Baseline	= ((Post-Dose Visit Value – Baseline)/Baseline)*100

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 10.5.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.

10.5.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Area	: gsk573719_gw642444/mid204990/final
QC Spreadsheet	: gsk573719_gw642444/mid204990/final/qc
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards.	
Generation of RTF Files	
• RTF files will be generated for all tables in the final reporting effort.	

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: ○ 4.03 to 4.23: General Principles ○ 5.01 to 5.08: Principles Related to Data Listings ○ 6.01 to 6.11: Principles Related to Summary Tables ○ 7.01 to 7.13: Principles Related to Graphics
Formats
• All data will be reported according to the treatment to which the subject was randomized unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (dp) will be adopted for reporting of data based on the raw data collected.

Reporting Standards	
• Numeric data will be reported to 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. • Mean number of rescue puffs/day, percentage of rescue-free days, E-RS and CAT will have a min and max to 1 dp and then follow IDSL standards for reporting other summary statistics. • FEV_1, FVC, and IC will have a min and max to 2 dp and then follow IDSL standards for reporting other summary statistics. • Odds 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.
• 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 and Early Withdrawal assessments will be presented within the subject's listings.	

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

10.6. Appendix 6: Derived and Transformed Data

10.6.1. General

Study Day

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

Period Study Day
• For period 1, period day will be the same as study day. For period 2, period day will be calculated as (Ref Date – 2nd Treatment Start Date + 1).

10.6.2. Study Population

Demographics
Age

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

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

Reversibility
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 Classifications
GOLD Grade 1-4
• Subjects will be classified into Global Initiative for Chronic Obstructive Lung Disease (GOLD) (GOLD, 2017 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 mMRC)

- Subjects will be classified into GOLD (mMRC) Categories A-D as follows:
  A. Low risk, less symptoms: mMRC <2 and <2 exacerbations in the past year and no exacerbation leading to hospitalisation in the past year
  B. Low risk, more symptoms: mMRC ≥2 and <2 exacerbations in the past year and no exacerbation leading to hospitalisation in the past year
  C. High risk, less symptoms: mMRC <2 and (≥2 exacerbations in the past year or ≥1 exacerbation leading to hospitalisation in the past year)
  D. High risk, more symptoms: mMRC ≥2 and (≥2 exacerbations in the past year or ≥1 exacerbation leading to hospitalisation in the past year)

GOLD Category A-D (Using CAT)

- Subjects will be classified into GOLD (CAT) Categories A-D as follows:
  A. Low risk, less symptoms: CAT <10 and <2 exacerbations in the past year and no exacerbation leading to hospitalisation in the past year
  B. Low risk, more symptoms: CAT ≥10 and <2 exacerbations in the past year and no exacerbation leading to hospitalisation in the past year
  C. High risk, less symptoms: CAT <10 and (≥2 exacerbations in the past year or ≥1 exacerbation leading to hospitalisation in the past year)
  D. High risk, more symptoms: CAT ≥10 and (≥2 exacerbations in the past year or ≥1 exacerbation leading to hospitalisation in the past year)

Compliance

Overall Compliance

- For randomized treatments dispensed from the Ellipta DPI, 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 for a treatment period then the percentage compliance for that period will be calculated as:

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

  For randomized treatments dispensed from the Respimat, the number of doses of study treatment taken by each subject 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 for a treatment period then the percentage compliance for that period will be calculated as:

  $$\text{Compliance} = \frac{\text{sum of all (dose counter start – dose counter stop)} \times 100}{2 \times \text{(exposure stop date – exposure start date +1)}}$$

Compliance
• If any dose counter stop in a treatment period is missing then the treatment compliance will be set to missing for that period. • Overall compliance in each period will be categorised as follows: < 80 % ≥ 80 % to < 95 % ≥ 95 % to ≤105 % >105 % to ≤120 % >120 %.

10.6.3. Safety

Adverse Events

AEs of Special Interest

- AEs 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 randomization codes being released.

Special Interest AE Group/ Subgroup	SMQ Group
Cardiovascular effects/ Cardiac Arrhythmia	
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	
LRTI excluding pneumonia	
Ocular effects (antimuscarinic)	Glaucoma (SMQ)
Paradoxical bronchospasm	
Asthma/bronchospasm	
Urinary retention	

Extent of Exposure

Exposure Duration

- Number of days of exposure to study drug in each period 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 in that period is missing it will be assumed to be the

Extent of Exposure
latest recorded exposure start or stop date in that period. • If a subject's overall exposure start date is missing then it will be assumed to be their Day 1 visit date from that period. • 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 in each period. • 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: 1-27 days, >27-55 days, >55 days

10.6.4. Efficacy

Spirometry
Trough
• The trough value for FEV_1, FVC and IC at each of Week 4 and Week 8 is calculated from the values at the assessments made 23 h and 24 h after dosing on the previous day. • If the actual time of an assessment is after the time of dosing on the current day, the value will not be used in the calculation of trough for the PP population. • For the PP population, a value will additionally be excluded from the trough FEV_1 calculation if the assessment is outside the time window of 22.0-25.0 h after dosing on the previous day. • 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.
Proportion of responders according to FEV_1
• A subject will be a considered a responder according to trough FEV_1 if their trough FEV_1 value has increased by at least 100mL from baseline. • A subject will be considered a non-responder if their trough FEV_1 value has decreased, has not changed, or has increased by less than 100mL compared to baseline. • Missing data will be handled as detailed in Section 10.7.2

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 tables below show 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. See Section 10.4.1.1 for details on the assignment of treatment phases. To be used for rescue medication:

Calculation of Daily eDiary endpoints

Period	First day	Last day
Period 1 Baseline	Latest of (7 days before Visit 2 (Day 1) and day of Visit 1 (Screening))	Day before Visit 2 (Day 1)
Period 1 Week 1-2	Period study day 1 (day of Visit 2)	Period study day 14
Period 1 Week 3-4	Period study day 15	Period study day 28
Period 1 Week 5-6	Period study day 29	Period study day 42
Period 1 Week 7-8	Period study day 43	Earliest of (Period study day 55 and day before Visit 4)
Period 1 Week 1-8	Period study day 1 (day of Visit 2)	Earliest of (Period study day 55 and day before Visit 4)
Period 2 Baseline	Latest of (7 days before Visit 5 (Day 1) and day of Visit 4)	Day before Visit 5 (Day 1)
Period 2 Week 1-2	Period study day 1 (day of Visit 5)	Period study day 14
Period 2 Week 3-4	Period study day 15	Period study day 28
Period 2 Week 5-6	Period study day 29	Period study day 42
Period 2 Week 7-8	Period study day 43	Earliest of (Period study day 55 and day before Visit 7)
Period 2 Week 1-8	Period study day 1 (day of Visit 5)	Earliest of (Period study day 55 and day before Visit 7)

To be used for E-RS:

Period	First day	Last day
Period 1 Baseline	Latest of (7 days before Visit 2 (Day 1) and day of Visit 1 (Screening))	Day before Visit 2 (Day 1)
Period 1 Week 1	Period study day 1 (day of Visit 2)	Period study day 7
Period 1 Week 2	Period study day 8	Period study day 14
Period 1 Week 3	Period study day 15	Period study day 21
Period 1 Week 4	Period study day 22	Period study day 28
Period 1 Week 5	Period study day 29	Period study day 35
Period 1 Week 6	Period study day 36	Period study day 42
Period 1 Week 7	Period study day 43	Period study day 49
Period 1 Week 8	Period study day 50	Earliest of (Period study day 55 and day before Visit 4)

Calculation of Daily eDiary endpoints

Period 2 Baseline	Latest of (7 days before Visit 5 (Day 1) and day of Visit 4)	Day before Visit 5 (Day 1)
Period 2 Week 1	Period study day 1 (day of Visit 5)	Period study day 7
Period 2 Week 2	Period study day 8	Period study day 14
Period 2 Week 3	Period study day 15	Period study day 21
Period 2 Week 4	Period study day 22	Period study day 28
Period 2 Week 5	Period study day 29	Period study day 35
Period 2 Week 6	Period study day 36	Period study day 42
Period 2 Week 7	Period study day 43	Period study day 49
Period 2 Week 8	Period study day 50	Earliest of (Period study day 55 and day before Visit 7)

Mean Number of Puffs and Percentage Rescue Free Days via e-diary

- For rescue use, 'day' refers to the period between one record of rescue use and the next.
- A rescue-free day is defined as a day where the total puffs is 0.
- For each summary period, the mean number of puffs per day and the percentage of rescue free days, will be calculated, using the number of days with non-missing values for the endpoint as denominator.
- Rescue use will be summarised over the periods defined above.
- For a subject to be counted in any time period (except for baseline where at at least half the days within the summary period are required) for a given endpoint they must have at least one diary entry recorded for that endpoint during that time period.

Mean Number of Occurrences and Percentage Rescue Free Days via e-MDI

- A rescue-free day is defined as a day where the total number of puffs is missing.
- Occurrence is defined as >1 puff within a 2 minute time window.
- For each summary period, the mean number of occurrences per day and the percentage of rescue free days, will be calculated, using last dose-first dose+1 as denominator.
- Rescue use will be summarised over the periods defined above.

EXACT PRO

EXACT Respiratory Symptoms

- The EXACT-PRO (Evidera, 2016) is a 14-item daily diary (typically completed at bedtime). The daily E-RS total score (and subscales) will be computed according to the E-RS in COPD user manual [Evidera, 2016].
- The 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 weekly intervals defined above.
- Mean weekly score = (sum of daily scores/# diary days completed). If fewer than 4 days of data are available in any 7-day period, a mean weekly score should not be calculated. If fewer than 3 days worth of data are available in the 6-day period (day 50 to day 55) then a mean weekly score should not be calculated.

Calculation of Daily eDiary endpoints
E-RS Responder
• E-RS Total Score Responder: on-treatment weekly mean change from baseline E-RS total score ≤ -2 • E-RS Total Score Non-responder: on-treatment weekly mean change from baseline E-RS total score > -2 • E-RS Breathlessness Responder: on-treatment weekly mean change from baseline E-RS Breathlessness subscale score ≤ -1 • E-RS Breathlessness Non-responder: on-treatment weekly mean change from baseline E-RS Breathlessness subscale score > -1 • E-RS Cough Responder: on-treatment weekly mean change from baseline E-RS Cough & Sputum subscale score ≤ -0.7 • E-RS Cough Non-responder: on-treatment weekly mean change from baseline E-RS Cough & Sputum subscale score > -0.7 • E-RS Cough & Sputum Responder: on-treatment weekly mean change from baseline E-RS Chest Symptoms subscale score ≤ -0.7 • E-RS Cough & Sputum Non-responder: on-treatment weekly mean change from baseline E-RS Chest Sypmtoms subscale score > -0.7

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 a responder if their on-treatment CAT score has decreased at least 2 units from baseline CAT total score. • A subject will be considered a non-responder if their on-treatment CAT score has decreased by less than 2 units, has not changed, or has increased compared to baseline. • Missing data will be handled as detailed in Section 10.7.2.

Inhaler Assessment

Ease of Use

- Ease of Use questionnaire consists of 5 ordinal responses: very easy (1), easy (2), neutral (3), difficult (4) and very difficult (5), for each question. 'Very easy' is considered as the highest rating while 'very difficult' is considered as the lowest rating. Subjects answer each question regarding to ELLIPTA inhaler and 'Other' inhaler, respectively.

  An ordinal variable (ease_ord) will be derived to based on the ease of use rating for each inhaler and based on the sequence of inhaler use. This variable will be used in the statistical analysis for ease of use data.

- If the sequence of inhaler use is ELLIPTA inhaler in 1st period and RESPMIMAT inhaler in 2nd period, then for each ease of use question
  ease_ord = -1, if subject's ease of use rating for ELLIPTA inhaler is higher
  ease_ord = 1, if subject's ease of use rating for RESPMIMAT inhaler is higher
  ease_ord = 0, if subject's ease of use rating are the same with both inhalers

- If the sequence of inhaler use is RESPMIMAT inhaler in 1st period and ELLIPTA inhaler in 2nd period, then for each preference question
  ease_ord = 1, if subject's ease of use rating for ELLIPTA inhaler is higher
  ease_ord = -1, if subject's ease of use rating for RESPMIMAT inhaler is higher
  ease_ord = 0, if subject's ease of use rating are the same with both inhalers

Critical Error Variable

- Whether a subject had at least one critical error and at least one overall error (critical and non-critical) will be derived for each inhaler.
- Table below shows critical errors in bold.
- Responses in ( ) indicate an error.

Respimat	
Preparation for first use	(0 = No) 1 = Yes
Keep cap close. Press safety catch and pull off clear base	(0 = No) 1 = Yes
Cap still closed. Insert narrow end of cartridge into inhaler and gently push against a firm surface to ensure that it has gone all the way in	(0 = No) 1 = Yes
Cap still closed. Replace clear base	(0 = No) 1 = Yes
Cap still closed. Turn clear base in direction of the arrows on the label until you hear a click	(0 = No) 1 = Yes
Flip cap open until it clicks into open position	(0 = No) 1 = Yes

Critical Error Variable

Point inhaler towards ground and press dose release button. Close cap and repeat steps 4-6 until the mist is visible. Then repeat steps 4-6 another 3 times before use	(0 = No) 1 = Yes
Exhaled directly into mouthpiece	0 = No (1 = Yes)
No seal by the lips round the mouthpiece during the inhalation	0 = No (1 = Yes)
Daily Use	0 = No 1 = Yes (*Not applicable to derived errors as question not appropriate to study design)
Keep cap closed. Turn clear base in direction of the arrows on the label until you hear a click	(0 = No) 1 = Yes
Flip cap open until it clicks into open position	(0 = No) 1 = Yes
Breathe out slowly and fully then close your lips around mouthpiece	(0 = No) 1 = Yes
While taking in a slow deep breath press dose release button ; keep breathing in slowly	(0 = No) 1 = Yes
Close cap	(0 = No) 1 = Yes
Ellipta	
Failed to open cover	0 = No (1 = Yes)
Shook the device upside down after dose preparation	0 = No (1 = Yes)
No exhalation before an inhalation	0 = No (1 = Yes)
Exhaled directly into mouthpiece	0 = No (1 = Yes)
No seal by the lips round the mouthpiece during the inhalation	0 = No (1 = Yes)
Inhalation manoeuvre: - long - steady - deep	0 = No (1 = Yes)
Blocked air inlet during inhalation manoeuvre	0 = No (1 = Yes)
Did not hold breath	0 = No (1 = Yes)
Did not close the device (*Note: this is an error but one which does not affect the medication that is inhaled)*	0 = No (1 = Yes)

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

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion is defined as attendance at Visit 7. • Withdrawn subjects were not replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

10.7.2. 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 : o 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. o Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such. o No imputation will be made for any missing numerical data, except in the sensitivity analysis of primary endpoints to assess the impact of missing data on study results. 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).
Responder	• Subjects with a missing baseline will have responder status as missing. • Subjects with missing post-baseline data and a subsequent non-missing scheduled assessment will not be considered a responder or non-responder but will be left as missing. • 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.

10.7.2.1. Handling of Missing Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.

Element	Reporting Detail
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 period start date of study treatment; in this case the study treatment period 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 period stop date of study treatment; in this case the study treatment period 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.

10.7.2.2. 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: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ 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: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month. ○ However, if these results in a date prior to Week 1 Day 1 of the respective period and the event could possibly have occurred during treatment from the partial information, then the pWeek 1 Day 1 date for the respective period will be assumed to be the start date. ○ The AE will then be considered to start on-treatment (worst case). ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month unless this is after the period stop date of study treatment; in this case the period study treatment stop date will be used. • The recorded partial date will be displayed in listings.

10.7.2.3. Handling of Missing Data for Statistical Analysis

For analysis of trough FEV1 at Week 8, sensitivity analyses will be produced using tipping point methodology (Ratitch, 2013). These methods are detailed in Section 7.1.2.

10.8. Appendix 8: Multicenter Studies

10.8.1. Methods for Handling Centres

- This study will be randomized centrally.
- Results will be presented for all centres combined; centre will not be accounted for in statistical analyses.

10.9. Appendix 9: Examination of Covariates, Subgroups & Other Strata

10.9.1. Handling of Covariates

- Consistency of treatment effect across covariates fitted in the primary efficacy endpoint analysis models will be examined by fitting separate models to examine treatment by period baseline, treatment by mean baseline and treatment by period interactions.
- No formal statistical analysis of sub-groups of the study population will be performed.
- The interaction terms will be tested at the 10% significance level. Significant interactions (<0.10) will be investigated further, for example running the analysis by each category. Continuous covariates may be grouped into dichotomous categories (values above and below median).

10.10. Appendix 10: Multiple Comparisons & Multiplicity

10.10.1. Handling of Multiple Comparisons & Multiplicity

See Section 2.4 for details on inferences that can be drawn on primary and 'other' endpoints for non-inferiority and superiority.

10.11. Appendix 11: Model Checking and Diagnostics for Statistical Analyses

Distributional assumptions underlying the model used for analyses using MMRM (non binary data) 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.

10.12. Appendix 12 – Abbreviations & Trade Marks

10.12.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
A&R	Analysis and Reporting
ASE	All Subjects Enrolled
ATC	Anatomical-Therapeutic-Chemical
CAT	COPD Assessment Test
CI	Confidence Interval
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
DOB	Date of Birth
DP	Decimal Places
DPI	Dry Powder Inhaler
eCRF	Electronic Case Record Form
E-RS	EXACT Respiratory Symptoms
FEV_1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
IC	Inspiratory Capacity
ICH	International Conference on Harmonisation
ICS	Inhaled Corticosteroid
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
GUI	Guidance
KR	Kenwood Roger
LS	Least squares
mMRC	Modified Medical Research Council
MMRM	Mixed Model Repeated Measures
PD	Protocol Deviation
PDMP	Protocol Deviation Management Plan
PP	Per Protocol
QC	Quality Control
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SE	Standard Error
SOP	Standard Operation Procedure
TA	Therapeutic Area

Abbreviation	Description
TFL	Tables, Figures & Listings
GSK	GlaxoSmithKline
UMEC	Umeclidinium Bromide
VI	Vilanterol

10.12.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
ELLIPTA

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

10.13. Appendix 13: List of Data Displays

10.13.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.40	
Efficacy	2.1 to 2.48	2.1 to 2.13
Safety	3.1 to 3.23	
Section	**Listings**	
ICH Listings	1 to 17	
Other Listings	18 to 32	

10.13.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in a separate document.

Section	Figure	Table	Listing
Study Population	SP_Fn	SP_Tn	SP_Ln
Efficacy	E_Fn	E_Tn	E_Ln
Safety	S_Fn	S_Tn	S_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / TST ID / Example Shell' or 'Programming Notes' column using the reference convention detailed in this table.

10.13.3. Deliverable [Priority]

Delivery	Description
SAC	Final Statistical Analysis Complete

10.13.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliver-able**
Subject Disposition					
1.1.	ASE		Summary of Subject Populations and Reasons for Screen Failures		SAC
1.2.	ITT		Summary of Attendance at Each Clinic Visit		SAC
1.3.	ITT		Summary of Completion and Premature Discontinuation of Study Treatment		SAC
1.4.	ITT		Summary of Study Completion and Withdrawal		SAC
1.5.	ITT		Summary of Subject Discontinuation at Each Period		SAC
1.6.	ITT		Summary of Subject Withdrawal at Each Period		SAC
1.7.	ITT		Summary of Reasons for Discontinuation of Treatment at End of Each Period		SAC
1.8.	ITT		Summary of Reasons for Withdrawal at End of Each Period		SAC
1.9.	ITT	IDSL – NS3	Summary of Number of Subjects by Country and Centre	Replace 'Centre ID' header with 'Investigator at Centre'	SAC
Protocol Deviations					
1.10.	ASE	IDSL – IE2	Summary of Inclusion/ Exclusion/ Randomization Criteria Deviations for Screen or Run-in failures	Include 'Number of Screen or Run-in Failures' row at the top of the table. This is to be used as the denominator for the % calculations.	SAC
1.11.	ITT	IDSL – IE1	Summary of Inclusion/ Exclusion/ Randomization Criteria Deviations for Intent-to-treat		SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliver-able**
1.12.	ITT	SP_T09 (DV1A)	Summary of Important Protocol Deviations		SAC
1.13.	ITT	SP_T10	Summary of Exclusions from the Per Protocol Analysis		SAC
Demography					
1.14.	ITT	IDSL - DM1	Summary of Demographic Characteristics, Intent-to-treat		SAC
1.15.	PP	IDSL - DM1	Summary of Demographic Characteristics, Per Protocol		SAC
1.16.	ITT	IDSL - DM5	Summary of Race and Racial Combinations		SAC
1.17.	ITT	IDSL – DM6	Summary of Race and Racial Combination Details		SAC
1.18.	ASE	EMA Table 1	Summary of Number of Subjects Enrolled by Country	EMA Reporting Package. Macro: EMA_COUNTRY	SAC
1.19.	ASE	EMA Table 2	Summary of Number of Subjects Enrolled by Age Category	EMA Reporting Package. Macro: EMA_AGEGRP	SAC
Medical Condition & Concomitant Medications					
1.20.	ITT	IDSL – MH4	Summary of Current Medical Conditions		SAC
1.21.	ITT	IDSL – MH4	Summary of Past Medical Conditions		SAC
1.22.	ITT	SP_T11	Summary of Family History of Cardiovascular Risk Factors at Screening		SAC
1.23.	ITT	SP_T12	Summary of COPD History at Screening		SAC
1.24.	ITT	SP_T13	Summary of COPD Exacerbation History at Screening		SAC
1.25.	ITT	IDSL-SU1	Summary of Smoking History at Screening	Using Years Smoked, Cigarettes/Day and Smoking Pack Years	SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliver-able**
1.26.	ITT	SP_T14	Summary of Smoking Status at Screening		SAC
1.27.	ITT	SP_T15	Summary of COPD Concomitant Medications Not Given for a COPD Exacerbation Taken Before Run-in		SAC
1.28.	ITT	SP_T15	Summary of COPD Concomitant Medications Not Given for a COPD Exacerbation Taken During Run-in or Washout	Display treatments instead of total	SAC
1.29.	ITT	SP_T15	Summary of COPD Concomitant Medications Not Given for a COPD Exacerbation Taken On-treatment	Display treatments instead of total	SAC
1.30.	ITT	SP_T15	Summary of COPD Concomitant Medications Not Given for a COPD Exacerbation Taken Post-treatment		
1.31.	ITT	SP_T15	Summary of Concomitant Medications Given for a COPD Exacerbation Taken On-treatment	Display treatments instead of total	SAC
1.32.	ITT	SP_T15	Summary of Concomitant Medications Given for a COPD Exacerbation Taken During Washout	Display treatments instead of total	
1.33.	ITT	SP_T15	Summary of Concomitant Medications Given for a COPD Exacerbation Taken Post-treatment		
1.34.	ITT	IDSL – CM1	Summary of Non-COPD Concomitant Medications Taken On-treatment	Display ATC and ingredient by treatments	SAC
1.35.	ITT	IDSL – CM1	Summary of Non-COPD Concomitant Medications Taken Post-treatment	Display ATC and ingredient by total	SAC
Baseline Severity					
1.36.	ITT		Summary of Screening Lung Function Test Results		SAC
1.37.	ITT		Summary of GOLD Grade 1-4, GOLD mMRC Category A-D, GOLD CAT Category A-D and Reversibility at Screening		SAC
1.38.	ITT		Summary of Screening IC Results		SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliver-able**
1.39.	ITT		Summary of mMRC Dyspnoea Scale at Screening		SAC
Treatment					
1.40.	ITT		Summary of Overall Percentage Treatment Compliance		SAC

10.13.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliver-able**
Spirometry					
2.1.	PP	E_T01	Summary of Baseline FEV_1 (L), Per Protocol		SAC
2.2.	PP	E_T02	Summary of Trough FEV_1 (L), Per Protocol		SAC
2.3.	PP	E_T03	Analysis of Trough FEV_1 (L), Per Protocol		SAC
2.4.	PP	E_T04	Covariance Parameter Estimates for Repeated Measures Analysis of Trough FEV1 (L), Per Protocol		SAC
2.5.	PP	E_T05	Type III Tests of Fixed Effects for Repeated Measures Analysis of Trough FEV1 (L), Per Protocol		SAC
2.6.	PP	E_T06	Significance Levels for Interactions of Treatment with Period, Period Baseline and Mean Baseline for Trough FEV1 (L), Per Protocol		SAC
2.7.	ITT	E_T01	Summary of Baseline FEV_1 (L), Intent-to-treat		SAC
2.8.	ITT	E_T02	Summary of Trough FEV_1 (L), Intent-to-treat		SAC
2.9.	ITT	E_T03	Analysis of Trough FEV_1 (L), Intent-to-treat		SAC
	ITT	E_T04	Covariance Parameter Estimates for Repeated Measures Analysis of Trough FEV1 (L), Intent-to-treat		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliver-able**
2.10.	ITT	E_T05	Type III Tests of Fixed Effects for Repeated Measures Analysis of Trough FEV1 (L), Intent-to-treat		SAC
2.11.	ITT	E_T08	Summary and Analysis of Proportion of Responders according to FEV_1 (L)		SAC
2.12.	PP		Analysis of Trough FEV1 (L) , Tipping Point Sensitivity Analysis, Per Protocol		SAC
2.13.	ITT		Analysis of Trough FEV1 (L) , Tipping Point Sensitivity Analysis, Intent-to-treat		SAC
2.14.	ITT	E_T01	Summary of Baseline FVC (L)		SAC
2.15.	ITT	E_T02	Summary of Trough FVC (L)		SAC
2.16.	ITT	E_T03	Analysis of Trough FVC (L)		SAC
IC					
2.17.	ITT	E_T01	Summary of Baseline IC (L)		SAC
2.18.	ITT	E_T02	Summary of Trough IC (L)		SAC
2.19.	ITT	E_T03	Analysis of Trough IC (L)		SAC
Rescue Medication					
2.20.	ITT	E_T09	Summary of Mean Number of Puffs of Rescue Medication per Day using e-diary		SAC
2.21.	ITT	E_T10	Analysis of Mean Number of Puffs of Rescue Medication per Day over Weeks 1-8 using e-diary		SAC
2.22.	ITT	E_T11	Summary of Percentage Rescue-free Days using e-diary		SAC
2.23.	ITT	E_T12	Analysis of Percentage Rescue-free Days over		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliver-able**
			Weeks 1-8 using e-diary		
2.24.	ITT	E_T09	Summary of Mean Number of Puffs of Rescue Medication per Day using eMDI		SAC
2.25.	ITT	E_T11	Summary of Percentage Rescue-free Days using eMDI		SAC
CAT					
2.26.	ITT	E_T02	Summary of CAT Score	Include baseline	SAC
2.27.	ITT	E_T03	Analysis of CAT Score		SAC
2.28.	ITT	E_T08	Summary and Analysis of Proportion of Responders According to CAT		SAC
E-RS					
2.29.	ITT	E_T02	Summary of Weekly Mean E-RS Total Score		SAC
2.30.	ITT	E_T02	Summary of Weekly Mean E-RS - Breathlessness Score		SAC
2.31.	ITT	E_T02	Summary of Weekly Mean E-RS - Cough and Sputum Score		SAC
2.32.	ITT	E_T02	Summary of Weekly Mean E-RS - Chest Score		SAC
2.33.	ITT	E_T03	Analysis of Weekly Mean E-RS Total Score		SAC
2.34.	ITT	E_T03	Analysis of Weekly Mean E-RS - Breathlessness Score		SAC
2.35.	ITT	E_T03	Analysis of Weekly Mean E-RS - Cough and Sputum Score		SAC
2.36.	ITT	E_T03	Analysis of Weekly Mean E-RS - Chest Score		SAC
2.37.	ITT	E_T08	Summary and Analysis of Proportion of Responders According to E-RS Total Score		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliver-able**
2.38.	ITT	E_T08	Summary and Analysis of Proportion of Responders According to E-RS Breathlessness Score		
2.39.	ITT	E_T08	Summary and Analysis of Proportion of Responders According to E-RS Cough and Sputum Score		SAC
2.40.	ITT	E_T08	Summary and Analysis of Proportion of Responders According to E-RS Chest Score		SAC
Inhaler Ease of use					
2.41.	IN	(example 200301)	Summary of Ease of Use Questionnaire		SAC
2.42.	IN	(example 200301)	Summary and Analysis of Ease of Use Rating	Present by sequence and total	SAC
2.43.	IN	(example 200301)	Summary of Ease of Use Rating	Present by sequence and total (example 200301)	
Inhaler Errors					
2.44.	IN	(example 200301)	Summary of Errors for the ELLIPTA Inhaler	Raw questionnaire data	SAC
2.45.	IN	(example 200301)	Summary of Errors for the Respimat Inhaler	Raw questionnaire data	SAC
2.46.	IN	(example 200301)	Summary of Number of Subjects with at least One Error	Include critical and overall. Present by sequence and total	SAC

10.13.6. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliver-able**
Spirometry					
2.1.	PP	E_F01	Box Plot of Change from Baseline in Trough FEV1 (L) at Week 8, Per Protocol		SAC
2.2.	PP	E_F02	Empirical Distribution Function Plot of Change from Baseline in Trough FEV_1 (L) at Week 8, Per Protocol		SAC
2.3.	PP	E_F03	Least Squares Mean Change from Baseline (95% CI) in Trough FEV_1 (L), Per Protocol		SAC
2.4.	ITT	E_F01	Box Plot of Change from Baseline in Trough FEV_1 (L) at Week 8, Intent-to-treat		SAC
2.5.	ITT	E_F02	Empirical Distribution Function Plot of Change from Baseline in Trough FEV_1 (L) at Week 8, Intent-to-treat		SAC
2.6.	ITT	E_F03	Least Squares Mean Change from Baseline (95% CI) in Trough FEV_1 (L), Intent-to-treat		SAC
2.7.	ITT	E_F03	Least Squares Mean Change from Baseline (95% CI) in Trough FVC (L)		SAC
IC					
2.8.	ITT	E_F03	Least Squares Mean Change from Baseline (95% CI) in Trough IC (L)		SAC
CAT					
2.9.	ITT	E_F03	Least Squares Mean Change from Baseline (95% CI) in CAT Score		SAC

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliver-able**
E-RS					
2.10.	ITT	E_F03	Least Squares Mean (95% CI) Change from Baseline in Weekly Mean E-RS Total Score		SAC
2.11.	ITT	E_F03	Least Squares Mean (95% CI) Change from Baseline in Weekly Mean E-RS Breathlessness Score		SAC
2.12.	ITT	E_F03	Least Squares Mean (95% CI) Change from Baseline in Weekly Mean E-RS Cough and Sputum Score		SAC
2.13.	ITT	E_F03	Least Squares Mean (95% CI) Change from Baseline in Weekly Mean E-RS Chest Score		SAC

10.13.7. Safety Tables

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliver-able**
Adverse Events					
3.1.	ITT	S_T01	Overview of Adverse Events		SAC
3.2.	ITT	S_T02 (AE1)	Summary of On-treatment Adverse Events		SAC
3.3.	ITT	S_T02 (AE1)	Summary of Post-treatment Adverse Events	Include footnote 'Note: AEs with onset during the washout or follow-up period or following IP discontinuation are considered post-treatment and have been assigned to the treatment previously received.'	SAC
3.4.	ITT	S_T02 (AE1)	Summary of On-treatment Adverse Events Reported by 3% (after rounding) or More Subjects in Any Treatment		SAC
3.5.	ITT	S_T02 (AE1)	Summary of the 10 Most Frequent On-treatment Adverse Events in Each Treatment	Count most frequent number of events, not subjects and %. Sort by descending total incidence (sum of number of subjects with event).	SAC
3.6.	ITT	S_T02 (AE1)	Summary of On-treatment Drug Related Adverse Events		SAC
3.7.	ASE	S_T02 (AE1)	Summary of Pre-treatment Fatal Serious Adverse Events		SAC
3.8.	ITT	S_T02 (AE1)	Summary of On-treatment Fatal Serious Adverse Events		SAC
3.9.	ITT	S_T02 (AE1)	Summary of Post-treatment Fatal Serious Adverse Events	Include footnote 'Note: AEs with onset during the washout or follow-up period or following IP	SAC

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliver-able**
				discontinuation are considered post-treatment and have been assigned to the treatment previously received.'	
3.10.	ITT	S_T02 (AE1)	Summary of On-treatment Drug-related Fatal Serious Adverse Events		SAC
3.11.	ASE	S_T02 (AE1)	Summary of Pre-treatment Non-fatal Serious Adverse Events		SAC
3.12.	ITT	S_T02 (AE1)	Summary of On-treatment Non-fatal Serious Adverse Events		SAC
3.13.	ITT	S_T02 (AE1)	Summary of Post-treatment Non-fatal Serious Adverse Events	Include footnote 'Note: AEs with onset during the washout or follow-up period or following IP discontinuation are considered post-treatment and have been assigned to the treatment previously received.'	SAC
3.14.	ITT	S_T02 (AE1)	Summary of On-treatment Drug-related Non-fatal Serious Adverse Events		SAC
3.15.	ITT	S_T03	Summary of On-treatment Adverse Events of Special Interest		SAC
3.16.	ITT	S_T02 (AE1)	Summary of On-treatment Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from the Study		SAC
3.17.	ASE	S_T02 (AE1)	Summary of Pre-treatment Adverse Events Leading Withdrawal from the Study		SAC
3.18.	ASE	IDSL -AE2	Relationship between Adverse Event System Organ Class, Preferred Term and Verbatim Text		SAC

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliver-able**
3.19.	ASE	EMA Table 3	Summary of Non-serious Adverse Events > 3% (before rounding) in any treatment	EMA Reporting Package Macro: EMA_AE	SAC
3.20.	ASE	Standard EMA output	Summary of On-treatment Adverse Events Categories by Age Subgroup	EMA Reporting Package Macro: EMA_AE	SAC
COPD exacerbations					
3.21.	ITT	S_T04	Summary of On-treatment COPD Exacerbations		SAC
3.22.	ITT	S_T04	Summary of Post-treatment COPD Exacerbations	Include footnote 'Note: Exacerbations with onset during the washout or follow-up period or following IP discontinuation are considered post-treatment and have been assigned to the treatment previously received.'	SAC
Extent of Exposure					
3.23.	ITT	S_T05	Summary of Exposure		SAC

10.13.8. ICH Listings

For all listings replace 'Centre ID'/'Inv. ID' header with 'Investigator at Centre'/'Inv. at Centre'. The CENTREID variable should be used for this.

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Study Population: Subject Disposition					
1.	ITT	IDSL_ ES2	Listing of Reasons for Withdrawal		SAC
Study Population: Protocol Deviations					
2.	ITT		Listing of Important Protocol Deviations		SAC
3.	ASE	IDSL – IE3	Listing of Inclusion/ Exclusion/ Randomization Criteria Deviations		SAC
Study Population: Treatment					
4.	ITT	IDSL – TA1	Listing of Randomized and Actual Treatments		SAC
Study Population: Demography					
5.	ITT	IDSL – DM2	Listing of Demographic Characteristics	Include BMI as the optional measurement. In addition, include a country column as the first sort variable. A flag will be included to identify those subjects in the PP population.	SAC
6.	ITT	IDSL – DM9	Listing of Race	Include a country column as the first sort variable.	SAC
7.	ITT		Listing of Screening Lung Function Tests		SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Efficacy: Spirometry and IC					
8.	ITT		Listing of Raw FEV1 (L) and FVC (L) Data	Flags will be included to: 1. identify those subjects in the PP population;	SAC
9.	ITT		Listing of Raw IC (L) Data		SAC
Safety: Adverse Events					
10.	ASE	IDSL_ AE7	Listing of Subject Numbers for Individual Adverse Events		SAC
11.	ASE	IDSL_ AE8	Listing of All Adverse Events	Additional columns detailing questions for SAE variables will need to be added.	SAC
12.	ASE	IDSL_ AE8	Listing of Non-fatal Serious Adverse Events	Additional columns detailing questions for SAE variables will need to be added.	SAC
13.	ASE	IDSL_ AE8	Listing of Fatal Serious Adverse Events	Additional columns detailing questions for SAE variables will need to be added.	SAC
14.	ASE	IDSL_ AE8	Listing of Adverse Events leading to Discontinuation of Study Treatment or Withdrawal from the Study	Additional columns detailing questions for SAE variables will need to be added.	SAC
15.	ITT	IDSL_ AE8	Listing of On-treatment Drug-related AEs	Additional columns detailing questions for SAE variables will need to be added.	SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Safety: Extent of Exposure					
16.	ITT		Listing of Exposure		SAC
Safety: DPI Malfunctions					
17.	ITT		Listing of Potential DPI Inhaler Malfunctions		SAC

10.13.9. Non-ICH Listings

For all listings replace 'Centre ID'/'Inv. ID' header with 'Investigator at Centre'/'Inv. at Centre'. The CENTREID variable should be used for this.

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Study Population: Subject Disposition					
18.	ASE	IDSL - ES2	Listing of Reasons for Withdrawal – Subjects Randomized but Not in the ITT Population		SAC
19.	ITT		Listing of the Follow-up Contact		SAC
Study Population: Protocol Deviations					
20.	ITT		Listing of Exclusions from the Per-protocol Analysis		SAC

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
21.	ITT	IDSL – TA1	Listing of Treatment Misallocations	Change Centre ID to Investigator ID: xxxxxx And also Investigator at Centre: xxxxxx	SAC
Study Population: Treatment					
22.	ITT		Listing of Overall Percentage Treatment Compliance		SAC
23.	ITT	SP_L1	Listing of Subjects Who Discontinued Study Treatment		SAC
Study Population: Medical Conditions & Concomitant Medications					
24.	ITT	IDSL – MH2	Listing of Medical Conditions		SAC
25.	ITT		Listing of Family History of Cardiovascular Risk Factors		SAC
26.	ITT		Listing of COPD History		SAC
27.	ITT		Listing of Smoking History and Smoking Status		SAC
28.	ITT	IDSL_ CM2	Listing of COPD Concomitant Medications		SAC
29.	ITT	IDSL_ CM2	Listing of non-COPD Concomitant Medications		SAC
30.	ITT	IDSL – CM6	Relationship between ATC Level 1, Ingredient and Verbatim Text for Non-COPD Medications		SAC

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Study Population: Baseline Severity					
31.	ITT		Listing of GOLD Grade/Categories and Reversibility		SAC
32.	ITT		Listing of mMRC Dyspnoea Scale at Screening		SAC
Efficacy: Spirometry and IC					
33.	ITT		Listing of Derived FEV_1 (L)		SAC
34.	ITT		Listing of Derived FVC (L)		SAC
35.	ITT		Listing of Derived IC (L)		SAC
Efficacy: eDiary endpoints					
36.	ITT		Listing of Derived Rescue Endpoints		SAC
37.	ITT		Listing of E-RS Scores		SAC
38.	ITT		Listing of Derived E-RS Scores		SAC
QoL: CAT					
39.	ITT		Listing of CAT Scores		SAC
Inhaler Assessments					
40.	ITT		Listing of Errors on ELLIPTA Inhaler	Indicate IN pop flag	SAC
41.	ITT		Listing of Errors on Respimat Inhaler	Indicate IN pop flag	SAC
42.	ITT		Listing of Derived Error Data	Indicate IN pop flag	SAC
43.	ITT		Listing of Ease of Use Questionnaire Data	Indicate IN pop flag	SAC

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Safety					
44.	ITT	IDSL_ VS4	Listing of Vital Signs		SAC
45.	ITT		Listing of ECG Values	Just list screening values	SAC
46.	ITT		Listing of COPD Exacerbations		SAC
Safety: Pneumonia					
47.	ITT	IDSL_ VS4	Listing of Chest X-ray Data		SAC
48.	ITT		Listing of all Pneumonia Data		SAC
Safety: Liver Events					
49.	ITT	IDSL_ VS4	Listing of Liver Events		SAC
50.	ITT		Listing of Virology		SAC

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Safety: Cardiovascular Events					
51.	ITT	IDSL_ VS4	Listing of Myocardial infarction/unstable angina		SAC
52.	ITT		Listing of Congestive heart failure		SAC
53.	ITT	IDSL_ VS4	Listing of Arrhythmias		SAC
54.	ITT		Listing of Valvulopathy		SAC
55.	ITT	IDSL_ VS4	Listing of Pulmonary hypertension		SAC
56.	ITT		Listing of Cerebrovascular events/stroke and transient ischemic attack		SAC
57.	ITT		Listing of Peripheral arterial thromboembolism		SAC
58.	ITT	IDSL_ VS4	Listing of Deep venous thrombosis/pulmonary embolism		SAC
59.	ITT		Listing of Revascularisation		SAC
60.	ITT	IDSL_ VS4	Listing of All cause deaths		SAC