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

Title	:	Reporting and Analysis Plan for study 206854: The Clinical Effectiveness of Fluticasone Furoate/Umeclidinium Bromide/ Vilanterol in a Single Inhaler (TRELEGY™ ELLIPTA™) when Compared with Non-ELLIPTA Multiple Inhaler Triple Therapies in COPD Patients within a Usual Care Setting.
Compound Number	:	GSK2834425 (GW685698+GSK573719+GW642444)
Effective Date	:	30-Oct-2019

Description:

- The purpose of this document is to describe the planned analyses and output to be included in the Clinical Study Report (CSR) for study 206854 (INTREPID: I**N**vestigation of **TR**ELEGY **E**ffectiveness: Usual **P**ract**I**ce **D**esign).
- This RAP is intended to describe the effectiveness and safety analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

RAP Author(s):

Author
PPD Statistician, Clinical Statistics

- **RAP Team Review Confirmations (Method: E- mail):**

Reviewer	Date
PPD Statistics Leader, Clinical Statistics	16-Oct-2019
PPD Programming Manager, Clinical Programming	14-Oct-2019
PPD RW Clinical Development Director (CIL)	13-Oct-2019
PPD Clinical Development Physician (MM)	14-Oct-2019
PPD RW Clinical Study Manager (OSL)	14-Oct-2019
PPD Principal Clinical Data Manager (DQL)	15-Oct-2019
PPD Safety Scientist, SERM, Safety and Medical Governance	15-Oct-2019
PPD Global Medical Director, COPD, Respiratory	14-Oct-2019
PPD Director, Patient Reported Outcomes, VEO	15-Oct-2019

- **Clinical Statistics & Clinical Programming Line Approvals (Method: Pharma TMF eSignature):**

Approver	Date
PPD Senior Statistics Director, Clinical Statistics	29-Oct-2019
PPD Programming Manager, Clinical Programming (Delegated to PPD, Director Clinical Programming, Statistical Programming & Governance)	30-Oct-2019

TABLE OF CONTENTS

PAGE

1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report (CSR) for study 206854 for Protocol:

Revision Chronology:		
2017N321744_00	06-NOV-2017	Original
2017N321744_01	15-FEB-2018	Amendment 1
2017N321744_02	28-SEP-2018	Amendment 2

Note that in line with the Protocol, this RAP will use the term "Participant" (except Appendix 9: List of Data Displays), while all data displays (Tables, Figures & Listings) produced as part of the planned dry-run and the Statistical Analysis Complete (SAC), will use the term "Subject" which reflects GSK Data Display Standards terminology.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the original protocol (Dated: 06-NOV-2017), protocol amendment 1 (Dated: 15-FEB-2018) and protocol amendment 2 (Dated 28-SEP-2018) 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**
Other Endpoint: Proportion of responders who experience CID. (Section 2.2)	**Other Endpoint:** Proportion of participants who experience CID.	The CID is a negative outcome and so the use of word "responder" may be misleading. Wording has been updated in the RAP to avoid misinterpretation.
Exploratory Endpoint: Numerical correlation of CE with CAT, moderate/severe exacerbations and FEV_1 (Section 2.2)	**Exploratory Endpoint:** Association of CE with CAT score, moderate/ severe exacerbations, FEV_1 and FVC	No formal statistical analysis was planned for this exploratory endpoint. Association between the endpoints will be investigated through graphical representation of the data and data summarisation (frequency tables as defined in Section 7.4.1)
Analysis Populations - FEV1: All members of the ITT population for whom an FEV_1 assessment was planned.	**Analysis Populations - FEV_1:** All members of the ITT population for whom a spirometry assessment was performed at any of Visit 1 or	Change of population definition to be consistent with the information collected in the study eCRF.

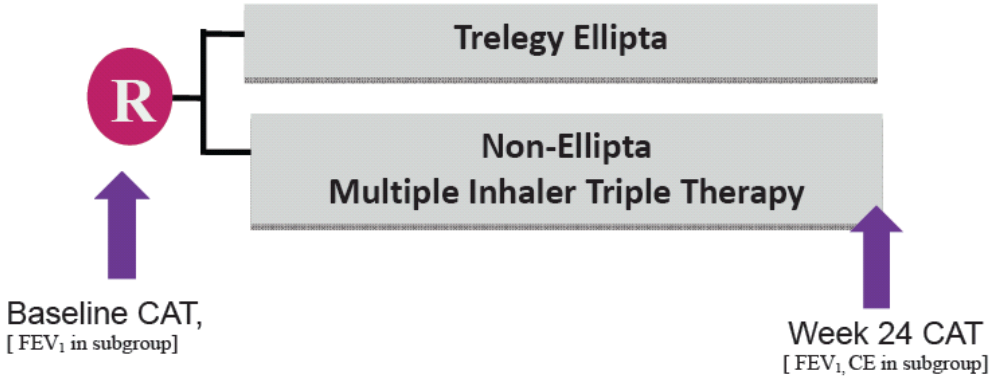
Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
	Visit 2. **Note:** If at least a single record exists in the electronic spirometry data provided for a participant then this constitutes evidence that spirometry measurements were taken (or attempted to be taken). The FEV_1 value may still be missing.	
Analysis Populations - CE: All members of the ITT population for whom a critical error assessment was planned. Note that participants within selected centres performing inhaler assessments who are not on an inhaler for which an error checklist is available will not be included in this population.	**Analysis Populations - CE:** All members of the ITT population for whom a critical error assessment was performed at Visit 2. **Note:** Participants within selected centres performing inhaler assessments who are not on an inhaler for which an error checklist is available will not be included in this population. Also, participants who are on more than one device must perform an assessment for all devices to be included in the population.	Change of population definition to be consistent with the information collected in the study eCRF.

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
To compare the effectiveness of TRELEGY ELLIPTA with non-ELLIPTA MITT for the impact of COPD on wellbeing and daily life after 24 weeks' treatment	Proportion of responders based on the COPD Assessment Test (CAT) at week 24. Response defined as change from baseline of CAT score ≥2 at 24 weeks
Secondary Objectives	**Secondary Endpoints**
To compare the effectiveness of TRELEGY ELLIPTA with non-ELLIPTA MITT on lung function after 24 weeks' treatment	Change from baseline in FEV_1 at 24 weeks (in a subset of participants)
To compare critical errors (CE) made by study participants using the ELLIPTA inhaler with participants using selected non-ELLIPTA MITT after 24 weeks' treatment	Percentage of participants making at least 1 critical error in inhalation technique at 24 weeks (in a subset of participants)
Other Objectives	**Other Endpoints**
To compare TRELEGY ELLIPTA with inhaled non-ELLIPTA MITT for a clinically	Proportion of participants who experience CID. CID is a composite outcome defined as any one of the following

Objectives	Endpoints
important deterioration (CID)	events: ▪ 100 mL reduction from baseline in FEV_1 at 24 weeks ▪ An exacerbation (requiring treatment with antibiotics and/or systemic steroids or hospitalisation) ▪ 2 units change (increase) from baseline in CAT score at 24 weeks
To quantify the incidence, rate and time to first moderate/severe COPD exacerbation for study participants on TRELEGY ELLIPTA compared with participants on non-ELLIPTA MITT	▪ Annualised rate of moderate/severe exacerbations (defined as: requiring treatment with antibiotics and/or systemic steroids or hospitalisation). ▪ Time to first moderate /severe exacerbation (defined as: requiring treatment with one or more of the following: antibiotics, systemic steroids, hospitalisation)
To compare the effectiveness of TRELEGY ELLIPTA with non-ELLIPTA MITT for COPD-related Healthcare Resource Utilisation (HCRU)	The frequency of COPD related HCRU including: ▪ Primary healthcare contacts. ▪ COPD related medication. ▪ Hospital admissions, outpatient appointments and A&E attendances. **Exploratory:** frequency of HCRU assessed using electronic health records.
Exploratory Objectives	**Exploratory Endpoints**
To assess the data for correlation between critical errors and clinical outcomes	Association of CE with CAT score, moderate/ severe exacerbations FEV_1 and FVC
To describe the participant study experience	Participant Treatment and Study Satisfaction Questionnaire at 24 weeks/EW Visit.
To describe the change from baseline in patient Health Related Quality of Life	Health Related Quality of Life Questionnaire
Safety Objectives	**Safety Endpoints**
To compare safety for study participants using the ELLIPTA inhaler with participants using non-ELLIPTA MITT after 24 weeks' treatment	▪ All serious adverse events ▪ Study treatment related adverse events ▪ Adverse events that lead to withdrawal from study treatment

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	This is a phase IV, randomised, open-label, effectiveness, study of 24 weeks duration in COPD patients to evaluate TRELEGY ELLIPTA [FF/UMEC/VI: 100mcg/62.5mcg/25mcg] inhalation powder taken once daily using a single ELLIPTA inhaler compared with any non-ELLIPTA Multiple Inhaler Triple Therapy (MITT) in the usual care setting. Participants who meet the study entry criteria will be invited to join the study by their physician. Those who give their informed consent will be assessed for eligibility. Study treatment is defined as the COPD maintenance therapy that the patient is prescribed whilst enrolled in the study from randomisation to the 24 week/EW visit. Patients meeting eligibility criteria will be randomised to receive 24 weeks prescription cover for one of the following: ▪ TRELEGY ELLIPTA ▪ non-ELLIPTA MITT Participants should remain on the treatment to which they are randomised. If this is not possible, then at the investigator's discretion, the participant may change treatment to a preferred alternative treatment (see Protocol, Section 5.2.1). If the preferred alternative treatment is, in the opinion of the treating physician, unsuitable for the participant, then treatment can be changed to a non-preferred alternative. A change in study treatment should not result in withdrawal from the study. All participants should remain in the study and complete the 24-week visit. If this is not possible then an EW visit should be completed.
Dosing	**TRELEGY ELLIPTA:** FF/UMEC/VI: 100mcg/62.5mcg/25mcg once daily (QD). **Non-ELLIPTA MITT:** ICS/LAMA/LABA products and dosing regimens as prescribed by their physician twice daily.
Time & Events	Appendix 2: Schedule of Activities

Overview of Study Design and Key Features	
Treatment Assignment	A participant will be assigned a subject number at the time the informed consent is signed in accordance with the randomisation schedule. Once a subject number is assigned to a participant it cannot be reassigned to any other participant in the study. The randomisation schedule will be generated using RANDALL NG and all participants will be centrally randomised using an Interactive Web Response System (IWRS), RAMOS NG. Randomisation (1:1) will be stratified by the "*Prior Treatment Therapy*" (treatment the participants receive prior to screening; ICS/LABA or LAMA/LABA or ICS/LAMA/LABA) with dynamic blocking allocation by Country.
Interim Analysis	No interim analysis is planned.

2.4. Statistical Hypotheses / Statistical Analyses

The primary objective of this study is to evaluate the effectiveness of TRELEGY ELLIPTA versus non-ELLIPTA MITT in COPD patients in a pragmatic setting over 24 weeks. The study will provide evidence to support HCP and payer discussions that TRELEGY ELLIPTA is more effective on CAT improvement than non-ELLIPTA MITT in a patient population representative of everyday clinical practice.

The primary effectiveness outcome is the proportion of CAT responders at week 24 (Visit 2) and the primary treatment comparison is TRELEGY ELLIPTA versus non-ELLIPTA MITT for
all participants.

In addition, other exploratory treatment comparisons of TRELEGY ELLIPTA with non-ELLIPTA MITT will be performed for the prior treatment stratification levels of ICS/ LABA/LAMA, ICS/LABA and LABA/LAMA separately for the primary outcome only.

The null hypothesis is that there is no difference in the proportion of CAT responders at week 24 between TRELEGY ELLIPTA and non-ELLIPTA MITT:

H0: T1 – T2 = 0

The alternative hypothesis is that there is a difference between treatment groups:

H1: T1 – T2 ≠ 0

where T1 and T2 are, the treatment means for TRELEGY ELLIPTA and non-ELLIPTA MITT respectively.

3. PLANNED ANALYSES

3.1. Interim Analyses

There are no interim analyses planned.

3.2. Final Analyses

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

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

This is an effectiveness study that collects data differently to a traditional clinical trial and also allows participants' Investigational Product (IP) to be modified during the study. The trial design (open label) and the ways the study medication data are recorded in the datasets means that steps must be taken to ensure that Statistics and Programming (S&P) remain blinded to study investigator prescribing of study medication until the S&P unblinding (i.e., review of unblinded datasets) takes place at DBR. Formal unblinding via RandALL will occur immediately prior to DBF, per standard practice. Details on the blinding strategy are included in the Blinding Strategy Charter.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Subjects Enrolled (ASE)	All participants for whom a record exists in the study database, including screen failures.	Study Population
Intent-to-Treat (ITT)	All randomised participants, excluding those who were randomised in error. A participant who is recorded as a screen failure and also randomised will be considered to be randomised in error. Any other participant who receives a randomisation number will be considered to have been randomised. Displays will be based on the treatment to which the participant was randomised unless otherwise stated.	Study Population Primary, Exploratory and Other Effectiveness Safety
FEV1	All members of the ITT population for whom a spirometry assessment was performed at any of Visit 1 or Visit 2. **Note:** If at least a single record exists in the electronic spirometry data provided for a participant then this constitutes evidence that spirometry measurements were taken (or attempted to be taken). The FEV_1 value	Secondary Effectiveness

Population	Definition / Criteria	Analyses Evaluated
	may still be missing.	
CE	All members of the ITT population for whom a critical error assessment was performed at Visit 2. **Note:** Participants within selected centres performing inhaler assessments who are not on an inhaler for which an error checklist is available will not be included in this population. Also, participants who are on more than one device must perform an assessment for all devices to be included in the population.	Secondary Effectiveness
Refer to Appendix 9: List of Data Displays which details the population used for each display.		

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (PDMP)

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations 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 Electronic Case Report Form (eCRF).

A listing of any treatment misallocations will be produced for the ITT population.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
1	Ellipta FF/UMEC/VI 100mcg/62.5mcg/25mcg QD	FF/UMEC/VI 100/62.5/25	1
2	Non-Ellipta Multiple Inhaler Triple Therapy (MITT) Usual Care	Non-Ellipta MITT	2
Treatment comparisons will be displayed as follows using the descriptors as specified: • FF/UMEC/VI 100/62.5/25 vs Non-Ellipta MITT			

5.2. Baseline Definitions

For all endpoints, the baseline value will be the value recorded at Visit 1 (Screening & Randomisation).

For the primary endpoint, baseline COPD Assessment Test (CAT) score will be the CAT score recorded at the CAT assessment at Visit 1. Note that for cases where a CAT assessment was not performed at Visit 1 as per Protocol and a historical CAT score was recorded in the eCRF by the Investigator instead, if the date of the historical CAT assessment was more than 14 days prior to Visit 1, then the baseline CAT score data will be considered as missing for the participant and will not be included in the analyses of the primary endpoint.

For the secondary endpoints of FEV_1 and Trough FEV_1, baseline FEV_1 and baseline Trough FEV_1 will be the pre-bronchodilator FEV_1 and pre-bronchodilator Trough FEV_1 value recorded from the spirometry performed at Visit 1, respectively.

If multiple pre-bronchodilator FEV_1 or Trough FEV_1 records exist for a participant at Visit 1, the latest record that is on or prior to the randomised treatment start date will be considered as baseline (see Section 10.6.3).

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

5.3. Multicentre Studies

In this multicentre global study, enrolment will be presented by country and investigative site, unless otherwise specified.

5.4. Examination of Covariates, Other Strata and Subgroups

The list of covariates and other strata to be used in statistical analyses is as described in table below, unless otherwise specified in Section 7.

Category	Details
Strata	The study randomisation will be stratified based on the treatment the participants receive prior to screening: ▪ ICS/LABA, ▪ LABA/LAMA or ▪ ICS/LAMA/LABA
Covariates	Primary endpoint of CAT score: ▪ Baseline CAT score ▪ Number of exacerbations in the prior year (categorical, see Section 10.6.2) ▪ Prior medication use strata (actual strata, see Section 10.6.2) ▪ Country Secondary endpoint of FEV_1: ▪ Baseline FEV_1 score ▪ Prior medication use strata (actual strata, see Section 10.6.2) ▪ Country ▪ Timing of Spirometry (see Section 7.2.1.5.1) Secondary endpoint of Trough FEV_1: ▪ Baseline Trough FEV_1 score ▪ Prior medication use strata (actual strata, see Section 10.6.2) ▪ Country Secondary endpoint of Critical Errors: ▪ Country ▪ Prior medication use strata (actual strata, see Section 10.6.2) Other endpoint of proportion of participants who experience a CID: ▪ Country ▪ Prior medication use strata (actual strata, see Section 10.6.2) ▪ Baseline Trough FEV1 ▪ Baseline CAT score ▪ Number of exacerbations in the prior year (categorical, see Section 10.6.2) Consideration will be given around other exploratory covariates for the study endpoints in a supplementary RAP.

5.4.1. Examination of Subgroups

No subgroups are considered in this RAP. Consideration of subgroups to be used in descriptive summaries and statistical analyses will be given in a supplementary RAP.

5.5. Multiple Comparisons and Multiplicity

There is a single primary endpoint and treatment comparison, so no adjustment for multiplicity is required for the primary effectiveness comparison.

With regards to the secondary, other and exploratory endpoints, inference will only be made if the primary analysis achieves significance. Inference for secondary, other or exploratory endpoints will then be made at the 5% significance level. Otherwise results will be for descriptive purposes only.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

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

Section	Component
10.3	Appendix 3: Assessment Windows
10.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
10.5	Appendix 5: Data Display Standards & Handling Conventions
10.6	Appendix 6: Derived and Transformed Data
10.7	Appendix 7: Reporting Standards for Missing Data

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the Intent-to-Treat (ITT) population (as defined in Section 4), unless otherwise specified.

Study population analyses including descriptive statistics of participant's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 9: List of Data Displays.

In addition, Section 10.6.2 includes details with regards to derivation of data for the study population analyses.

7. EFFECTIVENESS ANALYSES

7.1. Primary Effectiveness Analyses

7.1.1. COPD Assessment Test (CAT) Score

CAT score data are collected at Visit 1 (prior to randomisation) and at Visit 2/ EW visit. If participants are not able to attend the clinic visit at Visit 1, CAT assessment data can be collected at a domiciliary visit instead. If participants are not able to attend the clinic visit at Visit 2, CAT assessment can be performed at a domiciliary visit or at a telephone call.

Visit 1 or Visit 2 CAT score data collected at a domiciliary visit will be used in the statistical analysis and will also be included in data summaries and listings.

Visit 2 CAT score data collected at a telephone call, will not be considered for use in the statistical analyses, unless otherwise stated. This data will not be included in data summaries but will be included in listings.

CAT score data collected during assessments that are considered as EW assessments, will not be considered for use within the statistical analyses, unless otherwise stated. CAT score data collected during EW assessments will be included in data summaries and listings.

7.1.1.1. Endpoint / Variables

The primary endpoint will be the proportion of responders based on CAT at week 24 (Visit 2).

7.1.1.2. Summary Measure

The summary measure used for the treatment comparison will be an Odds Ratio (OR) and a 95% CI.

7.1.1.3. Population of Interest

The analysis will be based on the Intent-to-Treat (ITT) population (as defined in Section 4), unless otherwise specified.

7.1.1.4. Strategy for Intercurrent (Post-Randomisation) Events

The **list of intercurrent events/events leading to missing data** that may occur during the study and may affect the estimation of the treatment effect are:

- **Randomised Treatment Discontinuation:** participants may discontinue randomised COPD maintenance therapy and continue in the study without being prescribed another COPD maintenance therapy. This is considered an intercurrent event.
- **Randomised Treatment Modification**: participants may discontinue randomised COPD maintenance therapy and get prescribed another COPD maintenance therapy during the study. This is considered an intercurrent event.

- **Pulmonary Rehabilitation**: participants may change pulmonary rehabilitation status during the study. E.g., Participant considered to be undergoing pulmonary rehabilitation at Visit 1 but stopped during the study and so no longer on pulmonary rehabilitation at Visit 2. See Section 10.6.3 for definition of pulmonary rehabilitation status at Visit 1 and at Visit 2. This is considered an intercurrent event.
- **Oxygen Therapy**: If participants start oxygen therapy during the study and they have not had another oxygen therapy prior to the study start, this is considered as an intercurrent event. If participants start oxygen therapy during the study but they have recorded another oxygen therapy prior to the study start, this is not considered as an intercurrent event.
- **Early Withdrawal from Study**: participants may prematurely withdraw from the study which results in missing endpoint data.
- **Week 24 CAT Score not Available (other reasons than EW)**: CAT score at week 24 (Visit 2) may not be available for other reasons (not EW).

The strategies for handling these events for this endpoint are described in Table 2.

Table 2 Strategies for handling intercurrent events/events leading to missing data for the primary endpoint of proportion of CAT responders at week 24

	Intercurrent Events				Missing Data	
Estimand	**Randomised Treatment Discontinuation**	**Randomised Treatment Modification**	**Pulmonary Rehabilitation**	**Oxygen Therapy**	**Study Withdrawal**	**Week 24 CAT Score not Available**
Treatment Policy x Composite	Week 24 CAT score data to be used in the analysis regardless of the intercurrent event of randomised treatment discontinuation. (Treatment Policy)	If participants modify their randomised treatment during the study, they will be considered as non-responders for the week 24 CAT score. (Composite)	If participants change pulmonary rehabilitation status during the study, they will be considered as non-responders for the week 24 CAT score. (Composite)	If participants start oxygen therapy during the study and they have not had another oxygen therapy prior to the study start, they will be considered as non-responders for the week 24 CAT score. (Composite)	Missing week 24 CAT score data will be imputed based on the randomised treatment arm characteristics. This assumes MAR. See details in Section 10.7.2.	Missing week 24 CAT score data will be imputed based on the randomised treatment arm characteristics. This assumes MAR. See details in Section 10.7.2.

This primary estimand for the primary endpoint of week 24 CAT score will assess the randomised treatment effect, handling differently each of the intercurrent events/events leading to missing data described in Table 2 above.

7.1.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 9: List of Data Displays and will be based on GSK data standards and statistical principles.

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

7.1.1.5.1. Statistical Methodology Specification

Endpoint / Variables
Proportion of responders based on the COPD Assessment Test (CAT) score at week 24 (Visit 2). For definition of CAT responders, see Section 10.6.3.
Model Specification
The primary endpoint of proportion of CAT responders at week 24 will be analysed for the ITT Population using a logistic regression model with treatment as an explanatory variable and baseline CAT score (continuous), number of exacerbations in the prior year (categorical, see Section 10.6.2), prior medication use strata (categorical, see Section 10.6.2) and country (categorical) included as covariates. **Interaction Testing**: For the primary estimand, interactions between treatment and other factors will be investigated as follows by adding interaction terms to the model defined above. Separate models will be fitted to investigate the effect of treatment by covariate interactions: (i) with the addition of an interaction term for Treatment by Baseline CAT score, (ii) with addition of interaction term for Treatment by Number of Exacerbations in the Prior Year, (iii) with addition of interaction term for Treatment by Prior Medication Use Strata, (iv) with addition of interaction term for Treatment by Country. **Note:** The logistic regression model described for the primary analysis above will be used, with the addition of each specific interaction term. No multiple imputation will be performed for missing week 24 CAT score data. The p-value for each interaction test will be presented. If any interaction p-value is less than 0.10 further investigations will be carried out, for example running the analysis by each category of the subgroup. Any outputs from interaction investigation will also be presented.
Model Results Presentation
The odds ratio, 95% CI and p-value will be presented for the comparison between treatment arms. It will be based on a two-sided hypothesis testing approach of superiority.
Model Checking & Diagnostics
For the primary estimand, the model assumptions will be assessed by performing a logistic regression analysis using the primary estimand model specified in the *Model Specification* section above. No multiple imputation will be performed for the missing CAT score data at week 24. The Pearson residuals from this

analysis will be plotted.

Supportive Analyses

Additional supportive estimands will be defined for the primary endpoint of CAT score. The variable/endpoint, the summary measure and the population of interest for the supportive estimands will be as defined in Section 7.1.1.1, Section 7.1.1.2 and Section 7.1.1.3, respectively. The strategies for handling the intercurrent events/events leading to missing data for each of these supportive estimands are as described below:

Supportive Estimand I (Treatment Policy x Composite):

	Intercurrent Events				Missing data	
Estimand	**Randomised Treatment Discontinuation**	**Randomised Treatment Modification**	**Pulmonary Rehabilitation**	**Oxygen Therapy**	**Study Withdrawal**	**Week 24 CAT Score not Available**
Treatment Policy x Composite	Week 24 CAT score data to be used in the analysis regardless of the intercurrent event of randomised treatment discontinuation. (Treatment Policy)	Week 24 CAT score data to be used in the analysis regardless of the intercurrent event of randomised treatment modification. (Treatment Policy)	Week 24 CAT score data to be used in the analysis regardless of the intercurrent event of change of pulmonary rehabilitation status during the study. (Treatment Policy)	Week 24 CAT score data to be used in the analysis regardless of the intercurrent event of start oxygen therapy during the study. (Treatment Policy)	If participants prematurely withdraw from study, they will be considered as non-responders for the week 24 CAT score. (Composite)	If week 24 CAT score data are missing for other reasons than EW, participants will be considered as non-responders for the week 24 CAT score. (Composite)

Supportive Estimand I, will use the actual values of the week 24 CAT score, regardless of whether the intercurrent events described in the table above occurred in the study. A more conservative approach for the missing data will be followed, where participants with missing week 24 CAT score (because of EW or other reasons) will be considered as non-responders (composite strategy).

Supportive Estimand II (Treatment Policy x Composite):

	Intercurrent Events				Missing data	
Estimand	**Randomised Treatment Discontinuation**	**Randomised Treatment Modification**	**Pulmonary Rehabilitation**	**Oxygen Therapy**	**Study Withdrawal**	**Week 24 CAT Score not Available**
Treatment Policy x Composite	Week 24 CAT score data to be used in the analysis regardless of the intercurrent event of randomised treatment discontinuation.	If participants modify their randomised treatment during the study, they will be considered as non-responders	Week 24 CAT score data to be used in the analysis regardless of the intercurrent event of change of pulmonary	Week 24 CAT score data to be used in the analysis regardless of the intercurrent event of start	Missing week 24 CAT score data will be imputed based on the randomised treatment arm characteristics. This assumes	Missing week 24 CAT score data will be imputed based on the randomised treatment arm characteristics. This assumes

	(Treatment Policy)	for the week 24 CAT score. (Composite)	rehabilitation status during the study. (Treatment Policy)	oxygen therapy during the study. (Treatment Policy)	MAR. See details in Section 10.7.2.	MAR. See details in Section 10.7.2.

Supportive Estimand II, will use the actual values of the week 24 CAT score, regardless of whether the intercurrent events of randomised treatment discontinuation, change of pulmonary rehabilitation status or start of oxygen therapy have occurred during the study, but a composite strategy will be followed for the intercurrent event of randomised treatment modification. This is to assess the effect of the intercurrent event of randomised treatment modification on the estimate of the treatment effect. The same imputation approach as the one used for the primary estimand (Section 7.1.1.4) will be performed for missing CAT score data at week 24.

Supportive Estimand III (Hypothetical):

	Intercurrent Events				Missing data	
Estimand	**Randomised Treatment Discontinuation**	**Randomised Treatment Modification**	**Pulmonary Rehabilitation**	**Oxygen Therapy**	**Study Withdrawal**	**Week 24 CAT Score not Available**
Hypothetical	Ignore actual week 24 CAT score record. Assume is missing at random (MAR) and impute week 24 CAT score as what would have been if participant would not have discontinued from randomised study treatment.	Ignore actual week 24 CAT score. Assume is MAR and impute week 24 CAT score as what would have been if participant would not have modified the randomised treatment.	Ignore actual week 24 CAT score. Assume is MAR and impute week 24 CAT score as what would have been if participant would not have changed pulmonary rehabilitation status.	Ignore actual week 24 CAT score. Assume is MAR and impute week 24 CAT score as what would have been if participant would not have started oxygen therapy.	Missing week 24 CAT score data will be imputed assuming is MAR and impute values as what would have been if participant would not have withdrawn early from study.	Missing week 24 CAT score data will be imputed assuming is MAR and impute week 24 CAT score as what would have been if participant had an available CAT score at week 24.

Supportive Estimand III, will assess the treatment effect that would have been observed in a hypothetical scenario where no participants experienced the intercurrent events/events leading to missing data described in table above. This method fits a Bayesian normal repeated measures model and then imputes missing week 24 CAT scores assuming that the data is missing at random (i.e. that the participant continues to be treated with their randomised treatment). The imputed and "real"/ available data will be analysed and summarised using Rubin's rules. See details in Section 10.7.2.

7.2. Secondary Effectiveness Analyses

7.2.1. Forced Expiratory Volume in 1 Second (FEV_1)

Spirometry data are collected at Visit 1 (pre and post-salbutamol) and at Visit 2/ EW visit (only pre-salbutamol). If participants are not able to attend the scheduled clinic visit at

Visit 1/ Visit 2 to perform the spirometry assessment, the Visit 1/ Visit 2 spirometry assessment can be performed at a domiciliary visit.

Spirometry data collected at a domiciliary visit will be used in the secondary statistical analyses of FEV_1, unless otherwise stated. This data will also be included in data summaries and listings.

Spirometry data collected during assessments that are considered as EW assessments or have been inadvertently collected during the study and do not qualify as Visit 1/ Visit 2 spirometry, will not be considered for use within the statistical analyses, unless otherwise stated. Spirometry data collected at EW assessments will be included in data summaries and listings. Spirometry data inadvertently collected in the study that do not qualify as Visit 1/ Visit 2 spirometry will not be included in data summaries but will be included in listings.

7.2.1.1. Endpoint / Variables

Change from baseline in FEV_1 at 24 weeks.

7.2.1.2. Summary Measure

The summary measure will be the adjusted mean treatment differences.

7.2.1.3. Population of Interest

The analysis will be based on the FEV_1 population (as defined in Section 4), unless otherwise specified.

7.2.1.4. Strategy for Intercurrent (Post-Randomisation) Events

The list of **intercurrent events/events leading to missing data** that may occur during the study and may affect the estimation of the treatment effect are:

- **Randomised Treatment Discontinuation:** participants may discontinue randomised COPD maintenance therapy and continue in the study without being prescribed another COPD maintenance therapy. This is considered an intercurrent event.
- **Randomised Treatment Modification**: participants may discontinue randomised COPD maintenance therapy and get prescribed another COPD maintenance therapy during the study. This is considered an intercurrent event.
- **Pulmonary Rehabilitation**: participants may change pulmonary rehabilitation status during the study. E.g., Participant considered to be undergoing pulmonary rehabilitation at Visit 1 but stopped during the study and so no longer on pulmonary rehabilitation at Visit 2. See Section 10.6.3 for definition of pulmonary rehabilitation status at Visit 1 and at Visit 2. This is considered an intercurrent event.
- **Oxygen Therapy**: If participants start oxygen therapy during the study and they have not had another oxygen therapy prior to the study start, this is considered as an intercurrent event. If participants start oxygen therapy during the study but

they have recorded another oxygen therapy prior to the study start, this is not considered as an intercurrent event.

- **Early withdrawal from Study**: participants may prematurely withdraw from the study which results in missing endpoint data.
- **Week 24 FEV_1 Data not Available (other reasons than EW)**: FEV_1 data at week 24 (Visit 2) may not be available for other reasons (not EW).

The strategies for handling these events for this endpoint are described in Table 3.

Table 3 Strategies for handling intercurrent events/events leading to missing data for the secondary endpoint of change from baseline in FEV_1 at week 24

	Intercurrent Events				Missing data	
Estimand	**Randomised Treatment Discontinuation**	**Randomised Treatment Modification**	**Pulmonary Rehabilitation**	**Oxygen Therapy**	**Study Withdrawal**	**Week 24 FEV_1 not Available**
Treatment Policy	Week 24 FEV_1 data to be used in the analysis regardless of the intercurrent event of randomised treatment discontinuation. (Treatment Policy)	Week 24 FEV_1 data to be used in the analysis regardless of the intercurrent event of randomised treatment modification. (Treatment Policy)	Week 24 FEV_1 data to be used in the analysis regardless of the intercurrent event of change of pulmonary rehabilitation status during the study. (Treatment Policy)	Week 24 FEV_1 data to be used in the analysis regardless of the intercurrent event of start of oxygen therapy during the study. (Treatment Policy)	Missing week 24 FEV_1 data will be imputed based on the randomised treatment arm. Assumes MAR. See details in Section 10.7.2.	Missing week 24 FEV_1 data will be imputed based on the randomised treatment arm. Assumes MAR. See details in Section 10.7.2.

This primary estimand for the secondary endpoint of FEV_1 will assess the randomised treatment effect regardless of whether the intercurrent events/events leading to missing data described in Table 3 above have occurred in the study.

7.2.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 9: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints/variables defined in Section 7.2.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.2.1.5.1. Statistical Methodology Specification

Endpoint / Variables
Change from baseline in FEV_1 at 24 weeks.

Model Specification

The secondary endpoint of change from baseline in FEV_1 at week 24 will be analysed for the FEV_1 population using an analysis of covariance (ANCOVA) model with treatment as an explanatory variable and baseline FEV_1 (continuous), prior medication use strata (categorical, see Section 10.6.2) and country (categorical) included as covariates.

An additional covariate "*Timing of Spirometry*" (categorical) indicating when the spirometry assessment was performed (i.e., pre/post maintenance COPD therapy) at Visit 1 and Visit 2 will be defined. All possible combinations for timing of spirometry at Visit 1 and Visit 2 will form the levels of the covariate:

1	Visit 1: Pre-COPD maintenance therapy dose – Visit 2: Pre-COPD maintenance therapy dose
2	Visit 1: Pre-COPD maintenance therapy dose – Visit 2: Post-COPD maintenance therapy dose
3	Visit 1: Post-COPD maintenance therapy dose – Visit 2: Pre-COPD maintenance therapy dose
4	Visit 1: Post-COPD maintenance therapy dose – Visit 2: Post-COPD maintenance therapy dose

Interaction between *Treatment* and *Timing of Spirometry* will be checked. If the interaction p-value is less than 0.10 then the estimate of the treatment effect will be based on the model that includes *baseline* FEV_1, *prior medication use strata*, *country* and the *timing of spirometry* as covariates as well as the interaction term *treatment* by *timing of spirometry*. If the interaction p-value is not less than 0.10 then the estimate of the treatment effect will be based on the model which will only include *baseline* FEV_1, *prior medication use strata*, *country* and the *timing of spirometry* as covariates.

Model Results Presentation

Adjusted Least-square (LS) means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors as well as 95% CIs. The estimated treatment difference along with corresponding standard error, 95% CI and p-value will be presented.

Model Checking & Diagnostics

For the primary estimand, distributional assumptions underlying the model used for analysis will be examined. An ANCOVA analysis will be performed using the primary estimand model specified in the *Model Specification* section above. No multiple imputation will be performed for the missing week 24 FEV_1 data. The 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, will be produced.

7.2.2. Trough FEV_1

Spirometry data will be used in the statistical analyses in the same way as described in Section 7.2.1.

7.2.2.1. Endpoint / Variables

Change from baseline in Trough FEV_1 at 24 weeks. Trough FEV_1 is defined in Section 10.6.3.

7.2.2.2. Summary Measure

The summary measure will be the adjusted mean treatment differences.

7.2.2.3. Population of Interest

The analysis will be based on participants included in the FEV_1 population (as defined in Section 4), who also managed to withhold COPD maintenance treatment at both Visit 1 and Visit 2 spirometry assessment (see also Section 10.6.3 for definition of Trough FEV_1), unless otherwise specified.

7.2.2.4. Strategy for Intercurrent (Post-Randomisation) Events

The list of **intercurrent events/events leading to missing data** that may occur during the study and may affect the estimation of the treatment effect are as described in Section 7.2.1.4.

The strategies for handling these events for this endpoint are described in Table 4.

Table 4 Strategies for handling intercurrent events/events leading to missing data for the secondary endpoint of change from baseline in Trough FEV_1 at week 24

	Intercurrent Events				Missing data	
Estimand	**Randomised Treatment Discontinuation**	**Randomised Treatment Modification**	**Pulmonary Rehabilitation**	**Oxygen Therapy**	**Study Withdrawal**	**Week 24 FEV_1 not Available**
Treatment Policy	Week 24 Trough FEV_1 data to be used in the analysis regardless of the intercurrent event of randomised treatment discontinuation. (Treatment Policy)	Week 24 Trough FEV_1 data to be used in the analysis regardless of the intercurrent event of randomised treatment modification. (Treatment Policy)	Week 24 Trough FEV_1 data to be used in the analysis regardless of the intercurrent event of change of pulmonary rehabilitation status during the study. (Treatment Policy)	Week 24 Trough FEV_1 data to be used in the analysis regardless of the intercurrent event of start of oxygen therapy during the study. (Treatment Policy)	Missing week 24 Trough FEV_1 data will be imputed based on the randomised treatment arm. Assumes MAR. See details in Section 10.7.2.	Missing week 24 Trough FEV_1 data will be imputed based on the randomised treatment arm. Assumes MAR. See details in Section 10.7.2.

The primary estimand for the secondary endpoint of Trough FEV_1 will assess the randomised treatment effect regardless of whether the intercurrent events/events leading to missing data described in Table 4 have occurred in the study.

7.2.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 9: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints/variables defined in Section 7.2.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.2.2.5.1. Statistical Methodology Specification

Endpoint / Variables
Change from baseline in Trough FEV_1 at 24 weeks.
Model Specification
The secondary endpoint of change from baseline in Trough FEV_1 at week 24 will be analysed for the FEV_1 population using an analysis of covariance (ANCOVA) model with treatment as an explanatory variable and baseline Trough FEV_1 (continuous), prior medication use strata (categorical, see Section 10.6.2) and country (categorical) included as covariates.
Model Results Presentation
Adjusted Least-square (LS) means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors as well as 95% CIs. The estimated treatment difference along with corresponding standard error, 95% CI and p-value will be presented.
Model Checking & Diagnostics
For the primary estimand, distributional assumptions underlying the model used for analysis will be examined. An ANCOVA analysis will be performed using the primary estimand model specified in the *Model Specification* section above. No multiple imputation will be performed for the missing week 24 Trough FEV_1 data. The 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, will be produced.

7.2.3. Critical Errors (CE)

Inhaler error assessment data is collected at a clinic visit at Visit 2/ EW visit. Inhaler error data collected during assessments considered as EW assessments, will not be considered for use within the statistical analyses, unless otherwise stated. Inhaler error assessment data collected during EW assessments will be included in data summaries and listings.

7.2.3.1. Endpoint / Variables

Percentage of participants making at least one critical error in inhalation technique at 24 weeks.

7.2.3.2. Summary Measure

The summary measure used for the treatment comparison will be an Odds Ratio (OR) and a 95% CI.

7.2.3.3. Population of Interest

The analysis will be based on participants in the Critical Error (CE) population (as defined in Section 4), unless otherwise specified.

7.2.3.4. Strategy for Intercurrent (Post-Randomisation) Events

The following **intercurrent events/events leading to missing data** are considered for the secondary endpoint of critical errors:

- **Randomised Treatment Modification**: participants may discontinue randomised COPD maintenance therapy and get prescribed another COPD maintenance therapy during the study. The three following scenarios are considered after the intercurrent event of randomised treatment modification:
  a) New COPD maintenance therapy uses the same devices as randomised COPD maintenance therapy and error assessments are performed on these new devices.
  b) New COPD maintenance therapy uses different devices to randomised COPD maintenance therapy, but devices that are assessed in the study (checklists available) and for which error assessments are performed.
  c) New COPD maintenance therapy uses devices which are not being assessed in this study (no checklists available) and thus no error assessment is available at week 24 (Visit 2).
- **Early Withdrawal from Study**: participants may prematurely withdraw from the study and so no actual week 24 (Visit 2) inhaler error assessment is performed.
- **Week 24 Inhaler Error Assessment Data not Available (other reasons than EW), e.g.,** participants on multiple inhalers may have missed performing the assessment on the secondary device at week 24 (Visit 2); participant may miss a component of a device assessment and all other question responses indicate correct use.

The strategies for handling these events for this endpoint are described in Table 5.

Table 5 Strategies for handling intercurrent events/events leading to missing data for the secondary endpoint of percentage of participants making at least 1 critical error in inhalation technique at week 24

	Intercurrent Events	Missing data	
Estimand	**Randomised Treatment Modification**	**Study Withdrawal**	**Week 24 Inhaler Error Assessment Data not Available**
Hypothetical	For the purposes of this secondary endpoint analysis any inhaler error assessment data following randomised treatment modification event and falling under scenario a, will be included in the analysis. Any error assessment data following randomised treatment modification and falling under scenario b or c, will be treated as missing (See also Section 10.6.3).	If participant prematurely withdraw from study, no imputation will be performed for the missing actual week 24 inhaler error data.	If week 24 inhaler error data are not available (for other reasons than EW) no imputation will be performed.

The primary estimand of the secondary endpoint of critical errors will assess the treatment effect that would have been observed in a hypothetical scenario where no participant experienced the intercurrent events/events leading to missing data described in Table 5.

7.2.3.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 9: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints/variables defined in Section 7.2.3.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.2.3.5.1. Statistical Methodology Specification

Endpoint / Variables
Percentage of participants making at least one critical error in inhalation technique at 24 weeks.
Model Specification
The secondary endpoint of percentage of participants making at least one critical error at week 24 will be analysed for the CE population using a logistic regression model with treatment as an explanatory variable. Country (categorical) and prior medication use strata (categorical, see Section 10.6.2) will be included as covariates in the model. For the non-ELLIPTA MITT arm all devices for which we have error checklists will be considered. Any participant in the non-ELLIPTA MITT arm using a device for which we have no error checklist will not be considered for critical error assessment.
Model Results Presentation

The odds ratio, 95% CI and p-value will be presented for the comparison between treatment arms. It will be based on a two-sided hypothesis testing approach of superiority.

Model Checking & Diagnostics

For the primary estimand, the model assumptions will be assessed by plotting the Pearson residuals from this analysis.

Supportive Analyses

A supportive estimand will be defined for the secondary endpoint of CE. The variable/endpoint, the summary measure and population of interest for the supportive estimands will be as defined in Section 7.2.3.1, Section 7.2.3.2 and Section 7.2.3.3, respectively. The strategies for handling the intercurrent events/events leading to missing data for this supportive estimand are as described below:

Supportive Estimand (Treatment Policy)

	Intercurrent Events	Missing data	
Estimand	**Randomised Treatment Modification**	**Study Withdrawal**	**Week 24 Inhaler Error Assessment Data not Available**
Treatment Policy	All available inhaler error assessment data collected at week 24 (Visit 2) will be included in the analysis, regardless of the inhaler device the participants used at the week 24 assessment following the randomised treatment modification event. (Treatment Policy)	If participant prematurely withdrew from study, no imputation will be performed for the missing actual week 24 (Visit 2) inhaler error data. **Note:** If participant prematurely withdrew from study and an inhaler error assessment was performed at an EW visit, available EW data will be used in the analysis.	If week 24 inhaler error data are not available (for other reasons than EW) no imputation will be performed.

Supportive Estimand of the secondary endpoint of critical errors will assess the randomised treatment effect regardless of whether the intercurrent events/events leading to missing data described in the table above have occurred in the study.

Exploratory Analyses

In addition, further exploratory treatment comparisons between the individual inhalers assessed in the study will be performed, if there are at least 100 participants who performed an inhaler error assessment for each of the individual inhalers assessed in the study. The inhaler comparisons to be assessed are:

Ellipta vs Diskus	Ellipta vs MDI[1]
Ellipta vs Breezhaler	Ellipta vs Turbuhaler
Ellipta vs Handihaler	Ellipta vs Genuair

[1] This is for participants whose COPD maintenance therapy is administered via an MDI. Rescue medications administered via an MDI are not included.

- For each of these exploratory comparisons the variable/endpoint and the summary measure will be as defined in Sections 7.2.3.1 and Section 7.2.3.2.

- The population of interest will be participants from the ITT population (as defined in Section 4) with available critical error assessment data on any of the following devices: Ellipta, Breezhaler, Handihaler,

MDI, Turbuhaler, Genuair. **Note:** Participants whose COPD maintenance treatment is administered via multiple inhalers not all of which have an inhaler error checklist available in the study, but an inhaler error assessment was still performed for any of those that are assessed in the study, then these participants will be included in the population and the available inhaler error data will be use in the analysis (see also Section 10.6.3).

- **Intercurrent Events:** The inhaler error data at week 24 will be used regardless of the device the participants used at the week 24 (Visit 2) assessment following the randomised treatment modification event (Treatment Policy).

- **Handling Missing Data:** Events leading to missing data (e.g., study withdrawal), will be handled as described in Section 7.2.3.4, Table 5. This exploratory estimand will assess the device effect on participants who remain in the study and provide inhaler error data in any of the devices assessed in the study (i.e., devices for which a checklist is available).

- **Model Specification:** The percentage of participants making at least one critical error at week 24 will be analysed for each inhaler comparison separately, using a logistic regression model with device type as an explanatory variable. Country (categorical) and prior medication use strata (categorical, see Section 10.6.2) will be included as covariates in the model.

7.3. Other Effectiveness Analyses

7.3.1. Clinically Important Deterioration (CID)

For the endpoint of CID, CAT score data and spirometry data collected at domiciliary visits or at a telephone call (i.e., for CAT at Visit 2) will be used in the statistical analyses as described in Sections 7.1.1 and Section 7.2.1, respectively. CAT score data and spirometry data collected at EW assessments, will be used within the statistical analyses, unless otherwise stated. Spirometry data inadvertently collected in the study that do not qualify as Visit 1/ Visit 2/ EW visit spirometry will not be included in the statistical analyses.

7.3.1.1. Endpoint / Variables

Proportion of participants who experience Clinically Important Deterioration (CID). CID is a composite outcome defined in Section 10.6.3.

7.3.1.2. Summary Measure

The summary measure used for the treatment comparison will be an Odds Ratio (OR) and a 95% CI.

7.3.1.3. Population of Interest

The analysis will be based on the FEV_1 population (as defined in Section 4), unless otherwise specified.

7.3.1.4. Strategy for Intercurrent (Post-Randomisation) Events

The **list of intercurrent events/events leading to missing data** that may occur during the study and may affect the estimation of the treatment effect are:

- **Randomised Treatment Discontinuation:** participants may discontinue randomised COPD maintenance therapy and continue in the study without being prescribed another COPD maintenance therapy. This is considered and intercurrent event.
- **Randomised Treatment Modification**: participants may discontinue randomised COPD maintenance therapy and get prescribed another COPD maintenance therapy during the study. This is considered an intercurrent event.
- **Pulmonary Rehabilitation**: participants may change pulmonary rehabilitation status during the study. E.g., Participant considered to be undergoing pulmonary rehabilitation at Visit 1 but stopped during the study and so no longer on pulmonary rehabilitation at Visit 2. See Section 10.6.3 for definition of pulmonary rehabilitation status at Visit 1 and at Visit 2. This is considered an intercurrent event.
- **Oxygen Therapy**: If participants start oxygen therapy during the study and they have not had another oxygen therapy prior to the study start, this is considered as an

intercurrent event. If participants start oxygen therapy during the study but they have recorded another oxygen therapy prior to the study start, this is not considered as an intercurrent event.

- **Early Withdrawal from Study**: participants may prematurely withdraw from the study which results in missing endpoint data.
- **Week 24 CAT Score Data not Available (other reasons than EW)**: CAT score at week 24 (Visit 2) may not be available for other reasons (not EW).
- **Week 24 FEV_1 Data not Available (other reasons than EW)**: Trough FEV_1 data at week 24 (Visit 2) may not be available for other reasons (not EW).

The strategies for handling these events for this endpoint are described in Table 6.

Table 6 Strategies for handling intercurrent events/events leading to missing data for the endpoint of proportion of participants who experience CID

	Intercurrent Events				Missing data		
Estimand	**Randomised Treatment Discontinuation**	**Randomised Treatment Modification**	**Pulmonary Rehabilitation**	**Oxygen Therapy**	**Study Withdrawal**	**Week 24 Trough FEV_1 not Available**	**Week 24 CAT not Available**
Treatment Policy x Composite	Week 24 Trough FEV_1 data, CAT score data and on-study Exacerbation data to be used in the analysis regardless of the intercurrent event of randomised treatment discontinuation. (Treatment Policy)	Week 24 Trough FEV_1 data, CAT score data and on-study Exacerbation data to be used in the analysis regardless of the intercurrent event of randomised treatment modification. (Treatment Policy)	Trough FEV_1 data, CAT score data and on-study Exacerbation data to be used in the analysis regardless of the intercurrent event of change of pulmonary rehabilitation status during the study. (Treatment Policy)	If participants start oxygen therapy during the study and they have not had another oxygen therapy prior to the study start, they will be considered as meeting the criteria for CID. (Composite)	Missing week 24 Trough FEV_1 and CAT score data will be imputed based on the randomised treatment arm. Assumes MAR. See details in Section 10.7.2. **Note:** EW data will be included in the analysis.	Missing week 24 Trough FEV_1 data will be imputed based on the randomised treatment arm. Assumes MAR. See details in Section 10.7.2.	Missing week 24 CAT score data will be imputed based on the randomised treatment arm. Assumes MAR. See details in Section 10.7.2.

This primary estimand for the endpoint of proportion of participants who experience CID will assess the randomised treatment effect, handling differently each of the intercurrent events/events leading to missing data described in Table 6 above.

7.3.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 9: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints /variables defined in Section 7.3.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.3.1.5.1. Statistical Methodology Specification

Endpoint / Variables
Proportion of participants who experience a CID. CID is a composite outcome defined in Section 10.6.3.
Model Specification
The endpoint of proportion of participants who experience a CID will be analysed for the FEV_1 population using a logistic regression model with treatment as an explanatory variable and baseline Trough FEV_1 (continuous), baseline CAT score (continuous), number of exacerbations in the prior year (categorical, see Section 10.6.2), prior medication use strata (categorical, see Section 10.6.2) and country (categorical) included as covariates.
Model Results Presentation
The odds ratio, 95% CI and p-value will be presented for the comparison between treatment arms. It will be based on a two-sided hypothesis testing approach of superiority.
Model Checking & Diagnostics
For the primary estimand, the model assumptions will be assessed by performing a logistic regression analysis using the primary estimand model specified in the *Model Specification* section above. No multiple imputation will be performed for the missing CAT score data or the missing Trough FEV1 data at week 24. The Pearson residuals from this analysis will be plotted.
Sensitivity Analyses
A sensitivity analysis will be performed for the estimand defined in Sections 7.3.1.1 to Section 7.3.1.4, using the same model specified for the primary analysis described in the *Model Specification* section above, but excluding the number of exacerbations in the prior year (categorical) from the list of covariates. **Model Specification:** The proportion of participants who experience a CID will be analysed for the FEV_1 population using a logistic regression model with treatment as an explanatory variable and baseline Trough FEV_1 (continuous), baseline CAT score (continuous), prior medication use strata (categorical, see Section 10.6.2) and country (categorical) included as covariates.

7.3.2. Clinically Important Deterioration (Analyses of Components)

Trough FEV_1 data will be used in the analyses as described in Section 7.3.1.

7.3.2.1. 100 mL Reduction from Baseline in Trough FEV_1 at 24 weeks

7.3.2.1.1. Endpoint / Variables

Proportion of participants who experience a 100 mL reduction from baseline in Trough FEV_1 at 24 weeks.

7.3.2.1.2. Summary Measure

The summary measure used for the treatment comparison will be an Odds Ratio (OR) and a 95% CI.

7.3.2.1.3. Population of Interest

The analysis will be based on the FEV_1 population (as defined in Section 4), unless otherwise specified.

7.3.2.1.4. Strategy for Intercurrent (Post-Randomisation) Events

The **list of intercurrent events/events leading to missing data** that may occur during the study and may affect the estimation of the treatment effect are:

- **Randomised Treatment Discontinuation:** participants may discontinue randomised COPD maintenance therapy and continue in the study without being prescribed another COPD maintenance therapy. This is considered an intercurrent event.
- **Randomised Treatment Modification**: participants may discontinue randomised COPD maintenance therapy and get prescribed another COPD maintenance therapy during the study. This is considered an intercurrent event.
- **Pulmonary Rehabilitation**: participants may change pulmonary rehabilitation status during the study. E.g., Participant considered to be undergoing pulmonary rehabilitation at Visit 1 but stopped during the study and so no longer on pulmonary rehabilitation at Visit 2. See Section 10.6.3 for definition of pulmonary rehabilitation status at Visit 1 and at Visit 2. This is considered an intercurrent event.
- **Oxygen Therapy**: If participants start oxygen therapy during the study and they have not had another oxygen therapy prior to the study start, this is considered as an intercurrent event. If participants start oxygen therapy during the study but they have recorded another oxygen therapy prior to the study start, this is not considered as an intercurrent event.
- **Early Withdrawal from Study**: participants may prematurely withdraw from the study which results in missing endpoint data.
- **Week 24 Trough FEV_1 Data not Available (other reasons than EW)**: Trough FEV_1 data at week 24 (Visit 2) may not be available for other reasons (not EW).

The strategies for handling these events for this endpoint are described in Table 7.

Table 7 Strategies for handling intercurrent events/events leading to missing data for the endpoint of proportion of participants who experience a 100mL reduction from baseline in Trough FEV_1 at week 24

	Intercurrent Events				Missing data	
Estimand	**Randomised Treatment Discontinuation**	**Randomised Treatment Modification**	**Pulmonary Rehabilitation**	**Oxygen Therapy**	**Study Withdrawal**	**Week 24 Trough FEV1 not Available**
Treatment Policy x Composite	Week 24 Trough FEV_1 data to be used in the analysis regardless of the intercurrent event of randomised treatment discontinuation. (Treatment Policy)	Week 24 Trough FEV_1 data to be used in the analysis regardless of the intercurrent event of randomised treatment modification. (Treatment Policy)	Week 24 Trough FEV_1 data to be used in the analysis regardless of the intercurrent event of change of pulmonary rehabilitation status during the study. (Treatment Policy)	If participants start oxygen therapy during the study and they have not had another oxygen therapy prior to the study start, they will be considered as having experienced a 100mL reduction from baseline in Trough FEV_1. (Composite)	Missing week 24 Trough FEV_1 data will be imputed based on the randomised treatment arm. Assumes MAR. See details in Section 10.7.2. **Note:** Trough FEV_1 data collected at EW visits will be included in the analysis.	Missing week 24 Trough FEV_1 data will be imputed based on the randomised treatment arm. Assumes MAR. See details in Section 10.7.2.

This primary estimand for the endpoint of proportion of participants who experience a 100mL reduction from baseline in Trough FEV_1 at 24 weeks, will assess the randomised treatment effect, handling differently each of the intercurrent events/events leading to missing data described in Table 7 above.

7.3.2.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 9: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints /variables defined in Section 7.3.2.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

Statistical Methodology Specification

Endpoint / Variables
Proportion of participants who experience a 100 mL reduction from baseline in Trough FEV_1 at 24 weeks.
Model Specification
The endpoint of proportion of participants who experience a 100 mL reduction from baseline in Trough FEV_1 at 24 weeks will be analysed for the FEV_1 population using a logistic regression model with treatment as an explanatory variable and baseline Trough FEV_1 (continuous), prior medication use strata (categorical, see Section 10.6.2) and country (categorical) included as covariates.
Model Results Presentation
The odds ratio, 95% CI and p-value will be presented for the comparison between treatment arms. It will be based on a two-sided hypothesis testing approach of superiority.
Model Checking & Diagnostics
For the primary estimand, the model assumptions will be assessed by performing a logistic regression analysis using the primary estimand model specified in the *Model Specification* section above. No multiple imputation will be performed for the missing Trough FEV_1 data at week 24. The Pearson residuals from this analysis will be plotted.

7.3.2.2. 2 Units Change (Increase) from Baseline in CAT Score at 24 Weeks

7.3.2.2.1. Endpoint / Variables

Proportion of participants who experience a 2-unit change (increase) from baseline in CAT score at 24 weeks.

7.3.2.2.2. Summary Measure

The summary measure used for the treatment comparison will be an Odds Ratio (OR) and a 95% CI.

7.3.2.2.3. Population of Interest

The analysis will be based on the FEV_1 population (as defined in Section 4), unless otherwise specified.

7.3.2.2.4. Strategy for Intercurrent (Post-Randomisation) Events

The **list of intercurrent events/events leading to missing data** that may occur during the study and may affect the estimation of the treatment effect are:

- **Randomised Treatment Discontinuation:** participants may discontinue randomised COPD maintenance therapy and continue in the study without being prescribed another COPD maintenance therapy. This is considered an intercurrent event.
- **Randomised Treatment Modification**: participants may discontinue randomised COPD maintenance therapy and get prescribed another COPD maintenance therapy during the study. This is considered an intercurrent event.

- **Pulmonary Rehabilitation**: participants may change pulmonary rehabilitation status during the study. E.g., Participant considered to be pulmonary rehabilitation at Visit 1 but stopped during the study and so no longer on pulmonary rehabilitation at Visit 2. See Section 10.6.3 for definition of pulmonary rehabilitation status at Visit 1 and at Visit 2. This is considered an intercurrent event.
- **Oxygen Therapy**: If participants start oxygen therapy during the study and they have not had another oxygen therapy prior to the study start, this is considered as an intercurrent event. If participants start oxygen therapy during the study but they have recorded another oxygen therapy prior to the study start, this is not considered as an intercurrent event.
- **Early Withdrawal from Study**: participants may prematurely withdraw from the study which results in missing endpoint data.
- **Week 24 CAT Score not Available (other reasons than EW)**: CAT score at week 24 (Visit 2) may not be available for other reasons (not EW).

The strategies for handling these events for this endpoint are described in Table 8.

Table 8 Strategies for handling intercurrent events/events leading to missing data for the endpoint of proportion of participants who experience a 2-unit change (increase) from baseline in CAT score at week 24

	Intercurrent Events				Missing data	
Estimand	**Randomised Treatment Discontinuation**	**Randomised Treatment Modification**	**Pulmonary Rehabilitation**	**Oxygen Therapy**	**Study Withdrawal**	**Week 24 CAT not Available**
Treatment Policy x Composite	Week 24 CAT score data to be used in the analysis regardless of the intercurrent event of randomised treatment discontinuation. (Treatment Policy)	Week 24 CAT score data to be used in the analysis regardless of the intercurrent event of randomised treatment modification. (Treatment Policy)	Week 24 CAT score data to be used in the analysis regardless of the intercurrent event of change of pulmonary rehabilitation status during the study. (Treatment Policy)	If participants start oxygen therapy during the study and they have not had another oxygen therapy prior to the study start, they will be considered as having experienced a 2 unit increase from baseline in CAT score. (Composite)	Missing week 24 CAT score data will be imputed based on the randomised treatment arm characteristics. This assumes MAR. See details in Section 10.7.2. **Note:** CAT score data collected at EW visits will be included in the analysis.	Missing week 24 CAT score data will be Imputed based on the randomised treatment arm characteristics. This assumes MAR. See details in Section 10.7.2.

This primary estimand for the endpoint of proportion of participants who experience a 2-unit change (increase) from baseline in CAT score at 24 weeks, will assess the randomised treatment effect, handling differently each of the intercurrent events/events leading to missing data described in Table 8 above.

7.3.2.2.5. Statistical Analysis / Methods

Details of the planned displays are provided in Appendix 9: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints /variables defined in Section 7.3.2.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

Statistical Methodology Specification

Endpoint / Variables
Proportion of participants who experience a 2-unit change (increase) from baseline in CAT score at 24 weeks.
Model Specification
The endpoint of proportion of participants who experience a 2-unit change (increase) from baseline in CAT score at 24 weeks, will be analysed for the FEV_1 population using a logistic regression model with treatment as an explanatory variable and baseline CAT score (continuous), prior medication use strata (categorical, see Section 10.6.2) and country (categorical) included as covariates.
Model Results Presentation
The odds ratio, 95% CI and p-value will be presented for the comparison between treatment arms. It will be based on a two-sided hypothesis testing approach of superiority.
Model Checking & Diagnostics
For the primary estimand, the model assumptions will be assessed by performing a logistic regression analysis using the primary estimand model specified in the *Model Specification* section above. No multiple imputation will be performed for the missing CAT score data at week 24. The Pearson residuals from this analysis will be plotted.

7.3.3. Annualised Rate of Moderate/Severe Exacerbations

No formal statistical analysis is planned for the endpoint of the annualised rate of moderate/severe exacerbations and thus no estimands are defined for this endpoint. For derivation of the annualised rate see Section 10.6.3.

Unless otherwise specified, the annualised rate of on-randomised treatment moderate/severe exacerbations as well as the annualised rate of on-study moderate/severe exacerbations will be summarised by the randomised treatment group using descriptive statistics (n, mean, SD, median, min, max), based on the Intent-to-Treat (ITT) population (as defined in Section 4). The COPD exacerbation data will be listed.

Details of the planned displays are provided in Appendix 9: List of Data Displays and will be based on GSK data standards and statistical principles.

7.3.4. Time to first Moderate/Severe Exacerbation

No formal statistical analysis is planned for the endpoint of the time to first moderate/severe exacerbation and thus no estimands are defined for this endpoint.

Unless otherwise specified, the time to first on-randomised treatment moderate/severe exacerbations as well as the time to first on-study moderate/severe exacerbations will be summarised by the randomised treatment group, based on the Intent-to-Treat (ITT) population (as defined in Section 4), using Kaplan Meir Estimates.

The probability of having a moderate/severe exacerbation with a 95% CI for each treatment group and the median time to event will be presented. Kaplan-Meier curves

will also be presented showing the probability of having an event over time for each randomised treatment group separately plotted on the same figure.

Details of the planned displays are provided in Appendix 9: List of Data Displays and will be based on GSK data standards and statistical principles.

7.3.5. Healthcare Resource Utilisation (HCRU)

Analyses relating to HCRU outcomes obtained from the Electronic Health Record (EHR) database will be described in a supplementary RAP and reported independently of this RAP.

As part of this RAP, the number of participants who had unscheduled (routine COPD care not included) COPD related healthcare contacts (e.g., deteriorating COPD) and the number of contacts by type (e.g., telephone calls, physician office/practice visits etc) will be summarised by the randomised treatment group.

All available HCRU data collected during the study will be summarised, including data from participants who prematurely withdrew from study.

7.4. Exploratory Effectiveness Analyses

7.4.1. Association of Critical Errors with CAT, Moderate/ Severe Exacerbations FEV_1 and FVC

No formal statistical analysis is planned for this exploratory endpoint. The association of critical errors with CAT score at week 24 and the association of critical errors with FEV_1 and FVC at week 24 will be graphically presented. In addition, the association of critical errors with change from baseline in CAT score at week 24 and the association of critical errors with change from baseline in FEV_1 and change from baseline in FVC at week 24 will be graphically presented. This will be based on participants in the CE population whose COPD maintenance treatment is administered via inhalers all of which have an inhaler error checklist available in the study.

The association of critical errors with CAT response (i.e., responder vs non-responder) at week 24 will be summarised in a frequency table. In addition, the association of critical errors with on-randomised treatment moderate/severe exacerbations as well as the association of critical errors with on-study moderate/severe exacerbations will be summarised in a frequency table. See also Section 10.6.3.

The CAT score data, spirometry data (i.e., FEV1 and FVC) and critical error data collected at week 24 (Visit 2) will be used for this exploratory endpoint as described in Section 7.1.1, Section 7.2.1 and Section 7.2.3, respectively.

Details of the planned displays are provided in Appendix 9: List of Data Displays and will be based on GSK data standards and statistical principles.

7.4.2. Patient Study Experience

No formal statistical analysis is planned for the endpoint of Participant Treatment and Study Satisfaction Questionnaire at 24 weeks/ EW Visit.

The participant responses to the Treatment and Study Satisfaction Questionnaire at 24 weeks/ EW Visit will be summarised by the randomised treatment group and listed, based on the Intent-to-Treat (ITT) population (as defined in Section 4), unless otherwise specified. Frequency of the response categories ("*Strongly Agree"* to "*Strongly Disagree*") will be presented for each question by randomised treatment group. See also Section 10.6.3.

Details of the planned displays are provided in Appendix 9: List of Data Displays and will be based on GSK data standards and statistical principles.

7.4.3. Health Related Quality of Life Questionnaire (HRQoL)

No formal statistical analysis is planned for the endpoint of Health Related Quality of Life Questionnaire (HRQoL).

The HRQoL data from each visit (Visit 1 and Visit 2) will be summarised by the randomised treatment group and listed, based on the Intent-to-Treat (ITT) population, unless otherwise specified. For the numerical questions of the questionnaire (Item 2, 3, and 4, see Section 10.6.3) data will be summarised using descriptive statistics (n, mean, SD, median, min, max). For Item 1 of the questionnaire, the frequency of the categories selected at each visit (Visit 1 and Visit 2) will be summarised.

HRQoL data collected at an EW visit will also be included in the summaries and listings.

Details of the planned displays are provided in Appendix 9: List of Data Displays and will be based on GSK data standards and statistical principles.

8. SAFETY ANALYSES

The safety analyses will be based on the Intent-to-Treat (ITT) population (as defined in Section 4), unless otherwise specified.

8.1. Adverse Events Analyses

AEs not related to either study treatment or withdrawal from study treatment are not recorded, unless classified as serious adverse events.

Adverse events analyses including the descriptive statistics of Serious Adverse Events (SAEs), study treatment related AEs and AEs that lead to withdrawal from study treatment will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 9: List of Data Displays.

Serious adverse events (SAEs) associated with study participation or related to any GSK product, will be collected from the point of informed consent until randomisation. All SAEs will be collected from randomisation until completion of the Visit 2/ EW Visit, at the time points specified in the Schedule of Activities (SoA) in Section 10.2. Treatment related AEs and AEs leading to study treatment withdrawal, will be collected from randomisation until completion of Visit 2/EW Visit, at the time points specified in the SoA in Section 10.2. All SAEs, and relevant AEs will be summarised and displayed by randomised treatment group. The onset dates of the SAEs/relevant AEs relative to the randomised treatment start and stop dates will be used to determine in which period an AE occurs.

The AE/SAE text recorded in the eCRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and will be reported using the primary System Organ Class (SOC) and Preferred Term (PT). The number of participants with one or more events of any type will be calculated. Results will be displayed in the order of decreasing frequency, both across SOC and within SOC. A SOC will not be included if no SAEs/AEs in that SOC are reported. If the total incidence for any two or more AEs is equal, the events will be presented in alphabetical order.

Adverse events and Serious Adverse Events will also be listed, with SOC, event (PT), treatment group, number of participants with the event, and specific participant numbers. Demographic details (e.g., age, sex and race), as well as details of the individual AEs, will also be included in these listings. Listings will be sorted within participant by the date of onset of the AE.

Note that moderate and severe COPD exacerbation events will be recorded on the Exacerbation page in the participant's eCRF. Because exacerbations are typically associated with the disease under study, an exacerbation will not be reported according to the standard process for expedited reporting of SAEs to GSK unless the event meets any of the criteria defined in Section 9.5.7 of the Protocol.

Details of the SAE/AE summaries and listings are presented in Appendix 9: List of Data Displays.

8.2. Adverse Events of Special Interest Analyses

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting. Furthermore, emerging data from on-going studies may highlight additional adverse events of special interest. Therefore, the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting.

Serious Adverse Events of Special Interest (SAESI) will be summarised by the randomised treatment arms and by the class of medication taken at the time of the event. SAESI will also be listed. The details of the planned displays are provided in Appendix 9: List of Data Displays.

Table in Section 10.6.4 presents the groups of Serious Adverse Events of Special Interest (SAESI). Groups which are not standardized MedDRA queries (SMQs) comprise a selection of PTs defined by GSK. The complete list, including the PTs that contribute to each of the groups, will be provided by GCSP using the MedDRA version current at the time of reporting. This list will be finalized prior to unblinding the database.

8.3. Other Safety Analyses

Any pregnancies reported during the study will be summarised in case narratives. Any pregnancy complication or elective termination of a pregnancy for medical reasons should be recorded as an AE or SAE and included in summaries and listings of AEs/SAEs.

9. REFERENCES

GlaxoSmithKline Document Number 2017N321744_00, Study ID 206854. The Clinical Effectiveness of Fluticasone Furoate/Umeclidinium Bromide/Vilanterol in a Single Inhaler (TRELEGYTM ELLIPTATM) when Compared with Non-ELLIPTA Multiple Inhaler Triple Therapies in COPD Patients within a Usual Care Setting. Effective Date 06-NOV-2017.

GlaxoSmithKline Document Number 2017N321744_01 (Amendment 1), Study ID 206854. The Clinical Effectiveness of Fluticasone Furoate/Umeclidinium Bromide/Vilanterol in a Single Inhaler (TRELEGYTM ELLIPTATM) when Compared with Non-ELLIPTA Multiple Inhaler Triple Therapies in COPD Patients within a Usual Care Setting. Effective Date 15-FEB-2018.

GlaxoSmithKline Document Number 2017N321744_02 (Amendment 2), Study ID 206854. The Clinical Effectiveness of Fluticasone Furoate/Umeclidinium Bromide/Vilanterol in a Single Inhaler (TRELEGYTM ELLIPTATM) when Compared with Non-ELLIPTA Multiple Inhaler Triple Therapies in COPD Patients within a Usual Care Setting. Effective Date 28-SEP-2018.

Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: http://goldcopd.org.

10. APPENDICES

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

10.1.1. Exclusions from Per Protocol Population

A per protocol (PP) population is not defined for this study therefore there are no criteria leading to exclusion from a per protocol population. All deviations will be managed during the study according to the PDMP.

10.2. Appendix 2: Schedule of Activities

10.2.1. Protocol Defined Schedule of Events

PROCEDURE *		TREATMENT PERIOD				NOTES
	VISIT 0 **Consenting**	**VISIT 1** **Screening & Randomisation**	**Usual care / contact for COPD related event or serious adverse event**	**Early Withdrawal (EW) Visit**	**VISIT 2**	The following sequence of events must be followed 1.ICF, 2. Screening, 3. Randomisation. All three may occur on the same day with no more than 6 weeks between ICF and screening and no more than 6 weeks between screening and randomisation.
Study week		1	After week 1 and before Visit 2	After week 1 and before Visit 2	24 (±21 days)	EW Visit should only be conducted if the participant discontinues from participating in the study. Participants withdrawing from study treatment but remaining in the study should continue to Visit 2.
Informed consent form (ICF)	X					ICF must be signed before any study procedures/ assessments
Inclusion and exclusion criteria		X				Recheck clinical status before randomisation and/or 1st prescription for study treatment
Demography		X				
Height and weight		X				
Medical history: past and current medical conditions		X				This includes family history of premature CV disease.

PROCEDURE *		TREATMENT PERIOD				NOTES
	VISIT 0 **Consenting**	**VISIT 1** **Screening & Randomisation**	**Usual care / contact for COPD related event or serious adverse event**	**Early Withdrawal (EW) Visit**	**VISIT 2**	The following sequence of events must be followed 1.ICF, 2. Screening, 3. Randomisation. All three may occur on the same day with no more than 6 weeks between ICF and screening and no more than 6 weeks between screening and randomisation.
Study week		1	After week 1 and before Visit 2	After week 1 and before Visit 2	24 (±21 days)	EW Visit should only be conducted if the participant discontinues from participating in the study. Participants withdrawing from study treatment but remaining in the study should continue to Visit 2.
Historical eosinophil count. whole blood count, % eosinophils	X	X				Most recent historical eosinophil measure taken within the **previous** 36 months prior to patients consenting visit. (Visit 1 or Visit 0 whichever is applicable) • An absolute number of eosinophils and the % of eosinophils out of the total WBC • White Blood Cell count (WBC)
Chronic Obstructive Pulmonary Disease (COPD) and Exacerbation history		X				The number of moderate/ severe exacerbations in the 12 months prior to V1 will be collected.
Randomisation		X				
COPD assessment test (CAT)		X		X	X	CAT must be completed prior to randomisation and prior to any other study procedures. Participants who have changed or discontinued treatment will remain in the study and complete CAT assessment at the Visit 2/EW Visit.
COPD Exacerbation assessment			X	X	X	Moderate and severe exacerbations that occur between V1 and V2 will be recorded.

PROCEDURE *		TREATMENT PERIOD				NOTES
	VISIT 0 **Consenting**	**VISIT 1** **Screening & Randomisation**	**Usual care / contact for COPD related event or serious adverse event**	**Early Withdrawal (EW) Visit**	**VISIT 2**	The following sequence of events must be followed 1.ICF, 2. Screening, 3. Randomisation. All three may occur on the same day with no more than 6 weeks between ICF and screening and no more than 6 weeks between screening and randomisation.
Study week		1	After week 1 and before Visit 2	After week 1 and before Visit 2	24 (±21 days)	EW Visit should only be conducted if the participant discontinues from participating in the study. Participants withdrawing from study treatment but remaining in the study should continue to Visit 2.
COPD related healthcare resource use assessment			X	X	X	Details of primary healthcare contacts, known secondary care contacts and all COPD related medication use that occurs between V1 and V2 will be recorded in the eCRF.
Assessment of inhaler errors (subgroup only)				X	X	
Spirometry for lung function (subgroup only)		X		X	X	Spirometry should be performed before the day's dose of usual care or study medication. The assessment is pre-and post-salbutamol at Visit 1 and pre-salbutamol at Visit 2 /EW Visit. It should be started between approximately 6:00 am and 12:00 pm The most recent use of COPD maintenance inhaler/ study treatment should be noted.
Participant treatment & study satisfaction questionnaire				X	X	

PROCEDURE *		TREATMENT PERIOD				NOTES
	VISIT 0 **Consenting**	**VISIT 1** **Screening & Randomisation**	**Usual care / contact for COPD related event or serious adverse event**	**Early Withdrawal (EW) Visit**	**VISIT 2**	The following sequence of events must be followed 1.ICF, 2. Screening, 3. Randomisation. All three may occur on the same day with no more than 6 weeks between ICF and screening and no more than 6 weeks between screening and randomisation.
Study week		1	After week 1 and before Visit 2	After week 1 and before Visit 2	24 (±21 days)	EW Visit should only be conducted if the participant discontinues from participating in the study. Participants withdrawing from study treatment but remaining in the study should continue to Visit 2.
Health Related Quality of Life Questionnaire (HRQoL)		X		X	X	
Review of study treatment related Adverse Events (AE)		X	X	X	X	Clinical judgment should be used to determine whether there is a relationship between study treatment and each occurrence of each AE/SAE. Study treatment related adverse events must be recorded from V1. Where a causality relationship is determined, this must be recorded as a study treatment related AE. **AEs not related to either study treatment or withdrawal from study treatment are not recorded, unless classified as serious adverse events.** Refer to Protocol Amendment 2, Appendix 3 for definitions of AEs, SAEs and guidelines on assessment of causality by investigator

PROCEDURE *		TREATMENT PERIOD				NOTES
	VISIT 0 **Consenting**	**VISIT 1** **Screening & Randomisation**	**Usual care / contact for COPD related event or serious adverse event**	**Early Withdrawal (EW) Visit**	**VISIT 2**	The following sequence of events must be followed 1.ICF, 2. Screening, 3. Randomisation. All three may occur on the same day with no more than 6 weeks between ICF and screening and no more than 6 weeks between screening and randomisation.
Study week		1	After week 1 and before Visit 2	After week 1 and before Visit 2	24 (±21 days)	EW Visit should only be conducted if the participant discontinues from participating in the study. Participants withdrawing from study treatment but remaining in the study should continue to Visit 2.
Review of Adverse Events (AE) that lead to withdrawal from study treatment		X	X	X	X	All AEs that lead to withdrawal from study treatment, whether judged related to study treatment or not, should be recorded. The participant should be encouraged to remain in the study for collection of effectiveness and safety data. All AEs that lead to withdrawal from the study whilst the participant is on study treatment, **whether judged related to study treatment or not**, should be recorded.

PROCEDURE *		TREATMENT PERIOD				NOTES
	VISIT 0 **Consenting**	**VISIT 1** **Screening & Randomisation**	**Usual care / contact for COPD related event or serious adverse event**	**Early Withdrawal (EW) Visit**	**VISIT 2**	The following sequence of events must be followed 1.ICF, 2. Screening, 3. Randomisation. All three may occur on the same day with no more than 6 weeks between ICF and screening and no more than 6 weeks between screening and randomisation.
Study week		1	After week 1 and before Visit 2	After week 1 and before Visit 2	24 (±21 days)	EW Visit should only be conducted if the participant discontinues from participating in the study. Participants withdrawing from study treatment but remaining in the study should continue to Visit 2.
SAE review	X	X	X	X	X	SAEs that are related to study participation or to GSK products are collected from the time of consent to randomisation. All other SAEs are recorded from the time of randomisation. Clinical judgment should be used to determine the relationship between study treatment and each occurrence of each AE/SAE. Where a causality relationship is determined, this must be recorded as a study treatment related SAE. Refer to Protocol Amendment 2, Appendix 3 for definitions of AEs, SAEs and guidelines on assessment of causality by investigator.
Details of randomised study treatment and any study treatment changes		X	X	X	X	Reason for change in treatment, details and date of new treatment should be recorded.

PROCEDURE *		TREATMENT PERIOD				NOTES
	VISIT 0 **Consenting**	**VISIT 1** **Screening & Randomisation**	**Usual care / contact for COPD related event or serious adverse event**	**Early Withdrawal (EW) Visit**	**VISIT 2**	The following sequence of events must be followed 1.ICF, 2. Screening, 3. Randomisation. All three may occur on the same day with no more than 6 weeks between ICF and screening and no more than 6 weeks between screening and randomisation.
Study week		1	After week 1 and before Visit 2	After week 1 and before Visit 2	24 (±21 days)	EW Visit should only be conducted if the participant discontinues from participating in the study. Participants withdrawing from study treatment but remaining in the study should continue to Visit 2.
Details of medicine and therapy taken for respiratory and other selected conditions		X	X	X	X	
	* The timing and number of planned study assessments, including assessments may be altered during the study based on newly available data.					

10.3. Appendix 3: Assessment Windows

Clinic visits/phone calls are scheduled to take place as specified in the protocol and the Schedule of Activities table in Appendix 2: Schedule of Activities. All participants should remain in the study and complete the week 24 visit. If this is not possible then an early withdrawal visit should be completed.

If a participant withdraws early from the study and provides early withdrawal assessments (CAT, FEV_1, Inhaler errors), then consideration is given as to how/if these data are used. This is defined under the estimand framework in the appropriate analysis methodology sections (Section 7).

10.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

10.4.1. Study Phases

10.4.1.1. Study Phases for Assessments

Assessments will be classified according to the time of occurrence relative to the study treatment (i.e., randomised treatment) start/stop date.

Study Phase	Definition
Pre-randomised Treatment	Assessment < Study Treatment Start Date
On-randomised Treatment	Study Treatment Start Date ≤ Assessment ≤ Study Treatment Stop Date + 1
Post-randomised Treatment	(Assessment > Study Treatment Stop Date + 1) and (Assessment ≤ Study Conclusion Date) **Note:** Participants can prematurely discontinue from the randomised treatment or modify their randomised treatment at any time during the study, at the Investigator's discretion. Any assessment performed after the randomised treatment stop day + 1 and before the study conclusion date will be considered as "Post-randomised Treatment".
Post-Study	Assessment > Study Conclusion Date Note: this post-study data will not be included in any summaries or analyses (but will be listed).

10.4.1.2. Study Phases for Concomitant Medication

Any medication or vaccine for the treatment of a respiratory condition that the participant receives at the time of consent or receives during the study are collected.

Classification of the prior/concomitant medication is described in Table 9.

Table 9 Classification of prior/concomitant medication

	Pre-randomised Treatment		On-randomised treatment		Post randomised treatment
(a)	x——x	Randomised Treatment Start Date		Randomised Treatment Stop Date	
(b)	x——		——x		
(c)	x——		——		——x
(d)			x——x		
(e)			x——		——x
(f)					x——x
(g)	?——x				
(h)*	?——		——x		
(i)*	?——		——		——x
(j)**	x——		——		——?
(k)**			x——		——?
(l)					x——?
(m)***	?——		——		——?

x = start/stop date of prior/concomitant medication
? = missing start/stop date of prior/concomitant medication

* If a medication is stopped on-randomised treatment or post-randomised treatment and no start date is recorded it will be assumed that the medication was ongoing from the pre-randomised treatment phase
** If a medication is started pre-randomised treatment or on-randomised treatment and no stop date is recorded then usage will be assumed to be ongoing for the remainder of the study
*** If a medication has no start or stop date it will be assumed that the medication was ongoing from the pre-randomised treatment phase to the post-randomised treatment phase

Medications which start/stop on the same day as the randomised treatment start or randomised treatment stop date respectively, will be classed as on-randomised treatment.

Partial dates for concomitant medications (if present) will be imputed as described in Section 10.7.2.1 prior to the classification of the medications as described in Table 9.

Medications that start after the date of study conclusion (i.e., Concomitant Medication Start Date > Study Conclusion Date), will be classified as "Post-Study". This post-study data will not be included in any summaries or analyses but will be listed.

Medications will be grouped based on the Respiratory Medication Class (RMC) (see Section 10.6.2) and sorted in descending order of total incidence for Respiratory Class and in descending order of total incidence for the ingredient within each Respiratory Class. If the total incidence for any two or more ingredients is equal, the ingredients will be presented in alphabetical order.

10.4.1.3. Study Phases for COPD Exacerbations

COPD exacerbations will be classified according to the time of occurrence relative to the study treatment (i.e., randomised treatment) start/stop date.

Study Phase	Definition
Pre-randomised Treatment	COPD Exacerbation < Study Treatment Start Date
On-randomised Treatment	Study Treatment Start Date ≤ COPD Exacerbation ≤ Study Treatment Stop Date + 1 Note: If Prior Medication Stop Date = Randomised Treatment Start Date (date overlap) and COPD Exacerbation starts on that day, the COPD exacerbation will be considered as "On-randomised Treatment".
Post-randomised Treatment	(COPD Exacerbation > Study Treatment Stop Date + 1) and (COPD Exacerbation ≤ Study Conclusion Date) **Note:** Participants can prematurely discontinue from the randomised treatment or modify their randomised treatment at any time during the study, at the Investigator's discretion. Any exacerbation occurring after the randomised treatment stop day + 1 and prior to the study conclusion date will be considered as "Post-randomised Treatment".
On-Study	Randomisation Date ≤ COPD Exacerbation ≤ Latest of (Study Conclusion Date or Study Withdrawal Date)
Post-Study	COPD Exacerbation > Study Conclusion Date

Study Phase	Definition
	Note: this post-study data will not be included in any summaries or analyses (but will be listed).

10.4.2. Treatment Emergent Flag for Adverse Events/Serious Adverse Events

Adverse Events/Serious Adverse Events will be classified according to the time of occurrence relative to the study treatment (i.e., randomised treatment) start/stop date.

Study Phase	Definition
Pre-randomised Treatment	AE/SAE Start Date < Study Treatment Start Date
On-randomised Treatment	Study Treatment Start Date ≤ AE/SAE Start Date ≤ Study Treatment Stop Date + 1 Note: If Prior Medication Stop Date = Randomised Treatment Start Date (date overlap) and AE/SAE starts on that day, the AE/SAE will be considered as "On-randomised Treatment".
Post-randomised Treatment	AE/SAE Start Date > Study Treatment Stop Date + 1 **Note:** Participants can prematurely discontinue from the randomised treatment or modify their randomised treatment at any time during the study, at the Investigator's discretion. Any AE/ SAEs reported after the randomised treatment stop day +1 and prior to the study conclusion date will be considered as "Post-randomised Treatment".
On-Study	Randomisation Date ≤ AE/SAE Start Date ≤ Latest of (Study Conclusion Date or Study Withdrawal Date)
Onset Time Since Study Treatment Start Date (days)	Time since first dose will be derived as followed: • If Study Treatment Start Date or AE/SAE Start Date is missing **=>** missing • If Study Treatment Start date > AE/SAE Start Date **=>** AE/SAE Start Date – Study Treatment Start Date • If Study Treatment Start Date ≤ AE/SAE Start Date **=>** AE/SAE Start Date – Study Treatment Start Date + 1
Duration (Days)	AE/SAE Resolution Date – AE/SAE Onset Date + 1
Drug-related	If relationship is marked 'YES'.

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Compound	: /arenv/arprod/gsk2834425/206854
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK Analysis & Reporting (A&R) dataset standards.	
Generation of RTF Files	
• Rich Text Format (RTF) files will be generated for all Table displays for this reporting effort.	

10.5.2. Reporting Standards

General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx): o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics **Note:** All data displays (Tables, Figures & Listings) produced as part of the Statistical Analysis Complete (SAC), will use the term "Subject" which reflects GSK Data Display Standards terminology.
Formats
• All data will be reported according to the treatment the participant was randomised to unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time
• Reporting for tables, figures and formal statistical analyses: • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. • Actual time will be used for calculation of times to event and Kaplan-Meier plots. • Reporting for Data Listings: • Planned and actual time relative to study start date will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
Unscheduled Visits
• Unscheduled visits will not be included in summary tables and/or 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 Treatment Start Date (i.e., Randomised Treatment Start Date):
  • Reference Date = Missing → Study Day = Missing
  • Reference Date < Treatment Start Date → Study Day = Reference Date –Treatment Start Date
  • Reference Data ≥ Treatment Start Date → Study Day = Reference Date – (Treatment Start Date) + 1

Randomised Treatment Start/Stop Date
• Randomised treatment start date will be defined as the earliest treatment start date and randomised treatment stop date will be defined as the latest treatment stop date as captured in the "Study Treatment" (CONMEDS_CR_1) eCRF form. Missing or partial randomised treatment stop dates will be handled as described in Section 10.7.2.1.

10.6.2. Study Population

Disposition
Time to Study Withdrawal/ Treatment Discontinuation
For Kaplan-Meier plots of study withdrawal over time and discontinuation from study treatment over time, censoring will be performed as follows: • For study withdrawal, participants are represented from the date of start of the randomised treatment to the date of early withdrawal from the study (or date of death). Participants that completed the study are censored at the earliest of the date of completion and Day 169. • For discontinuation from study treatment, participants are represented from the date of start of the study randomised treatment to the date of discontinuation from study randomised treatment (or date of death). Participants that complete study randomised treatment are censored at the earliest of their study randomised treatment stop date and Day 169.

Demographics
Age
• In accordance with GSK policy, only year of birth is collected in the eCRF. In order to estimate participant's age, a complete birthdate will be estimated by using the year recorded in the eCRF and assigning month and day values of '30JUN.' • Age, in whole years, will be calculated based on the Screening Visit date. • Birth date will be presented in listings as 'YYYY.' • Completely missing dates of birth will remain as missing with no imputation applied. Consequently, the age of the participant will not be calculated and will remain missing.
Age Categories
Age categories are based on age at Screening and are defined as:

Demographics

- ≤ 64 years
- 65-74 years
- 75-84 years
- ≥ 85 years

Body Mass Index (BMI)

BMI will be calculated in the eCRF as Weight (kg) / Height $(m)^2$.

Race

High-level Food and Drug Administration (FDA) race categories and designated Asian subcategories are:

- American Indian or Alaska Native
- Asian
  - Central/South Asian Heritage
  - Japanese Heritage/East Asian Heritage/South East Asian Heritage
  - Mixed Asian Heritage (only required if data exists)
- Black or African American
- Native Hawaiian or other Pacific Islander
- White

These categories and subcategories will be summarised along with all combinations of high-level categories which exist in the data. All five of the high-level race categories and the Asian subcategories must appear on the display even if there are no participants in a particular category, but combinations that do not exist in the data do not need to be represented. Combinations will be represented as the concatenation of the high-level category terms, e.g., "White & Asian". The designated Asian subcategories will not be summarised as combinations with other categories.

In addition, the standard race categories collected per IDSL will be summarized along with categories for mixed race. The categories are:

- American Indian or Alaska Native
- Asian - Central/South Asian Heritage
- Asian – East Asian Heritage
- Asian – Japanese Heritage
- Asian – South East Asian Heritage
- Black/African American
- Native Hawaiian or other Pacific Islander
- White – Arabic/North African Heritage
- White – White/Caucasian/European Heritage
- Mixed Asian Race
- Mixed White Race
- Multiple

"Mixed Asian Race" is only used if more than one Asian category is selected, but no non-Asian races. Similarly, "Mixed White Race" is only used if both of the White categories are selected, and no non-White races. If multiple races of different types are selected, then the overall "Multiple" category is used.

A participant will only be represented in a single category. A participant who selects a combination of races will be counted as "Mixed Asian Race," "Mixed White Race," or "Multiple," but not in each of the constituent terms. Therefore, the counts will add up to the total number of participants with a response.

Demographics
Age Ranges
For the Summary of Age Ranges, the following ranges will be presented, as per the European Medicines Agency (EMA) clinical trial results disclosure requirements: • Adults (18-64) • ≥ 65-84 years • ≥ 85 years

Extent of Exposure and Post-randomised Treatment Study Duration
• Number of days of exposure to randomised treatment will be calculated based on the formula: **[Randomised Treatment Stop Date – Randomised Treatment Start Date] + 1** Participants who were randomised but did not report a randomised treatment start date will be categorised as having zero days of exposure. • Duration of post-randomised treatment time spent in the study will be calculated as: **[Study Conclusion Date – Randomised Treatment Stop Date]** • Duration of total time spent in the study will be calculated as: **[Study Conclusion Date – Randomisation Date] + 1** The following exposure categories will also be presented: ≥ 1 day, ≥ 4 weeks, ≥ 8 weeks, ≥ 12 weeks, ≥16 weeks, ≥ 20 weeks, ≥ 24 weeks, 23-25 weeks

Medical Conditions and Concomitant Medications
COPD Exacerbation History
• COPD exacerbations occurring in the past 12 months prior to Screening reported on the Exacerbation History eCRF form will be categorized as 0, 1, ≥ 2. • The number of COPD exacerbations reported in the past 12 months will be summarised according to the categories: 1) moderate COPD exacerbations, 2) severe COPD exacerbations, and 3) moderate/severe COPD exacerbations. Moderate COPD exacerbations: defined as exacerbations that required treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalization). Severe COPD exacerbations: defined as exacerbations that required in-patient hospitalization. Moderate/Severe COPD exacerbations: defined as the total number of moderate and severe COPD exacerbations.
COPD Concomitant Medications
• COPD concomitant medications will be grouped into the following Respiratory Medication Classes (RMC) based on pre-defined code lists derived from Anatomical Therapeutic Chemical (ATC)

Medical Conditions and Concomitant Medications

classifications:

- Androgens and estrogens
- Anti-IgE, Anti-IL5
- Anticholinergic
- Antiinfectives (antibiotics, antiseptics)
- Antimycotics
- Antivirals
- Beta-2 agonists
- Corticosteroid – inhaled
- Corticosteroid – depot
- Corticosteroid – systemic oral parenteral and intra-articular
- Corticosteroid – other
- Leukotriene receptor antagonist
- Long-acting anticholinergic
- Long-acting beta-2 agonist – Group 2 (once per day)
- Long-acting beta-2 agonist – Group 3 (twice per day)
- Mucolytics
- Nedocromil or cromolyn sodium
- Oxygen
- PDE4 inhibitors
- Short-acting anticholinergic
- Short-acting beta-2 agonist
- Xanthine
- Other COPD medication

Actual Prior Medication Use Strata

The actual prior medication use strata will be defined from the CONMEDS form of the CRF using the COPD maintenance medications taken prior to Randomisation.

Historical Eosinophils Data

Historical Haematology data of White Blood Cell (WBC) and Eosinophils data will be collected at Visit 2. This data will be summarised by the randomised treatment groups (using descriptive statistics) and will be listed. Eosinophils data will also be categorised as described below and summarised by the randomised treatment groups:

- < 0.15 10^9/L
- ≥ 0.15 10^9/L

Screening Lung Function

Reversibility

A participant's status as reversible to salbutamol is calculated at Screening and is based on the difference (absolute change and % change) between a participant's pre-salbutamol assessment of FEV_1 and their post-salbutamol assessment of FEV_1 and is defined as follows:

- Reversible, if the difference in FEV_1 is ≥ 12% and ≥ 200 mL, or
- Non-reversible, if the difference in FEV_1 is < 200 mL or, the difference is ≥ 200 mL and is < 12 % of the pre-salbutamol FEV_1

If a participant was not able to provide both a pre-salbutamol and post-salbutamol assessment, then the

Screening Lung Function
reversibility status will be missing.
GOLD Grade 1-4
Participants will be classified into Global Initiative on Obstructive Lung Disease (GOLD) Grades 1-4 using the post-salbutamol percent predicted FEV_1 assessment at Screening [GOLD, 2017]: • GOLD Grade 1 (Mild): percent predicted $FEV_1 \geq 80\%$ • GOLD Grade 2 (Moderate): $50\% \leq$ percent predicted $FEV_1 < 80\%$ • GOLD Grade 3 (Severe): $30\% \leq$ percent predicted $FEV_1 < 50\%$ • GOLD Grade 4 (Very Severe): percent predicted $FEV_1 < 30\%$ If a participant was not able to provide post-salbutamol assessment, then the GOLD Grade will be missing.
FEV_1/FVC ratio at Screening
Using the lung function data from the PFT dataset, the following additional calculations will be performed: • Pre-bronchodilator FEV_1/FVC ratio will be calculated as: **[Pre-bronchodilator FEV_1/FVC (%)] / 100** • Post-bronchodilator FEV_1/FVC ratio will be calculated as: **[Post-bronchodilator FEV_1 / Post-bronchodilator FVC]** Pre and post-bronchodilator FEV_1/FVC ratio at Screening will be summarised.

Cardiovascular Risk Factors
Participants with at least one of the following current or past medical conditions at Screening will be classed as having a cardiovascular (CV) risk factor. • Coronary artery disease • Myocardial infarction • Arrhythmia • Congestive heart failure • Hypertension • Cerebrovascular accident • Diabetes mellitus • Hypercholesterolemia The number of CV risk factors at Screening (0, 1, or ≥ 2) will be derived.

10.6.3. Effectiveness

Intercurrent Events

Pulmonary Rehabilitation Status at Visit 1 and Visit 2

For the Pulmonary Rehabilitation, the following information is collected in the eCRF at Visit 1 and Visit 2:

V1, Q1: Is the subject currently on a Pulmonary rehabilitation program?
V1, Q2: Has the subject started a Pulmonary rehabilitation program within the last 8 weeks prior to Visit 1?
V1, Q3: Has the subject stopped a Pulmonary rehabilitation program within the last 8 weeks prior to Visit 1?

V2, Q1: Is the subject currently on a Pulmonary rehabilitation program?
V2, Q2: Has the subject started a Pulmonary rehabilitation program since Visit 1?
V2, Q3: Has the subject stopped a Pulmonary rehabilitation program since Visit 1?

The Pulmonary Rehabilitation status for a participant at Visit 1 or Visit 2 can be defined as: a) "On Pulmonary Rehabilitation" or b) "Not on Pulmonary Rehabilitation".

- **Visit 1:** In order for a participant to be considered as "Not on Pulmonary Rehabilitation" at Visit 1, the participant should not be currently on a Pulmonary Rehabilitation program at Visit 1 (i.e., All Visit 1 questions should be answered with a "No").

- **Visit 2:** In order for a participant to be considered as "Not on Pulmonary Rehabilitation" at Visit 2, the participant should not be currently on a Pulmonary Rehabilitation program at Visit 2 (i.e., All Visit 2 questions should be answered with a "No" and also not considered on Pulmonary Rehabilitation at Visit 1).

Primary Endpoint

COPD Assessment Test (CAT)

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

- For the Effectiveness analysis of CAT score:

  If the language of the CAT assessed at week 24 (Visit 2) is different from the language used at baseline (Visit 1), the CAT score at the week 24 (Visit 2) will be set to missing.

  With regards to the primary endpoint analyses, a participant will be considered as a responder according to the CAT score if their week 24 (Visit 2) CAT score has decreased at least 2 units from the baseline CAT score. A participant will be considered as a non-responder if their week 24 (Visit 2) CAT score has

decreased by less than 2 units, has not changed, or has increased compared to the baseline CAT score. Baseline CAT score is as defined in Section 5.2.

- Ways of handling missing week 24 CAT score data are included in Section 7.1.1 as part of the estimands defined for this endpoint.

Secondary Endpoint

Multiple Lung Function Tests

- If there are multiple spirometry tests recorded for a participant at **Visit 1**, the data from the latest test that is on or prior to the treatment start date will be considered in the planned data summaries and statistical analyses.

- If there are multiple spirometry tests recorded for a participant at **Visit 2**, the data from the latest test prior to study conclusion date will be considered for the planned data summaries and statistical analyses.

All lung function test data will be listed.

Trough FEV_1

For the spirometry assessment at Visit 1 and Visit 2, the following information is collected in the PFT dataset:

Q1: Please select the class of COPD maintenance treatment (Options: **9**=ICS+LABA+LAMA; **10**=LABA+LAMA; **12**=ICS+LABA; **13**=LABA; **14**=LAMA)

Q2: (Goes with Q1) How long since the patient took their last dose of COPD maintenance treatment? (Options: **12**=0 to 4 hours; **13**=4 to 8 hours; **14**=8 to 12 hours; **15**=12 to 16 hours; **16**=16 to 24 hours; **17**=24 hours)

Q3: Please select the class of COPD maintenance treatment. If no additional maintenance to that provided in Q1 then please select "Not applicable". (Options: **9**=ICS+LABA+LAMA; **10**=LABA+LAMA; **12**=ICS+LABA; **13**=LABA; **14**=LAMA; "Not applicable")

Q4: (Goes with Q3) How long since the patient took their last dose of COPD maintenance treatment? Please select "Not applicable" if "Not applicable" selected in Q3. (Options: **12**=0 to 4 hours; **13**=4 to 8 hours; **14**=8 to 12 hours; **15**=12 to 16 hours; **16**=16 to 24 hours; **17**=24 hours; "Not applicable")

Trough FEV_1 will be defined as the FEV_1 value recorded while participants have withheld the COPD maintenance treatment.

- For COPD maintenance treatments taken once-daily, FEV_1 will be considered as Trough if the participant withheld the LABA and LAMA components of the maintenance treatment for at least 16 hours (category **16**=16-24 hours or **17**=24 hours selected in Q2 and Q4 (if applicable))

- For COPD maintenance treatments taken twice-daily, FEV_1 will be considered as Trough if the participant withheld the LABA and LAMA components of the maintenance treatment for at least 8 hours (category **14**=8-12 hours, **15**=12-16 hours, **16**=16-24 hours or **17**=24 hours selected in Q2 and Q4 (if applicable))

Note:

- If information is missing for some of the components of the maintenance COPD medication but available for the rest of the components, it will be assumed that the missing information is the same as the available information (e.g., if participant is on ICS + LABA + LAMA (MITT) and the LABA component was Trough but there is no information available for the LAMA component, then it will be assumed that LAMA component was also Trough. Similarly, if LABA component was recorded as non-Trough). **Reminder:** we do not consider the ICS as a monotherapy component for the definition of the Trough FEV1.

- If information is completely missing for all components of the maintenance COPD medication, it will be assumed that the FEV_1 is not Trough.

- The maintenance COPD medication frequencies will be identified by linking the medication class selected at the PFT eCRF form with the medications listed in the Study Treatment eCRF form.

Critical Errors

- For the primary estimand of the secondary endpoint of critical errors (Section 7.2.3.4, Table 5), if participants modify their COPD maintenance therapy during the study the following scenarios are considered:
  a) If the new therapy uses the same device(s) as the randomised COPD maintenance therapy, and error assessments are performed on these new device(s), this data will be used in the analysis.
  b) If the new therapy uses different device(s) to the randomised COPD maintenance therapy, but they are device(s) that are assessed in the study (checklists available) and for which error assessments are performed, then this data will be set to missing.
  c) If the new COPD maintenance therapy uses device(s) which are not being assessed in this study (no checklists available) then no error assessment is available at week 24 (Visit 2) and so this data is expected to be missing.

- For the supportive estimand of the secondary endpoint of critical errors, if participants modify their COPD maintenance therapy during the study the inhaler error data will be used regardless of whether the participant remained on the same device(s) after modifying the randomised treatment.

- According to the protocol, if participant is using more than one inhaler for the administration of the COPD maintenance therapy and inhaler error checklists are not available in the study for all the inhalers, then an inhaler error assessment should not be performed at Visit 2 by the participant. However, in the situation that an inhaler error assessment has been carried out for any of those inhalers for which a checklist is available, the data will not be used in the primary analyses (primary estimand) or the supportive analysis (supportive estimand) but they will be used in the exploratory analysis of the individual inhaler comparisons (Section 7.2.3.5.1).
- In the situation where a participant may miss a component of a device assessment and one or more of the other question responses (critical error) indicate an error was made, then the missing value has no additional impact on the response outcome as participant will be considered as having at least one critical error. In the situation where a participant may miss a component of a device assessment and all other responses to question indicate no error made, then the response to this endpoint (i.e., participant making at least one critical error) will be set to missing.

- More details around ways of handling missing week 24 CE data are included in Section 7.2.3 as part of the estimands defined for this endpoint.

Other Endpoints

Clinically Important Deterioration (CID)

CID is a composite outcome defined as any one of the following events:

1. 100 mL reduction from baseline in FEV_1 at 24 weeks. **Note:** Baseline Trough FEV_1 will be considered for this component.
2. An exacerbation (requiring treatment with antibiotics and/or systemic steroids or hospitalisation)
3. 2 units change (increase) from baseline in CAT score at 24 weeks

Note: Point 1 can only be considered for participants who are part of the FEV_1 population (as defined in Section 4).

Ways of handling missing data in the analyses are included in Section 7.3.1 and Section 7.3.2 as part of the estimands defined for this endpoint.

For the listing of the CID data, the CID response flag will be defined as:

- If any of the three CID criteria defined above has been met, the participant will be considered as having experienced CID regardless of if the response to the other criteria is missing.
- If the response to any of the three CID criteria defined above is missing and the other criteria have not been met, then the CID response will be set to missing.

Note: The CID analyses incorporates multiple imputation for missing CAT score and missing Trough FEV_1 data as described in Section 7.3.1.4.

Time to First Moderate/Severe Exacerbation

- Individual exacerbations are collected in the eCRF by the Investigator during the study.

  COPD exacerbations will be classified as pre-randomised treatment, on-randomised treatment, post-randomised treatment, and on-study or post-study as described in Section 10.4.1.3. Also, exacerbation severity is defined in Section 10.6.1.

- The time to first exacerbation based only on on-randomised treatment data will be calculated as:

[First On-randomised Treatment Exacerbation Onset Date – Randomised Treatment Start Date] + 1

  Participants will be represented from the date of start of the randomised treatment to the start date of their first on-randomised treatment exacerbation or date of censoring. Participants that have not experienced an on-randomised treatment exacerbation are censored at the earliest of the randomised treatment stop date + 1 or the date of death.

- The time to first on-study exacerbation will be calculated as:

  [First Exacerbation Onset Date – Randomisation Date] + 1

Exacerbations reported during the on-study phase will be considered (see Section 10.4.1.3 for details of assigning study phase).

Participants will be represented from the day they were randomised in the study to the start date of their first exacerbation or date of censoring. Participants that have not experienced an on-study exacerbation are censored at the earliest of the study conclusion date or the date of death.

Annualised Rate of Moderate/Severe Exacerbations

- The annualized rate of on-randomised treatment exacerbations will be calculated as:

  [Number of Exacerbations / Time on Randomised Treatment (in days)] x 365.25

  where:

Number of Exacerbations:	Number of On-randomised Treatment Moderate/Severe Exacerbations for each Participant
Time on Randomised Treatment:	[earliest of (Randomised Treatment End Date + 1 or Date of Death or Study Conclusion Date) - Randomised Treatment Start Date] +1

- The annualized rate of on-study exacerbations will be calculated as:

  [Number of Exacerbations / Time on Study (in days)] x 365.25

  where:

Number of Exacerbations:	Number of On-Study Moderate/Severe Exacerbations for each Participant
Time on Study:	[earliest of (Study Conclusion Date or Study Withdrawal Date) - Randomisation Date] +1

Exploratory Endpoints

Association of CE with CAT, moderate/ severe exacerbations, FEV1 and FVC

- **Association of CE with CAT score:**
  - A box-plot of the number of critical errors and the CAT score at week 24 will be populated. The number of errors (classified as: 0 errors; 1 error; ≥ 2 errors) will be presented on the x-axis and the week 24 CAT score (continuous) will be presented in the y-axis.
  - A box-plot of the number of critical errors and the change from baseline in CAT score at week 24 will be populated. The number of errors (classified as: 0 errors; 1 error; ≥ 2 errors) will be presented on the x-axis and the change from baseline in CAT score at week 24 (continuous) will be presented in the y-axis.
  - The number of critical errors (classified as: 0 errors; 1 error; ≥ 2 errors) and the CAT response at week 24 (classified as: Responders, Non-responders) will also be summarised in a frequency table.
- **Association of CE with FEV_1:**
  - A box-plot of the number of critical errors and the FEV_1 at week 24 will be populated. The number of

errors (classified as: 0 errors; 1 error; ≥ 2 errors) will be presented on the x-axis and the week 24 FEV_1 (continuous) will be presented in the y-axis.
  - A box-plot of the number of critical errors and the change from baseline in FEV_1 at week 24 will be populated. The number of errors (classified as: 0 errors; 1 error; ≥ 2 errors) will be presented on the x-axis and the change from baseline in FEV_1 at week 24 (continuous) will be presented in the y-axis.

- **Association of CE with FVC:**
  - A box-plot of the number of critical errors and the FVC at week 24 will be populated. The number of errors (classified as: 0 errors; 1 error; ≥ 2 errors) will be presented on the x-axis and the week 24 FVC (continuous) will be presented in the y-axis.
  - A box-plot of the number of critical errors and the change from baseline in FVC at week 24 will be populated. The number of errors (classified as: 0 errors; 1 error; ≥ 2 errors) will be presented on the x-axis and the change from baseline in FVC at week 24 (continuous) will be presented in the y-axis.

- **Association of CE with Moderate/Severe Exacerbations:**
  The number of critical errors (classified as: 0 errors; 1 error; ≥ 2 errors) and the number of exacerbations (classified as: 0 exacerbations; 1 exacerbation; ≥ 2 exacerbations), will be summarised in a three-way frequency table. One frequency table for the on-randomised treatment moderate/severe exacerbations and one for the on-study moderate/severe exacerbations.

Participant Treatment and Study Satisfaction Questionnaire

The Participant Treatment and Study Satisfaction Questionnaire include the following items:

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

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

Data will be summarized and listed as described in Section 7.4.2.

Health Related Quality of Life Questionnaire

The Health Related Quality of Life Questionnaire includes the following items:

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

Data will be summarised and listed as described in Section 7.4.3.

10.6.4. Safety

Serious Adverse Events

Serious Adverse Events of Special Interest

SAESI have been defined as SAEs which have specified areas of interest for FF, VI or UMEC or the overall COPD population. The following table presents the SAESI groups. Groups which are not SMQs are made up of a selection of preferred terms (PTs) defined by GSK. The complete list, including the PTs which contribute to each of the groups will be provided by Global Clinical Safety and Pharmacovigilance (GCSP) using the MedDRA version current at the time of reporting. This will be finalized prior to unblinding.

SAESI Group	SAESI Subgroup	Sub-SMQ
Cardiovascular effects	Cardiac arrhythmia	Arrhythmia related investigations, signs and symptoms (SMQ)
		Bradyarrhythmia terms, nonspecific (SMQ)
		Conduction defects (SMQ)
		Disorders of sinus node function (SMQ)
		Cardiac arrhythmia terms, nonspecific (SMQ)
		Supraventricular tachyarrhythmias (SMQ)
		Tachyarrhythmia terms, nonspecific (SMQ)
		Ventricular tachyarrhythmias (SMQ)
	Cardiac failure (SMQ)	
	Ischaemic heart disease (SMQ)	
	Hypertension (SMQ)	
	Central nervous system haemorrhages and cerebrovascular conditions (SMQ)	
Decreased bone mineral density and associated fractures		
Pneumonia		Infective pneumonia SMQ (Narrow)
Lower Respiratory Tract Infection (LRTI) excluding pneumonia SMQ (Narrow)		

For the planned summary of SAESI by class of medication:

- For the SAESI group of Pneumonia, events will be allocated to the treatment the participant was taking for the majority of the 28 days prior to the onset of the event. If the event occurred within 28 days of Randomisation, only the treatment taken post Randomisation is considered for the treatment allocation. For all other special interest groups, events are allocated to the treatment the participant was taking on the day of onset of the event.
- For SAESI group of Pneumonia, a participant will be considered at risk for a given treatment up until 28 days after the stop date of this treatment.

10.7. Appendix 7: Reporting Standards for Missing Data

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Participant study completion (i.e., as specified in the protocol) is defined as completion of the week 24 study visit (Visit 2). • Participant treatment completion is defined as no premature discontinuation or modification of the randomised COPD maintenance treatment at any time prior to formal study completion. • Withdrawn participants were not replaced in the study. • ICH-required data from participants who were withdrawn from the study will be listed and all available planned data will be included in relevant summary tables and figures, unless otherwise specified. • Withdrawal visits will be slotted as per Appendix 3: Assessment Windows or will be summarised as withdrawal visits.

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:
	  ○ These data will be indicated by the use of a "blank" in participant listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table.
	  ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

Handling of missing data in the statistical analyses of the primary, secondary or other endpoints (i.e., *CID*), is described in Section 7 as part of the estimands framework. When multiple imputation is the suggested method for handling missing data, then the imputation will follow the steps described below.

Element	Reporting Detail
Week 24 CAT	For the Primary Estimand and the Supportive Estimand II defined in Section 7.1.1.4 and Section 7.1.1.5.1, respectively, missing week 24 CAT score data will be imputed as described below: 1. In the original analysis dataset (Dataset A), a flag variable for each intercurrent event identified for the endpoint will be created, which will indicate the participants for which the intercurrent event has occurred. 2. If a participant has reported at least one intercurrent event for which a "composite" strategy is suggested, the continuous endpoint data (if available) for that participant will be set to missing. All participants remain in one dataset which will be used for the imputation. 3. First step of the imputation will be to run an imputation model (parameter-estimation model) to get pseudo-independent samples from the joint posterior distribution for the linear predictor parameters ("betas" associated with treatment, baseline CAT score (continuous), number of exacerbations in the prior year (categorical), prior medication

use strata (categorical) and country (categorical)) and the covariance parameters.

4. Next step is to impute the missing endpoint data (as continuous data) by constructing endpoint estimates from the samples. This will be done assuming that the data is missing-at-random (MAR) i.e., based on the randomised treatment arm characteristics. A sufficient number of *m* samples (imputations) will be used to ensure that the final estimates are consistent and independent of any seeds used in the sampling process. Note that the participants with an intercurrent event for which a composite strategy is planned, will technically also have their "missing" continuous data imputed but this will be ignored. Also, note that participants with missing baseline CAT score (or any other missing covariates) will not be included in the analysis as they will not have a change from baseline.

5. There will be *m* imputed sets of data for analysis.

6. For each set of data, a binary response variable indicating responders and non-responders based on the change from baseline CAT score at week 24 (Visit 2) will be created for each participant. Note that the imputed continuous data for those participants flagged as having a composite intercurrent event should be set back to missing and the response status defined as "non-response" by definition (composite strategy).

7. A univariate logistic regression analysis will be performed for each set of data as described in Section 7.1.1.5.1.

8. The "m" results from the analyses of each set of data are combined using Rubin's formulae [Rubin, 1987]. (Note: model estimates should be combined on the model scale rather than the exponentiated [odds ratio] scale and then turned into an odds ratio by exponentiating).

Note: This approach will also be used for the imputation of missing CAT score data for the analysis of 2 Units Change (Increase) from Baseline in CAT score at 24 weeks (CID analysis of components, Section 7.3.2.2), adjusting for the covariates specified for this analysis (i.e., baseline CAT, prior medication use strata and country) and for the imputation of missing Trough FEV_1 data for the analysis of 100mL reduction in Trough FEV_1 at 24 weeks (analysis of CID components, Section 7.3.2.1), adjusting for the covariates specified for these analyses (i.e., baseline Trough FEV_1, prior medication use strata and country.

For the Supportive Estimand III (Hypothetical) defined in Section 7.1.1.5.1, week 24 CAT score data will be imputed as described below:

1. In the original analysis dataset (Dataset A), a flag variable for each intercurrent event identified for the endpoint will be created, which will indicate the participants for which the intercurrent event has occurred.

2. For participants who have reported any of the intercurrent events identified for the endpoint, their response (if available) after the occurrence of the event (i.e., week 24 (Visit 2) CAT score) will be set to missing (Dataset B). All missing week 24 (Visit 2) CAT score values (those originally missing and those set to missing) will be imputed. Dataset B will be used for the imputation.
3. First step of the imputation will be to run an imputation model (parameter-estimation model) to get pseudo-independent samples from the joint posterior distribution for the linear predictor parameters ("betas" associated with treatment, baseline CAT score

	(continuous), number of exacerbations in the prior year (categorical), prior medication use strata (categorical) and country (categorical)) and the covariance parameters. 4. Next step is to impute the missing endpoint data (as continuous data) by constructing endpoint estimates from the samples. This will be done assuming that the data is missing-at-random (MAR) i.e. based on the randomised treatment arm characteristics. A sufficient number of *m* samples (imputations) will be used to ensure that the final estimates are consistent and independent of any seeds used in the sampling process. 5. There will be *m* imputed sets of data for analysis. 6. For each set of data for analysis, a binary response variable indicating the responders and non-responders based on the change from baseline CAT score at week 24 (Visit 2) will be created for each participant. 7. A univariate logistic regression analysis will be performed for each "new" analysis dataset as described in RAP Section 7.1.1.5.1. 8. The "m" results from the analyses of each dataset are combined using Rubin's formulae [Rubin, 1987]. (Note: model estimates should be combined on the model scale rather than the exponentiated [odds ratio] scale and then turned into an odds ratio by exponentiating).
Week 24 FEV_1/ Trough FEV_1	For the estimands defined in Sections 7.2.1 (FEV_1 analysis) and Section 7.2.2 (Trough FEV_1 analysis), missing week 24 FEV_1/Trough FEV_1 data will be imputed as described below: 1. In the original analysis dataset (Dataset A), a flag variable for each intercurrent event identified for the endpoint will be created, which will indicate the participants for which the intercurrent event has occurred. 2. Note that for the intercurrent events defined for these endpoints, no composite strategy is planned so Dataset A will be used as it is for the imputation. 3. First step of the imputation will be to run an imputation model (parameter-estimation model) to get pseudo-independent samples from the joint posterior distribution for the linear predictor parameters ("betas" associated with treatment, baseline FEV_1/Trough FEV_1 score (continuous), prior medication use strata (categorical), country (categorical) and timing of spirometry (categorical – only for the FEV_1 analysis)) and the covariance parameters. 4. Next step is to impute the missing endpoint data (as continuous data) by constructing endpoint estimates from the samples. This will be done assuming that the data is missing-at-random (MAR) i.e. based on the randomised treatment arm characteristics. A sufficient number of *m* samples (imputations) will be used to ensure that the final estimates are consistent and independent of any seeds used in the sampling process. Note that participants with missing FEV_1/Trough FEV_1 at Visit 1 (or any other missing covariates) will not be included in the analysis as they will not have a change from baseline. 5. There will be *m* imputed sets of data for analysis. 6. For each set of data, a univariate ANCOVA analysis will be performed for each set of

	data as described in Section 7.2.1.5.1 (FEV_1 analysis) and Section 7.2.2.5.1 (Trough FEV_1 analysis). 7. The "m" results from the analyses of each set of data are combined using Rubin's formulae [Rubin, 1987].
CID	For the estimand defined in Section 7.3.1.4, missing week 24 CAT score data and/or missing week 24 Trough FEV_1 data will be imputed as described below: 1. In the original analysis dataset (Dataset A), a flag variable for each intercurrent event identified for the endpoint will be created, which will indicate the participants for which the intercurrent event has occurred. 2. If a participant has reported at least one intercurrent event for which a "composite" strategy is suggested, the continuous week 24 Trough FEV_1 data and the CAT score data for that participant (if available) will be set to missing. All participants remain in the one dataset which will be used for the imputation. 3. For each of the following components of the CID endpoint: a) CAT score and b) Trough FEV_1, first step of the imputation will be to run an imputation model (parameter-estimation model) to get pseudo-independent samples from the joint posterior distribution for the linear predictor parameters ("betas" associated with treatment, baseline Trough FEV_1 (continuous), baseline CAT score (continuous), number of exacerbations in the prior year (categorical), prior medication use strata (categorical) and country (categorical)) and the covariance parameters. Note: Missing exacerbation data will not be imputed. 4. For each of the components of the CID mentioned in the previous step (CAT score and Trough FEV_1) next step is to impute the missing data (CAT score and Trough FEV_1 data) as continuous data by constructing endpoint estimates from the samples. This will be done assuming that the data is missing-at-random (MAR) i.e. based on the randomised treatment arm characteristics. A sufficient number of *m* samples (imputations) will be used to ensure that the final estimates are consistent and independent of any seeds used in the sampling process. Note that the participants with an intercurrent event for which a composite strategy is planned, will technically also have their "missing" continuous data imputed but this will be ignored. Also, note that participants with missing CAT score at Visit 1 or missing Trough FEV_1 data at Visit 1 (or any other missing covariates) will not be included in the analysis as they will not have a change from baseline. 5. There will be *m* imputed sets of data for analysis. 6. For each set of data, a binary response variable indicating participants who experience CID and those who do not (as defined in Section 10.6.3) will be created for each participant. Note that the imputed continuous data for those participants flagged as having a composite intercurrent event, should be set back to missing and the response status defined as "non-response" by definition (composite strategy). 7. A univariate logistic regression analysis will be performed for each set of data as described in Section 7.3.1.5.1. 8. The "m" results from the analyses of each set of data are combined using Rubin's formulae [Rubin, 1987]. (Note: model estimates should be combined on the model

	scale rather than the exponentiated [odds ratio] scale and then turned into an odds ratio by exponentiating).

10.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays.
Randomised Treatment Stop Date	• If participant remained on the randomised treatment throughout the study (i.e., no randomised treatment discontinuation or randomised treatment modification) and has a missing or partial randomised treatment stop date, then the randomised treatment stop date will be imputed in the following way: o If the date is completely missing, it will be imputed as the latest of Study Conclusion Date/ Visit 2 Date o If partial date is available (only month and year available), then the day will be imputed as the earliest of [the Last Day of the Month or the Study Conclusion Date/ Visit 2 Date] o If a partial date is available (only year available), then the day and month will be imputed as the earliest of [the Last Day of the Year or the Study Conclusion Date/ Visit 2 Date] • If participant has discontinued from randomised treatment or modified randomised treatment during the study or discontinued from study (Early Withdrawal) and has a missing or partial randomised treatment stop date, then the randomised treatment stop date will be imputed in the following way: o If the date is completely missing, it will be imputed as the Day Prior to the Start Date of the Modified Maintenance Treatment o If a partial date is available (only month and year available), then the day will be imputed as the earliest of [the Last Day of the Month or the Day Prior to the Start Date of the Modified Maintenance Treatment] o If a partial date is available (only year available), then the day and month will be imputed as the earliest of [the Last Day of the Year or the Day Prior to the Start Date of the Modified Maintenance Treatment] • In the special situation where, a participant has discontinued from randomised treatment or modified randomised treatment during the study or discontinued from study (Early Withdrawal) and has a missing or partial randomised treatment stop date, but the start date of the modified maintenance treatment is also missing or partial, then the randomised treatment stop date and the modified randomised treatment start date will be imputed in the following way: o If partial dates are available (only month and year available), and Visit 2 or Conclusion Date (if Visit 2 Date not available or Visit 2 Date = Conclusion Date) is in the same month, then the Modified Treatment Start Date will be imputed as the Day Prior to Visit 2/ Conclusion Date and the Randomised Treatment Stop Date as the Day Prior to the Imputed Modified Treatment Stop Date. E.g.,

Date	Original Date	Imputed Date
Randomised Treatment Stop Date	--Apr-2019	22-Apr-2019
Modified Treatment Start Date	--Apr-2019	23-Apr-2019

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<tr><td>Visit 2 Date</td><td>24-Apr-2019</td><td>N/A</td></tr>
</table>

For the scenario above, same rule will apply if one of the two dates are completely missing but the other is partial or if both dates are completely missing.

o If partial dates are available (only month and year available), and Visit 2 or Conclusion Date (if Visit 2 date not available or Visit 2 Date = Conclusion Date) is not in the same month, then the Modified Treatment Start Date will be imputed as the Last Day of the Month (of the partial date) and the Randomised Treatment Stop Date as the Day Prior to the Imputed Modified Treatment Stop Date.
E.g.,
<table>
<tr><th>Date</th><th>Original Date</th><th>Imputed Date</th></tr>
<tr><td>Randomised Treatment Stop Date</td><td>--Apr-2019</td><td>29-Apr-2019</td></tr>
<tr><td>Modified Treatment Start Date</td><td>--Apr-2019</td><td>30-Apr-2019</td></tr>
<tr><td>Visit 2 Date</td><td>10-May-2019</td><td>N/A</td></tr>
</table>

For the scenario above, if the Randomised Treatment Stop Date is partial and the Modified Treatment Start Date dates is completely missing, then the Randomised Treatment Stop Date will be imputed as the last day of the month (of the partial date) and the Modified Treatment Start Date as the Day After the Imputed Randomised Treatment Stop Date.
</td></tr>
<tr><td>Adverse Events/ Serious Adverse Events</td><td>• The eCRF does not allow for the possibility of partial dates to be recorded for AE/SAE start and end dates.
• 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.</td></tr>
<tr><td>Concomitant Medications</td><td>• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month
o If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.
• The recorded partial date will be displayed in listings.</td></tr>
</table>

10.8. Appendix 8: Abbreviations & Trade Marks

10.8.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
A&R	Analysis and Reporting
CAT	COPD Assessment Test
CDISC	Clinical Data Interchange Standards Consortium
CE	Critical Error
CI	Confidence Interval
CID	Clinically Important Deterioration
CIL	Clinical Investigation Lead
COPD	Chronic Obstructive Pulmonary Disease
CSR	Clinical Study Report
CV	Cardiovascular
DBF	Database Freeze
DBR	Database Release
DP	Decimal Places
DQL	Data Quality Lead
eCRF	Electronic Case Record Form
EHR	Electronic Health Record
EMA	European Medicines Agency
EW	Early Withdrawal
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
GOLD	Global Initiative on Obstructive Lung Disease
GSK	GlaxoSmithKline
HCP	Health Care Provider
HCRU	Healthcare Resource Utilisation
HRQoL	Health Related Quality of Life Questionnaire
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
IP	Investigational Product
IWRS	Interactive Web Response System
ITT	Intent-To-Treat
MAR	Missing at Random
MDI	Metered Dose Inhaler
MITT	Multiple Inhaler Triple Therapy
MM	Medical Monitor
OSL	Operational Study Lead
PDMP	Protocol Deviation Management Plan
PFT	Pulmonary Function Test
PP	Per Protocol

Abbreviation	Description
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
RW	Real World
SAC	Statistical Analysis Complete
SERM	Safety Evaluation and Risk Management
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
VEO	Value Evidence and Outcomes

10.8.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
CAT
DISKUS
ELLIPTA
RAMOS NG
RANDALL NG
TRELEGY

Trademarks not owned by the GlaxoSmithKline Group of Companies
BREEZHALER
GENUAIR
HANDIHALER
SAS
TURBUHALER

10.9. Appendix 9: List of Data Displays

10.9.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.n	1.1 to 1.n
Effectiveness	2.1 to 2.n	2.1 to 2.n
Safety	3.1 to 3.n	N/A
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	x+1 to y	

10.9.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 10: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Effectiveness	EFF_Fn	EFF_Tn	EFF_Ln
Safety	-	SAFE_Tn	SAFE_Ln

NOTES:

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

10.9.3. Deliverables

Delivery	Description
SAC	Final Statistical Analysis Complete

10.9.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	ASE	Non-Standard	Summary of Subject Populations and Reasons for Screen Failure		SAC
1.2.	ITT	Non-Standard	Summary of Attendance at Each Visit by Visit Type	*See IMPACT 1.02.* *For Visit 1, Visit type will be: 1) Patient usual care site; 2) Referral site; 3) Home visit. For Visit 2, Visit type will be the ones defined for Visit 1 with the addition of 4) Telephone Visit.* *Present EW visit separately using the Visit type categories defined for Visit 2.*	SAC
1.3.	FEV1	Non-Standard	Summary of Attendance at Each Visit by Visit Type	*As for Table 1.2.*	SAC
1.4.	CE	Non-Standard	Summary of Attendance at Each Visit by Visit Type	*As for Table 1.2.*	SAC
1.5.	ITT	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		SAC
1.6.	FEV1	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		SAC
1.7.	CE	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.8.	ITT	ES1	Summary of Study Status and Reasons for Study Withdrawal		SAC
1.9.	FEV1	ES1	Summary of Study Status and Reasons for Study Withdrawal		SAC
1.10.	CE	ES1	Summary of Study Status and Reasons for Study Withdrawal		SAC
1.11.	ITT	Non-Standard	Summary of Prior Medication Use Strata		SAC
1.12.	ASE	Non-Standard	Summary of Number of Subjects by Country	*Based on IDSL NS1 but display presented only by Country (not by Centre ID and Investigator ID). Only Total column is required.*	SAC
1.13.	ITT	NS1	Summary of Number of Subjects by Country and Centre		SAC
1.14.	ASE	IE1	Summary of Inclusion/Exclusion Criteria Deviations for Screen Failures		SAC
1.15.	ITT	IE1	Summary of Inclusion/Exclusion Criteria Deviations		SAC
Protocol Deviation					
1.16.	ITT	DV1	Summary of Important Protocol Deviations		SAC
Demographic and Baseline Characteristics					
1.17.	ASE	DM11	Summary of Age Ranges	*As per IDSL DM11 but also see Section 10.6.2.*	SAC
1.18.	ITT	DM1	Summary of Demographic Characteristics	*As per IDSL DM1 but also see Section 10.6.2.*	SAC
1.19.	FEV1	DM1	Summary of Demographic Characteristics	*As per IDSL DM1 but also see Section 10.6.2.*	SAC
1.20.	CE	DM1	Summary of Demographic Characteristics	*As per IDSL DM1 but also see Section 10.6.2.*	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.21.	ITT	DM1	Summary of Demographic Characteristics by Country		SAC
1.22.	ITT	DM1	Summary of Demographic Characteristics by Prior Medication Use Strata		SAC
1.23.	ITT	DM5	Summary of Race and Racial Combinations	*As per IDSL DM5 but also see Section 10.6.2.*	SAC
Medical Conditions					
1.24.	ITT	MH4	Summary of Current Medical Conditions		SAC
1.25.	ITT	MH4	Summary of Past Medical Conditions		SAC
1.26.	ITT	Non-Standard	Summary of Cardiovascular Risk Factors		SAC
1.27.	ITT	FH1	Summary of Family History of Cardiovascular Risk Factors		SAC
Disease Characteristics					
1.28.	ITT	Non-Standard	Summary of COPD Duration at Screening		SAC
1.29.	ITT	Non-Standard	Summary of COPD Exacerbation History at Screening		SAC
1.30.	FEV1	Non-Standard	Summary of Lung Function at Screening	*Table will include all available Screening data regardless of visit type (e.g., domiciliary visit etc). It will also include historical CAT score data (more than 14 days prior to V1 - not flagged as baseline).*	SAC
1.31.	FEV1	Non-Standard	Summary of Reversibility and GOLD Grade (1–4) at Screening	*See Section 10.6.2.*	SAC
1.32.	FEV1	Non-Standard	Summary of PIFR (L/min) at Screening		SAC
1.33.	ITT	Non-Standard	Summary of CAT Score and CAT Category at Screening	*CAT categories: CAT < 10 and CAT ≥ 10.*	SAC
1.34.	ITT	Non-Standard	Summary of Historical Eosinophils Data	*See Section 10.6.2.*	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Prior and Concomitant Medications					
1.35.	ITT	Non-Standard	Summary of Pre-randomised Treatment Respiratory Concomitant Medications Excluding those Taken for an Exacerbation	*Non-Standard but based on IDSL CM1. RMC classification to be used.*	SAC
1.36.	ITT	Non-Standard	Summary of On-randomised Treatment Respiratory Concomitant Medications Excluding those Taken for an Exacerbation	*Non-Standard but based on IDSL CM1. RMC classification to be used. Randomised COPD Maintenance Therapy will not be included in this summary.*	SAC
1.37.	ITT	Non-Standard	Summary of Post-randomised Treatment Respiratory Concomitant Medication Excluding those Taken for an Exacerbation	*Non-Standard but based on IDSL CM1. RMC classification to be used.*	SAC
1.38.	ITT	Non-Standard	Summary of Pre-randomised Treatment COPD Concomitant Medications Taken for an Exacerbation	*Non-Standard but based on IDSL CM1. RMC classification to be used.*	SAC
1.39.	ITT	Non-Standard	Summary of On-randomised Treatment COPD Concomitant Medications Taken for an Exacerbation	*Non-Standard but based on IDSL CM1. RMC classification to be used.*	SAC
1.40.	ITT	Non-Standard	Summary of Post-randomised Treatment COPD Concomitant Medications Taken for an Exacerbation	*Non-Standard but based on IDSL CM1. RMC classification to be used.*	SAC
1.41.	ITT	Non-Standard	Summary of Respiratory Concomitant Medication Combinations Taken at Screening Excluding Those Taken for an Exacerbation	*Non-Standard but based on IDSL CM1. RMC classification to be used. See IMPACT Table 1.67.*	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.42.	ITT	Non-Standard	Summary of Respiratory Concomitant Medication Taken at Treatment Discontinuation Excluding Those Taken for an Exacerbation	*Non-Standard but based on IDSL CM1. RMC classification to be used. See IMPACT Table 1.70.*	SAC
Treatment Exposure					
1.43.	ITT	Non-Standard	Summary of Treatment Exposure	*Exposure to Randomised Treatment.* *Also present the total time in study post-randomised treatment and the total time spent on-study.* *See 207609 Table 3.1.*	SAC
1.44.	ITT	Non-Standard	Summary of Unique Treatment Paths	*See study HZC115151, Table 1.34 (only bottom segment is required).*	SAC
Intercurrent Events					
1.45.	ITT	Non-Standard	Summary of Intercurrent Events		SAC
1.46.	FEV1	Non-Standard	Summary of Intercurrent Events		SAC
1.47.	CE	Non-Standard	Summary of Intercurrent Events		SAC

10.9.5. Study Population Figures

Study Population Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.1.	ITT	Non-Standard	Kaplan-Meier Plot of Time to Premature Discontinuation of Study Treatment		SAC
1.2.	ITT	Non-Standard	Kaplan-Meier Plot of Time to Study Withdrawal		SAC

10.9.6. Effectiveness Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Primary Endpoint					
2.1.	ITT	Non-Standard	Summary of CAT Score	*Summary at each visit (Baseline CAT, Week 24 and Change from Baseline – separate out EW visit).*	SAC
2.2.	ITT	Non-Standard	Summary and Analysis of the Percentage of Responders According to the CAT Score at Week 24 (Primary Estimand - Treatment Policy x Composite)	*Include Footnote:* *"Note: A Treatment policy strategy was used for the intercurrent event of Randomised Treatment Discontinuation. For the intercurrent events of Randomised Treatment Modification, change of Pulmonary Rehabilitation status and start of Oxygen Therapy, a Composite strategy was used."*	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.3.	ITT	Non-Standard	Summary and Analysis of the Percentage of Responders According to the CAT Score at Week 24 (Supportive Estimand I- Treatment Policy x Composite)	*Include Footnote:* *"Note: A Treatment policy strategy was used for the intercurrent event of Randomised Treatment Discontinuation, Randomised Treatment Modification, change of Pulmonary Rehabilitation status and start of Oxygen Therapy. Subjects who prematurely discontinue from study and subjects with missing Visit 2 (Week 24) CAT score (for other reason) are considered as non-responders".*	SAC
2.4.	ITT	Non-Standard	Summary and Analysis of the Percentage of Responders According to the CAT Score at Week 24 (Supportive Estimand II– Treatment Policy x Composite)	*Include Footnote:* *"Note: A Treatment policy strategy was used for the intercurrent events of Randomised Treatment Discontinuation, change of Pulmonary Rehabilitation status and start of Oxygen Therapy. For the intercurrent event of Randomised Treatment Modification, a Composite strategy was used.".*	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.5.	ITT	Non-Standard	Summary and Analysis of the Percentage of Responders According to the CAT Score at Week 24 (Supportive Estimand III– Hypothetical)	*Include Footnote:* *"Note: A Hypothetical strategy was used for the intercurrent events of Randomised Treatment Discontinuation, Randomised Treatment Modification, change of Pulmonary Rehabilitation status and start of Oxygen Therapy.".*	SAC
2.6.	ITT	Non-Standard	P-values for Interactions of Treatment with Covariates for Analysis of the Percentage of Responders According to the CAT Score at Week 24 (Primary Estimand - Treatment Policy x Composite)	*The p-value for each interaction test will be presented. If any interaction p-value is less than 0.10 further investigations will be carried out, for example running the analysis by each category of the subgroup. Any output from interaction investigation will also be presented in additional displays.*	SAC
Secondary Endpoints					
2.7.	FEV1	Non-Standard	Summary of FEV1	*Summary at each visit (Baseline FEV1, Week 24 and Change from Baseline – separate out EW visit).*	SAC
2.8.	FEV1	Non-Standard	Summary of Trough FEV1	*Summary at each visit (Baseline Trough FEV1, Week 24 and Change from Baseline – separate out EW visit).*	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.9.	FEV1	Non-Standard	Analysis of Change from Baseline in FEV1 at Week 24 (Primary Estimand – Treatment Policy)	*Include Footnote:* *"Note: A Treatment Policy strategy was used for the intercurrent events of Randomised Treatment Discontinuation, Randomised Treatment Modification, change of Pulmonary Rehabilitation status and start of Oxygen Therapy.".*	SAC
2.10.	FEV1	Non-Standard	Analysis of Change from Baseline in Trough FEV1 at Week 24 (Primary Estimand – Treatment Policy)	*Include Footnote:* *"Note: A Treatment Policy strategy was used for the intercurrent events of Randomised Treatment Discontinuation, Randomised Treatment Modification, change of Pulmonary Rehabilitation status and start of Oxygen Therapy.".*	SAC
2.11.	CE	Non-Standard	Summary of Critical and Overall Errors	*Each inhaler presented on different page. Frequency for each error type to be presented for each inhaler.* *Flag with "[1]" the error types which are considered as critical errors and include relevant footnote.* *Include footnote: "All inhalers apart from the Ellipta inhaler are used in combination with at least one other inhaler by the subjects.".*	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.12.	CE	Non-Standard	Analysis of the Percentage of Subjects Making at Least One Critical Error at Week 24 (Primary Estimand – Hypothetical)	*Include Footnote:* *"Note: A Hypothetical strategy was used for the intercurrent event of Randomised Treatment Modification.".*	SAC
2.13.	CE	Non-Standard	Analysis of the Percentage of Subjects Making at Least One Critical Error at Week 24 (Supportive Estimand – Treatment Policy)	*Include Footnote:* *"Note: A Treatment Policy strategy was used for the intercurrent event of Randomised Treatment Modification.".*	SAC
2.14.	ITT	Non-Standard	Analysis of the Percentage of Subjects Making at Least One Critical Error at Week 24 Ellipta vs Comparator Device (Exploratory Estimand – Treatment Policy)	*Exploratory analysis to be performed if at least 100 subjects/arm perform an inhaler assessment. Comparison of inhalers: Ellipta vs Diskus; Ellipta vs Breezhaler; Ellipta vs Handihaler; Ellipta vs MDI; Ellipta vs Turbuhaler; Ellipta vs Genuair to be presented in each page.*	SAC
Other Endpoints					

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.15.	FEV1	Non-Standard	Summary and Analysis of the Percentage of Subjects Who Experience Clinically Important Deterioration (Primary Estimand – Treatment Policy x Composite)	*Include Footnote:* *"Note: A Treatment Policy strategy was used for the intercurrent events of Randomised Treatment Discontinuation, Randomised Treatment Modification and change of Pulmonary Rehabilitation status. For the intercurrent event of start of Oxygen Therapy, a Composite strategy was used.".*	SAC
2.16.	FEV1	Non-Standard	Summary and Analysis of the Percentage of Subjects Who Experience Clinically Important Deterioration (Sensitivity Analysis – Treatment Policy x Composite Estimand)	*Same estimand as in Table 2.15, excluding the number of exacerbations in the prior year from the list of covariates in the model.*	SAC
2.17.	FEV1	Non-Standard	Summary and Analysis of the Percentage of Subjects Who Experience a 100 mL Reduction from Baseline in Trough FEV1 at 24 Weeks (Primary Estimand – Treatment Policy x Composite)	*Include Footnote:* *"Note: A Treatment Policy strategy was used for the intercurrent events of Randomised Treatment Discontinuation, Randomised Treatment Modification and change of Pulmonary Rehabilitation status. For the intercurrent event of start of Oxygen Therapy, a Composite strategy was used.".*	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.18.	FEV1	Non-Standard	Summary and Analysis of the Percentage of Subjects Who Experience a 2-unit Change (Increase) from Baseline in CAT Score at 24 Weeks (Primary Estimand – Treatment Policy x Composite)	*Include Footnote:* *"Note: A Treatment Policy strategy was used for the intercurrent events of Randomised Treatment Discontinuation, Randomised Treatment Modification and change of Pulmonary Rehabilitation status. For the intercurrent event of start of Oxygen Therapy, a Composite strategy was used.".*	SAC
2.19.	ITT	Non-Standard	Summary of On-randomised Treatment Moderate/Severe COPD Exacerbations		SAC
2.20.	ITT	Non-Standard	Summary of On-Study Moderate/Severe COPD Exacerbations		SAC
2.21.	ITT	Non-Standard	Summary of Annualised Rate of On-Study Moderate/Severe Exacerbations		SAC
2.22.	ITT	Non-Standard	Kaplan Meir Estimates of Time to First On-randomised Treatment Moderate/Severe COPD Exacerbations	*Just at Day 169.*	SAC
2.23.	ITT	Non-Standard	Kaplan Meir Estimates of Time to First On-Study Moderate/Severe COPD Exacerbations	*Just at Day 169.*	SAC
2.24.	ITT	Non-Standard	Summary of Unscheduled COPD Related Healthcare Contacts		SAC
Exploratory Endpoints					
2.25.	CE	Non-Standard	Association of Number of Critical Errors and CAT Response at Week 24	*Frequency table. Categories as described in Section 10.6.3.*	SAC
2.26.	CE	Non-Standard	Association of Number of Critical Errors and On-randomised Treatment Moderate/Severe Exacerbations	*A 3-way frequency table. Categories as described in Section 10.6.3.*	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.27.	CE	Non-Standard	Association of Number of Critical Errors and On-Study Moderate/Severe Exacerbations	*A 3-way frequency table. Categories as described in Section 10.6.3.*	SAC
2.28.	ITT	Non-Standard	Summary of Subject Treatment and Study Satisfaction Questionnaire Responses at Week 24/ EW Visit		SAC
2.29.	ITT	Non-Standard	Summary of Health Related Quality of Life Questionnaire Responses	*Summary at each Visit.*	SAC

10.9.7. Effectiveness Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Primary Endpoint					
2.1.	ITT	Non-Standard	Box-plot of Change from baseline in CAT Score at Week 24	*See Section 10.6.3.*	SAC
Other Endpoints					
2.2.	ITT	Non-Standard	Kaplan Meir Plot for Time to First On-randomised Treatment Moderate/Severe Exacerbation		SAC
2.3.	ITT	Non-Standard	Kaplan Meir Plot for Time to On-Study First Moderate/Severe Exacerbation		SAC
Exploratory Endpoints					
2.4.	CE	Non-Standard	Box-plot of Association of Critical Errors with CAT Score at Week 24	*See Section 10.6.3.*	SAC
2.5.	CE	Non-Standard	Box-plot of Association of Critical Errors with Change from Baseline in CAT Score at Week 24	*See Section 10.6.3.*	SAC
2.6.	CE	Non-Standard	Box-plot of Association of Critical Errors with FEV1 at Week 24	*See Section 10.6.3.*	SAC
2.7.	CE	Non-Standard	Box-plot of Association of Critical Errors with Change from Baseline in FEV1 at Week 24	*See Section 10.6.3.*	SAC
2.8.	CE	Non-Standard	Box-plot of Association of Critical Errors with FVC at Week 24	*See Section 10.6.3.*	SAC
2.9.	CE	Non-Standard	Box-plot of Association of Critical Errors with Change from Baseline in FVC at Week 24	*See Section 10.6.3.*	SAC

10.9.8. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	ITT	Non-Standard	Summary of Adverse Events Overview	*byval: On-randomised Treatment, Post-randomised Treatment.* *<u>Include Footnote:</u>* *"Note: Only treatment related AEs and AEs that lead to withdrawal from study treatment and Serious AEs are collected and summarised.".*	SAC
3.2.	ITT	AE1	Summary of Pre-randomised Treatment Adverse Events by System Organ Class and Preferred Term	*Same comments as for 3.1.* *Based on IDSL AE1 presenting also rates.*	SAC
3.3.	ITT	AE1	Summary of On-randomised Treatment Adverse Events by System Organ Class and Preferred Term	*Same comments as for 3.1.* *Based on IDSL AE1 presenting also rates.*	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.4.	ITT	AE1	Summary of Post-randomised Treatment Adverse Events by System Organ Class and Preferred Term	*Same comments as for 3.1.* *Based on IDSL AE1 presenting also rates.*	SAC
3.5.	ITT	AE1	Summary of On-Study Adverse Events by System Organ Class and Preferred term	*Same comments as for 3.1.* *Based on IDSL AE1 presenting also rates.*	SAC
3.6.	ITT	AE1	Summary of On-randomised Treatment Drug-related Adverse Events by System Organ Class and Preferred Term	*Based on IDSL AE1 presenting also rates.*	SAC
3.7.	ITT	AE1	Summary of Post-randomised Treatment Drug-related Adverse Events by System Organ Class and Preferred Term	*Based on IDSL AE1 presenting also rates.*	SAC
3.8.	ITT	AE1	Summary of On-randomised Treatment Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term	*Based on IDSL AE1 presenting also rates.*	SAC
3.9.	ITT	AE15	Summary of Common (>=1% in Either Treatment Group) On-randomised Treatment Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	*Include Footnote:* *"Note: Only treatment related AEs and AEs that lead to withdrawal from study treatment are summarised.".*	SAC
Serious and Other Significant Adverse Events					
3.10.	ITT	AE16	Summary of On-randomised Treatment Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.11.	ASE	AE1	Summary of Pre-randomised Treatment Serious Adverse Events by System Organ Class and Preferred Term	*Based on IDSL AE1 presenting also rates.*	SAC
3.12.	ITT	AE1	Summary of Pre-randomised Treatment Serious Adverse Events by System Organ Class and Preferred Term	*Based on IDSL AE1 presenting also rates.*	SAC
3.13.	ITT	AE1	Summary of On-randomised Treatment Serious Adverse Events by System Organ Class and Preferred Term	*Based on IDSL AE1 presenting also rates.*	SAC
3.14.	ITT	AE1	Summary of Post-randomised Treatment Serious Adverse Events by System Organ Class and Preferred Term	*Based on IDSL AE1 presenting also rates.*	SAC
3.15.	ITT	AE1	Summary of On-Study Serious Adverse Events by System Organ Class and Preferred Term	*Based on IDSL AE1 presenting also rates.*	SAC
3.16.	ITT	AE1	Summary of On-randomised Treatment Serious Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term	*Based on IDSL AE1 presenting also rates.*	SAC
3.17.	ITT	AE1	Summary of On-randomised Treatment Fatal Serious Adverse Events by System Organ Class and Preferred Term	*Based on IDSL AE1 presenting also rates.*	SAC
3.18.	ITT	AE1	Summary of Post-randomised Treatment Fatal Serious Adverse Events by System Organ Class and Preferred Term	*Based on IDSL AE1 presenting also rates.*	SAC
3.19.	ITT	Non-Standard	Summary of On-Study Fatal Serious Adverse Events by Class of Medication		SAC
3.20.	ITT	AE1	Summary of Pre-randomised Treatment Serious Adverse Events Leading to Withdrawal from Study by System Organ Class and Preferred Term	*Based on IDSL AE1 presenting also rates.*	SAC
3.21.	ITT	AE1	Summary of On-randomised Treatment Drug-Related Serious Adverse Events by System Organ Class and Preferred Term	*Based on IDSL AE1 presenting also rates.*	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.22.	ITT	AE1	Summary of On-randomised Treatment Drug-Related Fatal Serious Adverse Events by System Organ Class and Preferred Term	*Based on IDSL AE1 presenting also rates.*	SAC
3.23.	ITT	AE3	Summary of Common (>=1% in Either Treatment Group) On-randomised Treatment Serious Adverse Events by Preferred Term	*Present by PT (not SOC).*	SAC
3.24.	ITT	Non-Standard	Summary of On-randomised Treatment Serious Adverse Events of Special Interest	*Based on IDSL AE1 but present by Special Interest (SI) Group, SI Subgroup, Sub-SMQ and PT. Also, present rates.*	SAC
3.25.	ITT	Non-Standard	Summary of Post-randomised Treatment Serious Adverse Events of Special Interest	*Based on IDSL AE1 but present by Special Interest (SI) Group, SI Subgroup, Sub-SMQ and PT. Also, present rates.*	SAC
3.26.	ITT	Non-Standard	Summary of On-Study Serious Adverse Events of Special Interest by Class of Medication		SAC

10.9.9. ICH Listings

All ICH listings will be presented by Country, unless otherwise specified.

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	ASE	ES7	Listing of Reasons for Screen Failure		SAC
2.	ITT	TA1	Listing of Randomised and Actual Treatments		SAC
3.	ITT	TA1	Listing of Randomised and Actual Prior Medication Use Strata		SAC
4.	ITT	SD2	Listing of Reasons for Study Treatment Discontinuation		SAC
5.	ITT	ES2	Listing of Reasons for Study Withdrawal		SAC
Protocol Deviations					
6.	ITT	DV2	Listing of Important Protocol Deviations		SAC
7.	ASE	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations for Screen Failures		SAC
8.	ITT	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
Demographic and Baseline Characteristics					
9.	ITT	DM2	Listing of Demographic Characteristics		SAC
10.	ITT	DM9	Listing of Race		SAC
Prior and Concomitant Medications					
11.	ITT	Non-Standard	Listing of Respiratory Concomitant Medications	*Including flag to indicate those taken for an exacerbation (COPD).*	SAC
Treatment Exposure					
12.	ITT	Non-Standard	Listing of Exposure Data		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
13.	ASE	AE8	Listing of All Adverse Events	*Include Footnote:* *"Note: Only treatment related AEs and AEs that lead to withdrawal from study treatment and Serious AEs are collected and listed.".*	SAC
14.	ASE	AE7	Listing of Subject Numbers for Individual Adverse Events	*Footnote from Listing 13 is applicable to this display.* *Listing not presented by Country.*	SAC
Serious and Other Significant Adverse Events					
15.	ASE	AE8	Listing of Fatal Serious Adverse Events		SAC
16.	ASE	AE8	Listing of Non-Fatal Serious Adverse Events		SAC
17.	ASE	AE14	Listing of Reasons for Considering as a Serious Adverse Event		SAC
18.	ASE	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment		SAC
19.	ITT	AE8	Listing of Serious Adverse Events of Special Interest		SAC

10.9.10. Non-ICH Listings

All Non-ICH listings will be presented by Country, unless otherwise specified.

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
20.	ITT	Non-Standard	Listing of Study Treatment Misallocations	*Similar to IDSL TA1.*	SAC
21.	ITT	Non-Standard	Listing of Randomised Treatment and Randomised Treatment Modifications		SAC
22.	ITT	MH2	Listing of Medical Conditions		SAC
23.	ITT	Non-Standard	Listing of Family History of Cardiovascular Risk Factors		SAC
24.	ITT	Non-Standard	Listing of COPD Exacerbation History		SAC
25.	ITT	CM6	Relationship between ATC Level 1, Ingredient and Verbatim Text for Non-Respiratory Medications		SAC
26.	ITT	Non-Standard	Listing of f Historical Eosinophils Data		SAC
Effectiveness					
27.	ITT	Non-Standard	Listing of CAT Scores		SAC
28.	FEV1	Non-Standard	Listing of Lung Function Data	*Listing will also include PIFR data.*	SAC
29.	ITT	Non-Standard	Listing of Inhaler Critical and Overall Errors		SAC
30.	FEV1	Non-Standard	Listing of Clinically Important Deterioration Data		SAC
31.	ITT	Non-Standard	Listing of COPD Exacerbations		SAC
32.	ITT	Non-Standard	Listing of Participant Treatment and Study Satisfaction Questionnaire Responses		SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
33.	ITT	Non-Standard	Listing of Health Related Quality of Life Questionnaire (HRQoL) Responses		SAC
Safety					
34.	ITT	Non-Standard	SAE Terms of Special Interest	*Listing not presented by Country.*	SAC
35.	ITT	AE7	Listing of Subject Numbers for On-randomised Treatment Serious Adverse Events of Special Interest	*Listing not presented by Country.*	SAC

10.9.11. Patient Profile Listings

Patient Profile: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
36.	ITT	Non-Standard	Listing of Arrhythmias	*Include information required by IDSL standards.*	SAC
37.	ITT	Non-Standard	Listing of Congestive Heart Failure	*Include information required by IDSL standards.*	SAC
38.	ITT	Non-Standard	Listing of Cerebrovascular Events/ Stroke/ Transient Ischemic Attack	*Include information required by IDSL standards.*	SAC
39.	ITT	Non-Standard	Listing of Deep Vein Thrombosis/ Pulmonary Embolism	*Include information required by IDSL standards.*	SAC
40.	ITT	Non-Standard	Listing of Myocardial Infarction/ Unstable Angina	*Include information required by IDSL standards.*	SAC
41.	ITT	Non-Standard	Listing of Peripheral Arterial Thromboembolism	*Include information required by IDSL standards.*	SAC
42.	ITT	Non-Standard	Listing of Pulmonary Hypertension	*Include information required by IDSL standards.*	SAC
43.	ITT	Non-Standard	Listing of Revascularisation	*Include information required by IDSL standards.*	SAC
44.	ITT	Non-Standard	Listing of Valvulopathy	*Include information required by IDSL standards.*	SAC

10.10. Appendix 10: Example Mock Shells for Data Displays

The data display shells are contained in separate documents and are available upon request.