Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for A Phase IV, 12-week, randomised, double-blind, triple dummy study to compare single inhaler triple therapy, fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) with multiple inhaler therapy (budesonide/formoterol plus tiotropium) based on lung function and symptoms in participants with chronic obstructive pulmonary disease
Compound Number	:	GSK2834425 (GW685698 + GSK573719 + GW642444)
Effective Date	:	16-Apr-2019

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report (CSR) for Protocol 207608.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (DR, SAC) deliverable.

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1. INTRODUCTION

The purpose of this Reporting and Analysis Plan (RAP) is to describe the analyses to be included in the Clinical Study Report (CSR) for Protocol 207608, a Phase IV, 12-week, randomised, double-blind, triple dummy study to compare single inhaler triple therapy, fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) with multiple inhaler therapy (budesonide/formoterol plus tiotropium) based on lung function and symptoms in participants with chronic obstructive pulmonary disease (COPD).

Revision Chronology:		
2017N327125_00	11-OCT-2017	Original Protocol
2017N327125_01	17-JUL-2018	Protocol Amendment 1

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

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

Table 1 Changes to Protocol-Defined Analysis Plan

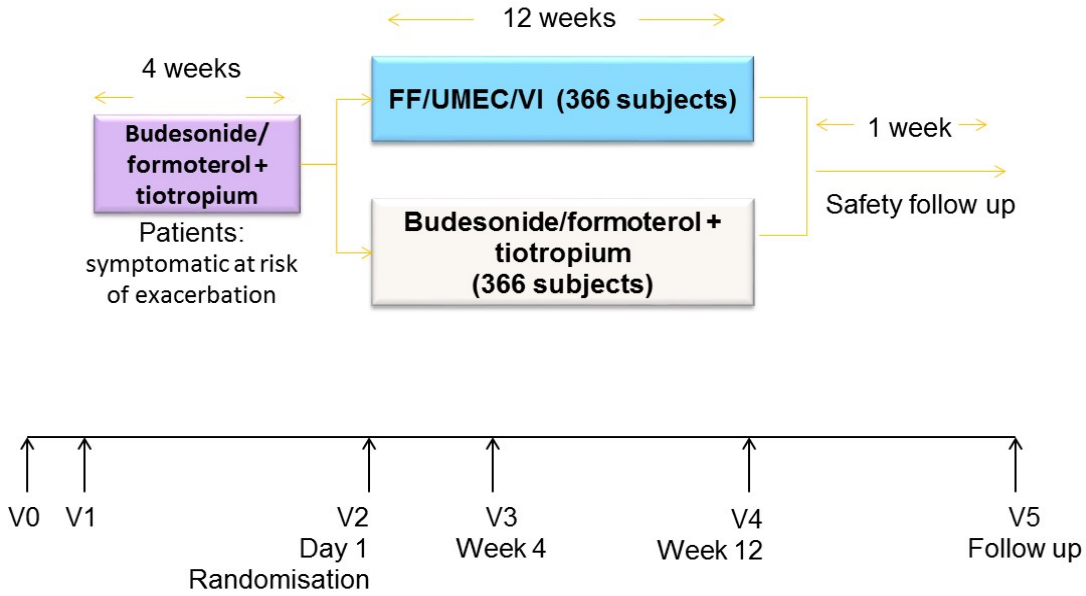
Protocol	Reporting & Analysis Plan	Rationale for Change
Section 10.3 ("Populations for Analyses" definition of Intent-to-Treat (ITT) population) reads in part, "All randomised participants, excluding those who were randomised in error. A participant who is recorded as a screen or run-in failure and also randomised will be considered to be randomised in error. Any other participant who receives a randomisation number will be considered to have been randomised."	The verbatim protocol text is amended in Section 4 ("Analysis Populations") of this document to read, "All randomised participants, excluding those who were randomised in error. A participant who is recorded as a screen or run-in failure and also randomised, but did not receive a dose of study treatment, will be considered to be randomised in error. Any other participant who receives a randomization number will be considered to have been randomised."	Clarification of the definition of "randomized in error."
Use of the word "subject"	Text in this document will use the word "participant" in lieu of the word "subject," except in the following cases: 1. Text that is quoted verbatim from the protocol 2. In the phrase "subject listing" 3. In the phrase "subject number"	Decision by GSK's R&D Clinical Data Standards Board (CDSB), published on GSK's Intranet 18-JUN-2018. The text below is excerpted from this published notice: Until an industry-wide resolution has been achieved, the R&D CDSB has decided to continue with the discrepant

Protocol	Reporting & Analysis Plan	Rationale for Change
	4. In reference to the protocol-defined All Subjects Enrolled population 5. In titles and content of prospectively-defined statistical output generated in GSK's HARP system	terminologies and ask teams to: • Data Quality Lead to add a note to the Reviewers Guide in submissions that the term "Subjects" is used to refer to "Participants" in the protocol. • Statistician to add the same note to RAPs to say that all displays (Tables, Figures & Listings) will use the term "Subjects'". RAP text will refer to "Participants" in-line *[sic]* with the master RAP template and protocol.
Refinements of descriptions of efficacy analyses	This document identifies the primary and supplementary estimands, and describes the four attributes of each, the population, the variable of interest, the intercurrent events of interest, and the summary measure(s) of interest in Section 7 ("Efficacy Analyses").	Issuance by the International Conference on Harmonization (ICH) of an addendum to the ICH E9 guidance that outlines the concept of the estimand and its four attributes. Industry adoption of the concepts outlined in this addendum began after finalization of this study protocol.
Section 10.3 Definition of Modified Per Protocol (mPP) population: • All participants in the ITT Population who do not have a full protocol deviation considered to impact efficacy. • Data following a COPD exacerbation or pneumonia will be excluded from analysis due to the potential impact of the exacerbation or the medications used to treat it. • Participants with partial protocol deviations considered to impact efficacy will be included in the mPP Population but will have their data excluded from analyses from the time of deviation onwards. • This population will only be used for the primary analysis for the primary endpoint.	Definition of mPP population: • All participants in the ITT population who do not have a protocol deviation of not meeting eligibility criteria or not meeting randomization criteria.	Full protocol deviaitons post randomisation, along with the COPD exacerbation or pneumonia occurred post-randomizaiton, are defined as the intercurrent events in the primary estimand for the efficacy analyses based on the mPP population, see Section 7.1.4.

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

Objectives	Endpoints
Primary	**Primary**
• To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on lung function	• Weighted mean change from baseline in forced expiratory volume in 1 second (FEV_1) over 0-24 hours at Week 12
	Secondary
	• Change from baseline in trough FEV_1 on Day 2, Day 28, Day 84 and Day 85 • Weighted mean change from baseline in FEV_1 over 0-24 hours on Day 1
Other	
• To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on Health Status	• Proportion of responders based on the St. George's Respiratory Questionnaire (SGRQ) Total Score at Week 4 and Week 12 • Change from baseline in SGRQ Total Score at Week 4 and Week 12
• To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on Health Status	• Proportion of responders based on the COPD Assessment Test (CAT) Score at Week 4 and Week 12 • Change from baseline in CAT Score at Week 4 and Week 12
• To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on COPD exacerbations	• Moderate or severe exacerbation event
• Assess how inspiratory airflow limitation affects ability to use the ELLIPTA	• Peak Inspiratory Flow Rate (PIFR) at Screening (Week -4)
Safety	
• To evaluate the safety profile of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium over 12 weeks of treatment	• Incidence of adverse events (AEs) • Vital signs

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	• 12-week treatment period • Randomised • Double-blind • Triple-dummy • Parallel-group • 1-week safety follow-up • Approximately 800 participants with advanced COPD will enter the run-in period in order to randomise approximately 732 participants and to achieve an estimated 620 evaluable participants in the modified Per Protocol (mPP) population at Week 12. • A study with 620 evaluable participants for the primary analysis will have 90% power to determine non-inferiority of FF/UMEC/VI to budesonide/formoterol plus tiotropium (BUD/FOR + TIO) based on 0-24 hour weighted mean FEV_1 at Week 12, an estimate of residual standard deviation (SD) for weighted mean FEV_1 of 230 mL, at the one-sided 2.5% significance level when the margin of non-inferiority is 50 mL and the true mean treatment difference is assumed to be 10 mL. • Participants will be provided with short-acting albuterol/salbutamol to be used on an as-needed basis (rescue medication) throughout the study. • Participants who permanently discontinue double-blind study treatment are not required to withdraw from the study. Participants who have permanently discontinued study treatment and have not withdrawn consent will be encouraged to continue in the study and complete all remaining protocol-specified clinic visits as indicated in the Schedule of Activities (Appendix 2).
Dosing	Randomised treatments are: • FF/UMEC/VI (100/62.5/25 mcg) via ELLIPTA once daily in the morning • Budesonide/formoterol (320/9 mcg) via metered dose inhaler (MDI) twice daily (morning and evening) plus tiotropium (18 mcg) via HandiHaler once daily in the morning
Time & Events	• Refer to Appendix 2: Schedule of Activities

Overview of Study Design and Key Features	
Treatment Assignment	• 4-week run-in on open-label budesonide/formoterol (320/9 mcg) via MDI twice daily (morning and evening) plus tiotropium (18 mcg) via the Handihaler once daily and placebo via the ELLIPTA once daily (both in the morning) • Randomization 1:1 to FF/UMEC/VI or BUD/FOR + TIO • PAREXEL software and Interactive Web Response System (IWRS) will be used to generate the randomization schedule and for treatment allocation. Centralized randomization will be used.
Interim Analysis	• No interim analysis is planned.

2.4. Statistical Hypotheses

The primary objective of this study is to compare FF/UMEC/VI with BUD/FOR + TIO in COPD participants. The primary endpoint is 0-24 hour weighted mean FEV1 at Week 12. The primary analysis is the comparison of this endpoint for FF/UMEC/VI versus BUD/FOR + TIO with the mPP population. The null hypothesis is that the difference in 0-24 hour weighted mean FEV_1 between treatment groups is less than or equal to a pre-specified non-inferiority margin Δ:

H0: $T1 - T2 \leq -\Delta$

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

H1: $T1 - T2 > -\Delta$

where T1 and T2 are the adjusted treatment means for FF/UMEC/VI and BUD/FOR + TIO, respectively.

The non-inferiority margin has been set at 50 mL. This non-inferiority margin for 0-24 hour weighted mean FEV_1 has previously been accepted by the Food and Drug Administration (FDA) (Combivent versus Ipratropium head to head study).

If the lower bound of the two-sided 95% confidence interval around the (FF/UMEC/VI versus BUD/FOR + TIO) treatment difference is above -50 mL then FF/UMEC/VI will be considered non-inferior to BUD/FOR + TIO.

If non-inferiority is achieved with the primary analysis on the mPP population, inference of superiority will be made with the primary endpoint on the ITT population. If the lower bound of the two-sided 95% confidence interval around the FF/UMEC/VI versus BUD/FOR + TIO treatment difference is above zero, superiority will be established.

Further details of inferences to be made, including inference of superiority (if non-inferiority is achieved), based on treatment comparison confidence intervals and p-values are described in Section 7 (“Efficacy Analyses”).

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analyses are planned.

3.2. Final Analyses

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

1. All participants have completed the study or have been withdrawn as defined in the protocol.
2. All required database cleaning activities have been completed and final database release (DBR) has been declared by GSK Data Management.
3. All criteria for unblinding the randomization codes have been met and the final database has been locked.
4. Randomization codes have been distributed according to PAREXEL and PAREXEL Informatics' standard operating procedures and treatment details have been unblinded.
5. Database freeze (DBF) has been declared by GSK Data Management.

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 and any participant who was not screened but experienced an SAE between the date of informed consent and the planned date of the Screening visit.	• Participant disposition • AEs
Run-in	• All participants who are eligible at Screening and entered the Run-in period.	• AEs
Intent-to-Treat (ITT)	• All randomised participants, excluding those who were randomised in error. A participant who is recorded as a screen or run-in failure and also randomised, but did not receive a dose of study treatment, will be considered to be randomised in error. Any other participant who receives a randomization number will be considered to have been randomised. • Displays will be based on the treatment to which the participant was randomised.	• Study population • Efficacy • Safety
Modified Per Protocol (mPP)	• All participants in the ITT population who do not have a protocol deviation of not meeting eligibility criteria* or not meeting randomization criteria*.	• Primary treatment comparison of the primary endpoint only

Note: *Those considered to affect the primary outcome as listed in Section 10.1.2 Table 2.

4.1. Protocol Deviations

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

Exclusions from the mPP analysis population will also be summarised and listed. (Refer to Appendix 1: Protocol Deviation Management and Definitions for Modified Per Protocol Population).

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Specification Form (PDSF).

- Data will be reviewed prior to Study Data Tabulation Model (SDTM) database lock to ensure all important deviations and deviations which lead to exclusion from the mPP analysis are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

Participants who received an incorrect study treatment container will be captured as an important protocol deviation. Whether or not the incorrect container was the wrong study treatment will be identified following DBF in the Analysis Data Model (ADaM) dataset. Overall treatment noncompliance based on active study treatment will also be identified following DBF and will be flagged as exclusionary from the mPP population in the ADaM DV dataset.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

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

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
PAREXEL Informatics Randomization and Trial Management System		Data Displays for Reporting	
Code	Description	Description	Order in Display
A	FF/UMEC/VI 100/62.5/25 mcg Ellipta	FF/UMEC/VI 100/62.5/25	1
B	Budesonide/formoterol 320/9 mcg MDI + Tiotropium 18 mcg Handihaler	BUD/FOR 320/9 + TIO 18	2

Treatment comparisons will be labelled "FF/UMEC/VI vs. BUD/FOR + TIO."

5.2. Baseline Definitions

The baseline value of all endpoints, except as noted below, will be the latest assessment with a non-missing value taken prior to the first dose of blinded study medication, including those from unscheduled visits. If time of assessment is not collected, Day 1 (Visit 2) assessments are assumed to be taken prior to first dose and will be used as baseline.

Baseline Definitions for All Study Endpoints			
Endpoint	Study Assessments Collected Prior to Dosing		Baseline Definition
	Screening (Visit 1)	Day 1 Pre-Dose (Visit 2)	
Efficacy			
Weighted Mean FEV_1, Trough FEV_1, Serial FEV_1, FVC*	X	X	Day 1 baseline defined as the average of the two Day 1 pre-dose measurements. If one of the measurements is missing, then the baseline will be the single remaining value.
SGRQ Total score		X	Day 1
CAT score	X	X	Day 1
Safety			
Vital signs	X		Most recent individual value prior to first dose (either Screening or a repeat test). Systolic and diastolic blood pressure values should come from the same assessment.
*: FVC is not a protocol specified efficacy endpoint.			

5.3. Multicentre Studies

It is anticipated that approximately 80 sites from the United States and Europe (Czech Republic, the Netherlands and Germany) will participate in the study. Therefore, it is likely that many centres will enrol very small numbers of participants. Consequently, all centres within the same country will be pooled. This amalgamation will be used wherever country is incorporated into a summary (e.g., enrolment summarised and presented by country and centre).

"Geographical region" is denoted in the protocol as a covariate in the statistical models assessing several efficacy measures. For the purposes of these analyses, two geographical regions will be defined: Europe (Czech Republic, the Netherlands and Germany) and the United States.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

No randomisation stratification was used in this study.

Covariates to be included in the statistical analyses as outlined in Section 7 ("Efficacy Analyses") of this document are baseline and geographical region. Additional covariates may also be considered in an ad hoc manner at the discretion of the study team, and if considered, will be addressed in the CSR.

5.4.2. Examination of Subgroups

No subgroup analyses are planned.

5.5. Multiple Comparisons and Multiplicity

As the primary non-inferiority treatment comparison of FF/UMEC/VI to BUD/FOR + TIO is being made on a single primary endpoint based on the mPP population, no multiplicity adjustment will be performed for inference of non-inferiority.

If non-inferiority is achieved, inference for superiority based on the ITT population will be assessed as described in Section 7.1.5 ("Statistical Analyses / Methods"). No multiplicity adjustments will be made.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

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

Study population summaries will be based on the ITT population and mPP population, unless otherwise specified.

Study population summaries of participant disposition, protocol deviations, demographic and disease characteristics, medical conditions, prior and concomitant medications, and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 9: List of Data Displays.

7. EFFICACY ANALYSES

7.1. Primary Efficacy Analyses

The primary efficacy analysis will assess the difference between treatments in the context of non-inferiority of FF/UMEC/VI versus BUD/FOR + TIO with the mPP population. The same analysis will be performed with the ITT population as a supporting analysis and to assess superiority of FF/UMEC/VI versus BUD/FOR + TIO. However, inference of superiority with the ITT population will only be made if non-inferiority is achieved with the mPP population analysis. Inferences to be drawn are described in detail below in Section 7.1.5 ("Statistical Analyses / Methods").

7.1.1. Endpoint / Variables

The primary efficacy endpoint is change from baseline in weighted mean FEV_1 over 0-24 hours at Week 12.

7.1.2. Summary Measure

The summary measure of interest is the adjusted mean treatment difference.

7.1.3. Population of Interest

The primary efficacy analysis for the test of non-inferiority will be based on the mPP population. The efficacy analysis for the test of superiority and a supporting analysis for the non-inferiority test will be based on the ITT population.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

Intercurrent events considered to have an impact on the estimand for the mPP population analysis are the following events that occur during the double-blinded treatment period:

- Discontinuation of randomised study treatment
- Taking the wrong randomised study treatment
- Taking a prohibited medication
- Accidental unblinding of randomised study treatment
- Treatment noncompliance (overall compliance < 80% or >120% over the 12-week treatment period, based on active randomized study treatment)
- FEV_1 assessment following a moderate/severe COPD exacerbation or pneumonia
- Unblinding of randomised study treatment due to safety concerns (including by the Investigator or Global Clinical Safety and Pharmacovigilance [GCSP])

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

- Discontinuation of randomised study treatment

7.1.4.1. Primary Estimand for mPP Population

The primary treatment effect to be estimated for the mPP population will be the hypothetical effect if all participants had stayed on their randomised treatment, no participant received the wrong treatment or a prohibited medication, no participant was noncompliant with active treatment [as defined in Section 7.1.4. ("Strategy for Intercurrent (Post-Randomization) Events") and Appendix 6: Derived and Transformed Data], no participant had a FEV_1 assessment following a COPD exacerbation or pneumonia, and no study treatment was unblinded. For participants who do not have an intercurrent event following randomization, weighted mean FEV_1 over 0-24 hours on Day 1 and at Week 12 will be used in the analysis. For participants with at least one intercurrent event prior to Week 12, the primary endpoint of weighted mean FEV_1 over 0-24 hours at Week 12 will be set as missing. Weighted mean FEV1 over 0-24 hours on Day 1 will be included in the analysis for all participants in the mPP population with the exception of taking the wrong randomised study treatment on Day 1. Missing data will be assumed to be missing at random (MAR).

7.1.4.2. Primary Estimand for ITT Population

The primary treatment effect to be estimated for the ITT population will be the hypothetical effect if all participants had stayed on their randomised study treatment. Weighted mean FEV_1 over 0-24 hours at Week 12 for participants who are still on randomized study treatment up to Week 12 will be used in the analysis. For participants who discontinue randomised study treatment prior to Week 12, weighted mean FEV_1 over 0-24 hours at Week 12 will be set as missing. Missing data will be assumed to be MAR.

7.1.4.3. Supplementary Estimand for ITT Population

The supplementary treatment effect to be estimated for the ITT population will be the treatment policy effect of initial randomised treatment. All recorded data up to the time of study withdrawal will be included in the analysis, regardless of the occurrence of an intercurrent event. Missing data will be assumed to be MAR. This supplementary treatment effect will only be estimated if the overall discontinuation of randomized study treatment rate is >5%.

7.1.5. 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, the endpoint defined in Section 7.1.1 will be summarised using descriptive statistics, graphically presented and listed.

7.1.5.1. Statistical Methodology Specification

Endpoint / Variables
• Change from baseline in weighted mean FEV_1 over 0-24 hours at Week 12
Model Specification
• The primary endpoint will be analyzed for the mPP population using a mixed model repeated measures (MMRM) analysis, including weighted mean FEV_1 at Day 1 and Week 12. The model will include covariates of baseline FEV_1, geographical region, treatment, visit, and visit by baseline interaction. A visit by treatment interaction term will also be included to allow treatment effects to be estimated at each visit separately. • While missing data are not explicitly imputed in the primary MMRM analysis, there is an underlying assumption that the data are MAR. All available on-treatment assessments will be utilized and via modeling of the within-subject correlation structure, the derived treatment differences will be adjusted to take into account missing data. • Two models will be fitted; one with a response variable of weighted mean FEV_1, and one with a response variable of change from baseline in weighted mean FEV_1. • The models will be fit with an unstructured variance-covariance matrix. • The model will utilize the OBSMARGINS (OM) option to generate a dataset with a row for every participant-visit combination that contains all the covariates and a macro variable containing the mean baseline for the participants included in the analysis. This is used to derive the adjusted means using coefficients which are based on the participants in the analysis. • The analysis will be repeated in the same manner for the ITT population to estimate the primary estimand for the ITT population. If the overall discontinuation of randomized study treatment rate is >5%, the analysis will be repeated for the ITT population using all data collected (on- and post-treatment) to estimate the supplementary estimand for the ITT population.
Model Checking & Diagnostics
• The Kenward and Roger method (KR) for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used. In the event the model fails to run using the KR method, then the residual method will be used. • Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e., checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
Model Results Presentation
• Least squares (LS) means and LS mean changes from baseline with their corresponding standard errors (SEs) and 95% confidence intervals (CIs) will be presented for each treatment by visit, together with estimated treatment differences (FF/UMEC/VI vs. BUD/FOR + TIO) and the corresponding 95% CIs and p-values. • A plot of LS mean changes from baseline and 95% CIs from the model will be generated for each treatment by visit.
Inference to be Drawn
• Analysis with mPP population: If the treatment comparison on the primary endpoint has a lower confidence limit below the non-inferiority margin, non-inferiority is not demonstrated. No inference will be drawn from p-values for treatment comparisons on any other endpoints.

- Analysis with mPP population: If the treatment comparison on the primary endpoint has a lower confidence limit above the non-inferiority margin but below 0, non-inferiority is established but the p-value will not be used to give an indication of the strength of that non-inferiority. Inference will be drawn from p-values for treatment comparisons (with ITT population) on other non-lung function endpoints, i.e., SGRQ and CAT, which will be declared statistically significant if <0.05. No inference will be drawn from p-values on the trough FEV_1 endpoint.
- Analysis with ITT population: If the treatment comparison on the primary endpoint has a lower confidence limit above 0, superiority is established and the p-value can be used to give an indication of the strength of that superiority. Inference will be drawn from p-values for treatment comparisons on all other endpoints, which will be declared statistically significant if <0.05.

Subgroup Analyses

- No subgroup analyses are planned.

Supportive Analyses - Interactions

For the mPP and ITT analyses, interactions between treatment and other factors will be investigated as follows by adding interaction terms to the statistical model:

- An assessment of whether the effect of treatment on weighted mean FEV_1 is modified by geographic region or baseline FEV_1 will be made by fitting separate repeated measures models, identical to the primary analysis models but also including additional terms as described below.
- For the factor of geographical region, the primary analysis model will be used with additional terms for the factor by treatment and factor by treatment by visit interactions. The p-value for the factor by treatment interaction at Week 12 will be obtained using contrast statements. If the p-value is ≥ 0.10 the interaction will be considered not statistically significant. If the p-value is < 0.10, further investigation will be undertaken, for example by running the primary analysis by each geographic region.
- For baseline FEV_1, the primary analysis model will be used with additional terms for baseline by treatment and baseline by treatment by visit interactions. The p-value for the baseline by treatment interaction at Week 12 will be obtained using contrast statements. If the p-value is ≥ 0.10 the interaction will be considered not statistically significant. If the p-value is < 0.10, further investigation will be undertaken, for example by running the analysis by dichotomous categories of baseline FEV_1 values (values above and below the median).
- The p-value for each interaction test will be presented.

Supportive Analyses – Serial FEV_1

- Serial FEV_1 measurements collected on Day 1 and at Week 12 will be summarized by treatment group and nominal time points. The change from baseline values in serial FEV_1 will also be summarized by treatment group.
- Change from baselin in serial FEV1 will be analyzed according to nominal time point on Day 1 and at Week 12 separately, using all non-missing serial assessments. For each visit (Day 1 and Week 12), a repeated measures model will be used including covariates for baseline FEV_1, geographical region, treatment, time point, time point by treatment interaction and time point by baseline interaction. Other model details are the same as those described above for the primary efficacy analysis.

- For each visit, LS mean and LS mean change from baseline values for each treatment group at each time point will be presented with their associated SEs and 95% CIs. The estimated treatment difference along with corresponding SE and 95% CI and p-value at each time point will be presented.
- The LS mean change from baseline values for FEV_1 over time for each treatment group on Day 1 and at Week 12, along with the corresponding 95% CIs, will be plotted.
- The LS mean treatment differences along with corresponding 95% CIs for change from baseline in FEV_1 over time will also be plotted on Day 1 and at Week 12.
- These supportive analyses of serial FEV_1 will be conducted for the primary estimand for the ITT population.

Sensitivity Analyses

Sensitivity Analysis of the Primary Estimand for the mPP Population

- A missing data sensitivity analysis for the primary estimand (hypothetical effect) will be conducted to investigate the impact of missing data and to examine the robustness of the primary analysis to departures from the assumption that missing data are MAR. A tipping point analysis of weighted mean FEV_1 change from baseline over 0-24 hours at Week 12 for the mPP population will be performed including all recorded data up to the time of the first of any intercurrent events (including study treatment discontinuation) or time of study withdrawal.
- The tipping point analysis will explore the impact of missing data by using differing assumptions regarding the mean treatment effect in participants who discontinue study treatment or have data excluded from the mPP analysis. Mean treatment effects to be investigated will range from a change from baseline of -150mL to +150mL in increments of 50mL.
- For each value of the assumed mean change from baseline on FF/UMEC/VI, the full range of values for the assumed mean change from baseline for BUD/FOR + TIO will be investigated, thus including scenarios where participants in the FF/UMEC/VI arm excluded from the mPP analysis have a lower treatment effect than participants in the BUD/FOR + TIO arm excluded from the mPP analysis and vice versa. The analysis results will be used to explore the conditions under which the conclusion of non-inferiority no longer holds.
- For each participant with missing or excluded data at Week 12, a value will be imputed based on a random draw from a normal distribution with mean equal to the corresponding assumed mean change from baseline and standard deviation taken from the observed change from baseline data for the combined treatment arms at Week 12. Data for participants with missing baseline values will not be imputed. Analysis of the complete Week 12 dataset (including the imputed values) will be carried out using an analysis of covariance (ANCOVA) model with covariates of treatment group, geographical region and baseline.
- Multiple imputation (MI) methods will be used and results will be combined across imputations using Rubin's method.
- The seeds generated and assigned to each analysis will be documented separately prior to DBF.
- A table will be produced displaying the 95% CI lower limits for the treatment differences at Week 12 under the above assumptions for the mean changes from baseline for each of the treatment arms.

Sensitivity Analysis of the Primary Estimand for the ITT Population

- If superiority of FF/UMEC/VI versus BUD/FOR + TIO with respect to weighted mean FEV_1 over 0-24 hours at Week 12 is established with the ITT population, a missing data sensitivity analysis for the primary estimand (hypothetical effect) will be conducted to investigate the impact of missing data and to examine the robustness of the analysis to departures from the assumption that missing data are MAR.

• A tipping point analysis of weighted mean FEV_1 change from baseline over 0-24 hours at Week 12 will be conducted for the ITT population in the same manner as that described above for the mPP population, with the exception that instead of lower limits of 95% CIs, a table will be produced displaying the p-values for the treatment differences at Week 12. • The tipping point analysis will be performed including all recorded data up to the time of study treatment discontinuation. The analysis results will be used to explore the conditions under which the conclusion of superiority no longer holds.
Sensitivity Analysis of the Supplementary Estimand for the ITT Population
• A missing data sensitivity analysis for the supplementary estimand (treatment policy effect of initial randomised treatment) will be conducted to investigate the impact of missing data and to examine the robustness of the ITT population analysis to departures from the assumption that missing data are MAR. (The supplementary estimand analysis and sensitivity analysis will be performed if the overall discontinuation of study treatment rate is >5%). • A tipping point analysis of weighted mean FEV1 change from baseline over 0-24 hours at Week 12 will be conducted for the supplementary estimand of the ITT population in the same manner as that described above for the (tipping point) sensitivity analysis of the primary estimand for the ITT population. The analysis will be performed including all recorded data (on- and post-treatment), and the results will be used to explore the conditions under which the conclusion of superiority no longer holds.

7.2. Secondary Efficacy Analyses

The secondary efficacy analyses will assess the differences between treatments in the context of superiority of FF/UMEC/VI over BUD/FOR + TIO.

7.2.1. Endpoint / Variables

The secondary efficacy endpoints are change from baseline in trough FEV_1 on Day 2, Day 28, Day 84 and Day 85, and change from baseline in weighted mean FEV_1 over 0-24 hours on Day 1.

7.2.2. Summary Measure

The summary measures of interest are the adjusted mean treatment differences.

7.2.3. Population of Interest

The secondary efficacy analyses will be based on the ITT population.

7.2.4. Strategy for Intercurrent (Post-Randomization) Events

The secondary efficacy analyses will use the same strategy for intercurrent events as the ITT population primary analysis as described in Section 7.1.4.2. ("Primary Estimand for ITT Population").

7.2.5. 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 defined in Section 7.2.1 will be summarised using descriptive statistics, graphically presented and listed (where appropriate).

7.2.5.1. Statistical Methodology Specification

Endpoint / Variables
• Change from baseline in trough FEV_1 at Day 2, Day 28, Day 84 and Day 85 • Change from baseline in weighted mean FEV_1 over 0-24 hours at Day 1
Model Specification
• The secondary efficacy endpoint of change from baseline in trough FEV_1 will be analyzed using a MMRM analysis, including trough FEV_1 recorded at each of the visit days, Day 2, Day 28, Day 84 and Day 85. The model will include covariates of baseline FEV_1, geographical region, treatment, visit, and visit by baseline interaction. A visit by treatment interaction term will also be included to allow treatment effects to be estimated at each visit separately. • While missing data are not explicitly imputed in the primary MMRM analysis, there is an underlying assumption that the data are MAR. All available on-treatment assessments will be utilized and via modeling of the within-subject correlation structure, the derived treatment differences will be adjusted to take into account missing data. • Two models will be fitted; one with a response variable of trough FEV_1, and one with a response variable of change from baseline in trough FEV_1. • The models will be fit with an unstructured variance-covariance matrix. • The model will utilize the OBSMARGINS (OM) option to generate a dataset with a row for every participant-visit combination that contains all the covariates and a macro variable containing the mean baseline for the participants included in the analysis. This is used to derive the adjusted means using coefficients which are based on the participants in the analysis. • The secondary efficacy endpoint of change from baseline in weighted mean FEV_1 over 0-24 hours at Day 1 is assessed as part of the primary statistical model described above in Section 7.1.5.1 ("Statistical Methodology Specification") for the primary efficacy analysis of change from baseline in weighted mean FEV_1 over 0-24 hours at Week 12.
Model Checking & Diagnostics
• Refer to Section 7.1.5.1 as described for the primary analysis.
Model Results Presentation
• Refer to Section 7.1.5.1 as described for the primary analysis.
Subgroup Analyses
• No subgroup analyses are planned.
Sensitivity and Supportive Analyses
• No sensitivity or supportive analyses are planned.

7.3. Other Efficacy Analyses

7.3.1. Endpoint / Variables

The following endpoints will be used to assess the superiority of FF/UMEC/VI over BUD/FOR + TIO:

- SGRQ Total score
- Proportion of responders according to SGRQ Total score
- CAT score
- Proportion of responders according to CAT score
- COPD exacerbations

7.3.2. Summary Measure

Mean values and changes from baseline in the SGRQ Total score (and domain scores) and the CAT score at Weeks 4 and 12 will be summarised by visit and treatment group. The treatment comparisons of FF/UMEC/VI to BUD/FOR + TIO will be assessed in terms of the adjusted mean treatment differences at Weeks 4 and 12.

The proportions of participants identified as responders according to the SGRQ Total score and according to the CAT score at Weeks 4 and 12 will be summarised by visit and treatment group. The treatment comparisons of FF/UMEC/VI to BUD/FOR + TIO will be assessed in terms of odds ratios at Weeks 4 and 12.

COPD exacerbations will be summarised by treatment group for on-treatment and post-treatment events.

7.3.3. Population of Interest

The SGRQ and CAT analyses and summaries of exacerbations will be based on the ITT population.

7.3.4. Strategy for Intercurrent (Post-Randomization) Events

The SGRQ and CAT analyses will use the same strategy for intercurrent events as the ITT population primary analysis as described in Section 7.1.4.2. (“Primary Estimand for ITT Population”). COPD exacerbations will be summarised as on-treatment and post-treatment events.

7.3.5. 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 defined in Section 7.3.1 will be summarised using descriptive statistics, and graphically presented and listed (where appropriate).

7.3.5.1. Statistical Methodology Specification

7.3.5.1.1. SGRQ Total score and CAT score

Endpoint / Variable
• Change from baseline in SGRQ Total score at Weeks 4 and 12 • Change from baseline in CAT score at Weeks 4 and 12
Model Specification
• Same model as that described above in Section 7.2.5.1 (“Statistical Methodology Specification”) for the secondary ry efficacy analysis • Two models will be fitted; one with a response variable of SGRQ Total score/CAT score and one with a response variable of change from baseline in SGRQ Total score/CAT score

7.3.5.1.2. Proportion of responders according to SGRQ Total score and according to CAT score

Endpoint / Variables
• Proportion of responders according to SGRQ Total score at Weeks 4 and 12 • Proportion of responders according to CAT score at Weeks 4 and 12
Model Specification
• The proportions of responders as determined by SGRQ Total score/CAT score will be analyzed with a generalized linear mixed model. The model will include terms for baseline score, geographical region, treatment, visit, and visit by baseline and visit by treatment interactions. BUD/FOR + TIO will be used as the reference level for treatment. • The model will be fit with an unstructured variance-covariance matrix with a single model to include all visits (Weeks 4 and 12). • Computation of CIs for the odds ratios will be based on the individual Wald tests. • See Section 10.7.2. (“Handling of Missing Data”) for details on how to handle missing data.
Model Checking & Diagnostics
Pearson residuals will be plotted by using the PLOTS=RESIDUALPANEL option for the model statement in SAS.
Model Results Presentation
The number and percentage of responders and non-responders at each visit will be summarized by treatment group. The odds ratios, 95% CIs and p-values will be presented for the FF/UMEC/VI vs. BUD/FOR + TIO treatment comparison at each visit.

7.3.5.1.3. Exacerbations

Endpoint
• Moderate/severe exacerbations
Model Specification

• No formal statistical model will be used. Exacerbations will be summarized by treatment group.
• Details of the exacerbation summaries include:
  • number and percent of participants reporting an exacerbation overall and by severity (mild, moderate, severe and moderate/severe)
  • number and percent of participants with each number of moderate/severe exacerbations (0, 1, ≥2)
  • total number of exacerbations overall and by severity and corresponding annual raw exacerbation rate
• For each exacerbation, the outcome, severity, duration, whether the exacerbation led to hospitalization, led to emergency room visit, oral/systemic corticosteroids being taken, and antibiotics being taken will be summarised.
• On- and post-treatment exacerbations will be summarised separately.

8. SAFETY ANALYSES

Safety analyses will be based on the ITT population and will include all study data (both on-treatment and post-treatment), unless otherwise specified.

8.1. Adverse Events Analyses

Adverse events (AEs) analyses will be based on GSK Core Data Standards.

Serious adverse events (SAEs) associated with study participation will be collected from the point of informed consent onward. All AEs, including all SAEs, will be collected from the start of Screening (Visit 1), and will be summarised and displayed by randomised treatment group. The onset dates of the AEs relative to the randomized treatment start and stop dates will be used to determine in which period an AE occurs.

The AE 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 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 will also be listed, with SOC, event (PT), treatment group, number of participants with the event, and specific subject 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.

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

8.2. Adverse Events of Special Interest Analyses

The table in Section 10.6.4 (“Safety”) presents the groups of Adverse Events of Special Interest (AESI). 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.

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.

8.3. Other Safety Analyses

Summary statistics of vital signs collected at Visit 1 (Screening) and Visit 4 (Week 12), and change from screening baseline values will be presented by treatment group. Vital signs collected at the Study Treatment Discontinuation Visit and on the Pneumonia Details eCRF form will be included in 'minimum/maximum post-baseline' summaries but will not be summarized separately.

On- and post-treatment bone fractures collected on the Fractures Details eCRF form and on- and post-treatment pneumonia assessments collected on the Pneumonia Details eCRF form will be summarised separately by treatment group. A summary of chest x-rays (on- and post-treatment) will include data from the Exacerbation Chest X-ray and Pneumonia Chest X-ray eCRF pages.

12-lead ECG findings (normal, abnormal – not clinically significant, abnormal – clinically significant) collected at Visit 1 (Screening) will be summarized with frequency distributions by treatment group. Screening lab results will be summarised with descriptive statistics by treatment group.

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

9. REFERENCES

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10. APPENDICES

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

10.1.1. Exclusion of Data from the ITT Analyses

In general, all data recorded for participants who were randomised (excluding those randomised in error) will be included in ITT analyses. The following will result in exclusion of data from ITT analyses:

Spirometry data will be excluded from trough FEV_1 ITT analyses if the actual time of assessment is after the time of morning dosing on that day and post-dose serial spirometry will be excluded from weighted mean FEV_1 ITT analyses if the actual time of assessment is before the time of morning dosing on that day.

10.1.2. Exclusions from the Modified Per Protocol Population

The mPP population is the primary analysis population, comprising all participants from the ITT population with the exception of:

- Study eligibility criteria not met (those considered to affect the primary outcome as listed below in Table 2).
- Randomization criteria not met (those considered to affect the primary outcome as listed below in Table 2).

Table 2 Eligibility/randomization criteria deviations considered to affect the primary outcome

Protocol Deviation Category	Important Deviation	Excluded from mPP
Eligibility inclusion criterion		
1. Informed consent	Yes	TBD*
2. Type of participant: outpatient	Yes	No
3. Age	Yes	Yes
4. Gender	Yes	No
5. COPD diagnosis	Yes	Yes
6. Smoking history	Yes	Yes
7. Severity of COPD symptoms (CAT)	Yes	Yes
8. Severity of disease	Yes	Yes
9. Existing COPD maintenance treatment	Yes	Yes
Eligibility exclusion criterion		
1. Pregnancy	Yes	No
2. Asthma	Yes	Yes
3. Alpha1-antitrypsin deficiency	Yes	Yes
4. Other respiratory disorders	Yes	Yes
5. Lung resection	Yes	Yes
6. Risk factors for pneumonia	Yes	TBD*
7. Pneumonia and/or moderate or severe COPD exacerbation	Yes	Yes

Protocol Deviation Category	Important Deviation	Excluded from mPP
Eligibility inclusion criterion		
8. Other respiratory tract infection	Yes	Yes
9. Abnormal chest x-ray	Yes	TBD*
10. Other diseases/abnormalities	Yes	TBD*
11. Unstable liver disease	Yes	No
12. Unstable or life threatening cardiac disease	Yes	No
13. Abnormal and clinically significant 12-lead ECG finding	Yes	No
14. Contraindications	Yes	No
15. Cancer	Yes	No
16. Oxygen therapy	Yes	Yes
17. Medication prior to spirometry	Yes	Yes
18. Pulmonary rehabilitation	Yes	Yes
19. Drug/alcohol abuse	Yes	No
20. Non-compliance with study procedures	Yes	Yes
21. Questionable validity of consent	Yes	TBD*
22. Affiliation with Investigator site	Yes	No
23. Inability to read	Yes	Yes
24. Medication prior to screening	Yes	Yes
Randomization exclusion criterion		
1. Non-compliance with run-in study medication	Yes	No
2. COPD exacerbation or pneumonia	Yes	Yes
3. Changes in COPD medication	Yes	Yes

Note: *TBD – To be determined on a case-by-case basis and documented in the PDSF

10.2. Appendix 2: Schedule of Activities

10.2.1. Protocol Defined Schedule of Events

Protocol Activity	Pre-Screen	Screen		Treatment		Follow-up	
	Visit 0	Visit 1 Screen/ Run-in	Visit 2 Randomisation	Visit 3	Visit 4	Study Treatment Discontinuation Visit	Visit 5 Safety Follow-up Contact
Study Day	-56 to -28	Day -28	Day 1	Day 28	Day 84-85		Day 91
Week	-8 to -4	-4	0	4	12		13
Window		-3/+8d (Day -31 to -21)		-4/+2d (Day 24 to 30)	-4/+2d (Day 80 to 86)		-1/+4d (Day 90 to 95)
Written Informed Consent [a]	X	X					
Genetic Informed Consent [b]	X	X					
Demography [c]	X	X					
Medical History, including cardiovascular history		X					
COPD and Exacerbation History		X					
Concomitant Medication Assessment	X	X	X	X	X	X	X
Inclusion/Exclusion Criteria		X	X				
Smoking history & status		X			X	X	
Smoking Cessation Counselling		X			X	X	
Register Visit in IWRS	X	X	X	X	X	X	X
CAT [d]		X	X	X	X		
SGRQ-C[d]			X	X	X		
Reversibility Testing and PIFR [e]		X					
Trough FEV1 [f]				X			
24h serial spirometry [g]			X		X		
Inhalation device training		X	X				
Exacerbation Assessment		X	X	X	X	X	X
Physical examination [h]		X			X	X	
Adverse Events Assessment		X	X	X	X	X	X
Vital signs [i]		X			X	X	
ECG		X					
Chest X-ray [j]		X					
Oropharyngeal examination		X	X	X	X	X	
Blood Draw for Genetics research [k]			X				
Hematology/biochemistry [l]		X					
Urine Pregnancy Test [m]		X			X	X	
Hepatitis B and C tests		X					
Dispense run-in treatment		X					
Dispense study treatment			X	X			

Protocol Activity	Pre-Screen	Screen		Treatment		Follow-up	
	Visit 0	Visit 1 Screen/ Run-in	Visit 2 Randomisation	Visit 3	Visit 4	Study Treatment Discontinuation Visit	Visit 5 Safety Follow-up Contact
Study Day	-56 to -28	Day -28	Day 1	Day 28	Day 84-85		Day 91
Week	-8 to -4	-4	0	4	12		13
Window		-3/+8d (Day -31 to -21)		-4/+2d (Day 24 to 30)	-4/+2d (Day 80 to 86)		-1/+4d (Day 90 to 95)
Administer run-in treatment in clinic [n]		X					
Administer study treatment in clinic [o]			X	X	X		
Assess run-in treatment compliance			X				
Assess study treatment compliance				X	X	X	
Collect run-in treatment			X				
Collect study treatment				X	X	X	
Dispense albuterol/salbutamol		X	X	X	X		
Collect albuterol/salbutamol			X	X	X	X	
Dispense paper Medical Problems worksheet	X	X	X	X	X		
Review paper Medical Problems worksheet		X	X	X	X	X	X

a. Informed consent must be conducted at the Pre-screen Visit prior to performing any study procedures including the changing or withholding of medications. The informed consent may be given at Screening Visit 1 if the participant does not take or has not taken any protocol excluded medications. The Pre-screen and Screening Visits can occur on the same day.
b. Genetics research consent may be obtained at the same time as the study IC and must be obtained prior to obtaining a genetic blood sample. Participants do not have to participate in the genetic research part of this study, it is optional.
c. Demography may be captured at either the Pre-screen Visit or Screening Visit (for participants who do not have a Pre-screen Visit).
d. SGRQ-C and CAT will be completed electronically and should be conducted in the following order and before other study assessments: CAT, SGRQ-C.
e. At Screening Visit 1 PIFR spirometry and both pre and post-bronchodilator spirometry will be conducted. PIFR will be assessed 10 minutes prior to pre-bronchodilator spirometry. Participants are required to withhold their usual morning doses of their COPD meds including rescue albuterol/salbutamol for the protocol designated period prior to PIFR spirometry and reversibility testing.
f. Trough FEV1 will be performed pre-dose at 30 mins and 5 mins prior to taking the morning dose of study treatment, between 6am and 11am and after withholding rescue albuterol/salbutamol for ≥4 hours.
g. Serial spirometry at Visit 2 and Visit 4 will be done pre-dose at 30 mins and 5 mins and post dose at 5 mins, 15 mins, 30mins,1hr, 3hrs, 6hrs, 12hrs, 15hrs, 21hrs, 23hrs, 24hrs. Participants that discontinue study treatment but remain in the study will complete serial spirometry at Week 12, if they consent to do so.
h. Physical examination may include height, weight, blood pressure and temperature.
i. Vital signs, including blood pressure and pulse must be performed prior to spirometry and prior to taking morning dose of study treatment.
j. Chest X-ray is required at Screening (or historical x-ray obtained within 3 months prior to Screening) and at any time there is a suspected pneumonia or a mod/severe exacerbation.
k. Genetic consent must be obtained prior to obtaining a blood sample. The sample can be collected at any time after Visit 2, providing consent is obtained.

l. Hematology and chemistry panels will include full and differential blood count and liver chemistry.
m. All female participants of child bearing potential will have a urine pregnancy test at Visits 1, 4 and Study Treatment Discontinuation Visit (if applicable).
n. Participants must withhold their morning dose of existing COPD medication or study treatment and not take their run-in treatment until instructed to do so by study staff.
o. Participants must withhold their morning dose of study treatment at each clinic visit and not take their study treatment until instructed to do so by study staff.

When multiple assessments and procedures are performed, suggested sequence order is CAT, SGRQ-C, vital signs, ECG, spirometry, clinical lab assessments.

10.3. Appendix 3: Assessment Windows

In general terms, data will be reported per the nominal time of clinic visits and assessments as specified in the protocol. For example, if a participant's recorded values for the Week 4 visit were actually made on the 21st day of treatment, they will be presented as Week 4 values in the summary tables.

Participants who permanently stop randomized study treatment early between scheduled clinic visits should undergo all assessments listed for the Study Treatment Discontinuation Visit. Data collected at this visit will be listed and used in summary tables as part of the 'minimum/maximum post-baseline' summary if appropriate.

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

10.4.1. Study Phases

Assessments and events will be classified per time of occurrence relative to the start and/or stop date of the randomized study treatment. The earliest and latest exposure randomized study treatment start and stop dates will be used to determine whether an assessment or event was pre-treatment, on-treatment or post-treatment. If it is not possible to tell whether an assessment or event was on-treatment or not, it will be considered as on-treatment.

10.4.1.1. Study Phases for Concomitant Medications

Treatment phases for summaries of COPD and non-COPD concomitant medications will be assigned as follows:

Treatment Phase	Definition
Prior to Screening	Medications taken between date of Screening – 90 days and date of Screening (inclusive) defined as: (conmed start date <= date of Screening or 'Taken prior to study?' is 'Yes') and (conmed stop date >= date of Screening – 90 or (conmed stop date is completely missing and date of Screening is non-missing)) Note: This screening data will only be summarized for COPD medications. All screening data will be listed.
Run-in	Medications taken any time between the date of Screening and randomized treatment start date (exclusive) defined as: (conmed start date < randomized treatment start date or randomized treatment not started or conmed start date is missing) and (conmed stop date > date of Screening or (conmed stop date is completely missing and date of Screening is non-missing))
On-treatment	If randomized treatment stop date > randomized treatment start date then this includes medications taken between the randomized treatment start date and randomized treatment stop date - 1 (inclusive) defined as follows: (conmed start date < randomized treatment stop date or conmed start date is missing) and (conmed stop date >= randomized treatment start date or (conmed stop date is completely missing and randomized treatment start date is non-missing)) If randomized treatment stop date = randomized treatment start date then this includes medications taken on the randomized treatment start date (which is equal to the randomized treatment stop date) defined as follows: (conmed start date <= randomized treatment stop date or conmed start date is missing) and (conmed stop date >= randomized treatment start date or (conmed stop date is completely missing and randomized treatment start date is non-missing))

Treatment Phase	Definition
Post-treatment	If randomized treatment stop date > randomized treatment start date then this includes medications taken between the date of randomized treatment stop date and the date of study conclusion (inclusive) defined as follows: (conmed start date <= study conclusion date or conmed start date is missing) and (conmed stop date >= randomized treatment stop date or (conmed stop date is completely missing and randomized treatment stop date is non-missing)) If randomized treatment stop date = randomized treatment start date then this includes medications taken between the date of randomized treatment stop date + 1 and the date of study conclusion (inclusive) defined as follows: (conmed start date <= study conclusion date or conmed start date is missing) and (conmed stop date > randomized treatment stop date or (conmed stop date is completely missing and randomized treatment stop date is non-missing))

NOTES:

- A concomitant medication will be classed in every period of the study in which it was taken (e.g., prior to screening, run-in, on- treatment, post-treatment).
- See Section 10.7.2.1 for handling of partial dates.

10.4.1.2. Study Phases for Other Data

Any events/assessments for participants not in the ITT population will be assigned a Pre-treatment phase.

For all events and assessments where time is recorded, pre-treatment, on-treatment and post-treatment phases will be defined as below:

Study Phase	Definition
Pre-Treatment	• Event onset date/time or assessment date/time < randomized treatment start date/time
On-Treatment	• Randomized treatment start date/time ≤ event onset date/time or assessment date/time ≤ randomized treatment stop date + 1, or any event/assessment with a missing or partial onset date unless there is evidence it was not on-treatment
Post-Treatment	• Event onset date/time or assessment date/time ≥ randomized treatment stop date + 2, and event onset date/time or assessment date/time ≤ study conclusion date

For all events and assessments (with the exception of concomitant medications) where time is not recorded, pre-treatment, on-treatment and post-treatment phases will be defined as below:

Study Phase	Definition
Pre-Treatment	• Event onset date or assessment date < randomized treatment start date
On-Treatment	• Randomized treatment start date ≤ event onset date or assessment date ≤ randomized treatment stop date + 1, or any event/assessment with a missing or partial onset date unless there is evidence it was not on-treatment
Post-Treatment	• Event onset date or assessment date ≥ randomized treatment stop date + 2 and event onset date or assessment date ≤ study conclusion date

10.4.2. Treatment Emergent Flag for Adverse Events

Study Phase	Definition
Pre-Treatment	• AE start date < randomized treatment start date
On-Treatment	• Randomized treatment start date ≤ AE start date ≤ randomized treatment stop date + 1
Post-Treatment	• AE start date ≥ randomized treatment stop date + 2
Onset Time Since First Dose (days)	Time since first dose will be derived as followed: • If randomized treatment start date or AE start date is missing => missing • If randomized treatment start date > AE start date then => AE start date – randomized treatment start date • If randomized treatment start date ≤ AE start date then => AE start date – randomized treatment start date + 1

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Reporting Process

Software	
• The currently supported version of SAS software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Compound	: /arenv/arprod/gsk2834425/mid207608/final_01
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards current to GSK reporting [Study Data Tabulation Model (SDTM) Implementation Guide Version 3.2 or higher and Analysis Data Model (ADaM) Implementation Guide Version 1.0 or higher].	
Generation of RTF Files	
• Rich Text Format (RTF) files will be generated for the final reporting effort for use in writing the CSR.	

10.5.2. Reporting Standards

General

• All data displays (Tables, Listings and Figures) will use the term “Subject” which reflects CDISC and GSK Data Display Standards terminology.
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated:
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics

Formats
• All data will be reported according to the treatment to which the participant was randomized unless otherwise stated. However, there may be additional adhoc displays for individual participants using the actual treatment received. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places will be adopted for reporting of data based on the raw data collected. • The reported precision from non-eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of decimal places. • Numeric data will be reported (in listings) at the precision collected in the eCRF or recorded in the raw dataset if from non-eCRF sources. • Percentages between 1% and 99%, inclusive, will be rounded to integers. Percentages greater than 0%, but less than 1%, will be reported as <1%, and percentages greater than 99%, but less than 100%, will be reported as >99%.   •
Planned and Actual Time
• Reporting for tables, figures and statistical analyses: • Planned time relative to randomized treatment dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. Actual time will be used in calculation of weighted mean FEV_1.

• Reporting for listings:
  • Planned and actual time relative to randomized treatment dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned measurements will be presented within the listings.	

Unscheduled Visits	
• Unscheduled visits will not be included in figures or in summary tables except as a part of a 'minimum/maximum post-baseline' assessment. • 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 Principles 7.01 to 7.13. • The programs for statistical analysis tables will create SAS datasets with the unrounded numbers from the statistical models to be used in any graphs. This will include all LS means, standard errors, treatment differences or ratios and CIs. This will be done for all analysis tables regardless of whether or not a figure is planned as part of SAC.	

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 date ≥ treatment start date → Study day = reference date – treatment start date +1

Randomized Treatment Start and Stop Dates
• Randomized treatment start date will be defined as the earliest treatment start date.Randomized treatment stop date will be defined as the latest date of randomized treatment exposure date or date of last dose from treatment discontinuation eCRF page. Treatment stop date will be imputed as study completion date if the date of last dose cannot be confirmed but investigational product is returned at the end of study visit (follow up) or if the date of last dose can be confirmed in protocol deviation log to be after study completion date.

10.6.2. Study Population

Demographics
Age
Age is calculated in the IWRS and will be imported from the IWRS into the clinical database. The IWRS will use GSK standard IDSL algorithms to calculate age. In accordance with GSK policy, only year of birth is collected in the IWRS. In order to estimate participant age, a complete birthdate will be estimated by using the year recorded by the IWRS and assigning month and day values of PPD 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, in whole years, will be calculated based on the Pre-Screening Visit date (or Screening Visit date, if pre-screening is not evaluated).
Age Categories

Age categories are based on age at pre-screening (or screening, if pre-screening is not evaluated) and are defined as:
  • ≤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:
  1. Black or African American
  2. American Indian or Alaska Native
  3. Asian
  a. Central/South Asian Heritage
  b. Japanese/East Asian Heritage/South East Asian Heritage

Demographics
c. Mixed Asian Heritage (only required if data exists) 4. Native Hawaiian or other Pacific Islander 5. 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: 1. African American/African Heritage 2. American Indian or Alaska Native 3. Asian - Central/South Asian Heritage 4. Asian – East Asian Heritage 5. Asian – Japanese Heritage 6. Asian – South East Asian Heritage 7. Asian – Mixed Race 8. Native Hawaiian or other Pacific Islander 9. White – Arabic/North African Heritage 10. White – White/Caucasian/European Heritage 11. White – Mixed Race 12. Multiple "Asian – Mixed Race" is only used if more than one Asian category is selected, but no non-Asian races. Similarly, "White – Mixed 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 "Asian – Mixed Race," "White – Mixed 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, and the percentages will add to 100%.

Participant Disposition
Study Withdrawal and Study Treatment Discontinuation
• For Kaplan-Meier plots of study withdrawal over time and discontinuation from randomized study treatment over time, censoring will be performed as follows: ○ For study withdrawal, participants are represented from their Day 1 date to the date of early withdrawal from the study (or date of death). Participants that complete the study are censored at the earliest of the date of completion and Day 85. ○ For discontinuation from randomized study treatment, participants are represented from their Day 1 date to the date of discontinuation from randomized study treatment (or date of death). Participants that complete randomized treatment per protocol are censored at the earliest of their randomized study treatment stop date and Day 84.

Treatment Compliance
Treatment Compliance

If a dose counter start count is missing then it will be assumed to be 30 for the ELLIPTA and HandiHaler or 120 for the MDI. If any dose counter stop count is missing then the treatment compliance will be set to missing for that participant and for that inhaler.

Compliance will be calculated as follows:

- ELLIPTA compliance = (dose counter start – dose counter stop) x 100 / (exposure stop date – exposure start date + 1)
- HandiHaler compliance = (number of capsules dispensed – number of capsules returned) x 100 / (exposure stop date – exposure start date + 1)
- MDI compliance = (dose counter start – dose counter stop) x 100 / [4* (exposure stop date – exposure start date +1)]
- Overall compliance is calculated as the overall compliance for inhalers with active treatment.
- For participants in the FF/UMEC/VI treatment group, Overall compliance = ELLIPTA compliance
- For participants in the BUD/FOR + TIO treatment group, Overall compliance = (HandiHaler compliance + MDI compliance) / 2

Overall and individual inhaler compliance will be summarised for the double-blind treatment period and will be categorized as follows:

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

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

Medical Conditions and Concomitant Medications

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. The number of CV risk factors at Screening (0, 1, or >=2) will be derived.

- Angina pectoris
- Coronary artery disease
- Myocardial infarction
- Arrhythmia
- Congestive heart failure
- Hypertension
- Cerebrovascular accident
- Diabetes mellitus
- Hypercholesterolemia

COPD Exacerbation History

COPD exacerbations occurring in the past 12 months prior to the Screening Visit reported on the Exacerbation History eCRF page 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: mild COPD exacerbations, moderate COPD exacerbations, severe COPD exacerbations, and moderate/severe COPD exacerbations.

Mild exacerbations are defined as exacerbations that were managed without oral/systemic corticosteroids

Medical Conditions and Concomitant Medications
and/or antibiotics (not involving hospitalization). Moderate COPD exacerbations are defined as exacerbations that required treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalization). Severe COPD exacerbations are defined as exacerbations that required in-patient hospitalization. Moderate/severe COPD exacerbations are 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) classifications: • Androgens and estrogens • Anti-IgE, Anti-IL5 • Anticholinergic • Antiinfectives (antibiotics, antiseptics) • Antimycotics • Antivirals • Beta-2 agonists • Corticosteroid • 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
COPD Medication Combinations
COPD medications taken prior to Screening will be grouped into the following categories based on the RMC classification: • ICS • LABA • LAMA • Xanthine • PDE4 inhibitors • Any combination of the above • Other • None

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:

Screening Lung Function
• 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
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 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 $FEV_1 < 30\%$

10.6.3. Efficacy

Lung Function
On-Treatment Weighted Mean FEV_1
24-hour serial spirometry at Day 1 and Week 12 will be performed -30 mins and -5 mins pre-dose, and post-dose after 5 mins, 15 mins, 30 mins, 1 hr, 3 hrs, 6 hrs, 12 hrs, 15 hrs, 21 hrs, 23 hrs and 24 hrs. The calculated baseline value at Day 1 or trough value (average of the two pre-dose measurements, or individual value if only one of the measurements is present) at Week 12 will be set as the 0-hr observation for their respective visits. FEV_1 values from post-dose assessments (5 mins to 24 hrs) which are actually performed before the time of AM dosing will be excluded from the calculation. The post AM-dose observations will use the actual time of assessment for calculations. The weighted mean will only be calculated if there are at least 4 non-missing values between 0-24 hours (0 hr; at least one of the (5 mins, 15 mins, 30 mins, 1 hr, 3 hrs) values; at least one value between PM dosing and 23 hrs; and 24 hrs). The weighted mean will be derived by calculating the area under the FEV1 time curve over the actual time of assessment relative to the time of dosing using the trapezoidal rule, and then dividing by the actual time between AM dosing and the final assessment at 24 hrs. Area under the curve (AUC) will be calculated as the $AUC_{(t0\text{-}tL\ hrs)}$ as follows: $$AUC_{(t_0-t_L\ hrs)} = \frac{1}{2}\sum_{i=0}^{L-1}(C_i + C_{i+1})(t_{i+1} - t_i)$$ where, • i = collected measurement • L = last collected measurement • C_i = result of collected measurement i • t_i = actual time of assessment for collected measurement i Weighted mean (WM) will then be calculated as follows: $$WM_{(t_0-t_L\ hrs)} = AUC_{(t_0-t_L\ hrs)} / (t_L - t_0)$$
Post-Treatment Weighted Mean FEV_1
Post-treatment weighted mean FEV1 will also be derived for participants who have discontinued the

Lung Function

randomized study treatment but continue in the study, and attend clinic visit at Week 12.

The average of the two measurements at the planned time -30 mins and -5 mins (or individual value if only one of these two measurements is present) at Week 12 will be set as the 0 hr observation. The midpoint of planned time -5 min and 5 min will be set as 0 hr. If -5min or +5min assessment is missing, 0 hr will be set as minus of +5 min time or plus of -5min time, respectively. FEV_1 values from the actual time 5 mins to 24 hrs will be used to calculate the weighted mean FEV1 over 0-24 hours.

The weighted mean will only be calculated if there are at least 4 non-missing values between 0-24 hours (0 hr; at least one of the (5 mins, 15 mins, 30 mins, 1 hr, 3 hrs) values; at least one of the (12 hrs, 15 hrs, 21 hrs, 23 hrs) values; and 24 hrs).

The weighted mean will be derived by calculating the area under the FEV1 time curve over the actual time of assessment using the trapezoidal rule, and then dividing by the time between 0 hr and the final assessment at 24 hrs.

Area under the curve (AUC) will be calculated as the $AUC_{(t0\text{-}tL\ hrs)}$ as follows:

$$AUC_{(t_0-t_L\ hrs)} = \frac{1}{2}\sum_{i=0}^{L-1}(C_i + C_{i+1})(t_{i+1} - t_i)$$

where,

- i = collected measurement
- L = last collected measurement
- C_i = result of collected measurement i
- t_i = actual time of assessment for collected measurement i

Weighted mean (WM) will then be calculated as follows:

$WM_{(t_0-t_L\ hrs)} = AUC_{(t_0-t_L\ hrs)} / (t_L - t_0)$

Trough FEV_1

For Day 28 and Day 84, trough FEV_1 is defined as the average of the pre-dose FEV_1 measurements recorded before the morning dose of randomized study treatment. If only one pre-dose measurement is recorded, then it will serve as the trough value. For Day 2 and Day 85, trough FEV_1 is defined as the mean of the 23-hour and 24-hour serial spirometry FEV_1 measurements. If only one of the two measurements is recorded, then it will serve as the trough value.

Patient-Reported Outcomes

St. George's Respiratory Questionnaire - COPD (SGRQ-C) Total Score

The SGRQ-C includes 14 questions with a total of 40 items grouped into three domains (Symptoms, Activity and Impacts).

The details for how to score the SGRQ-C are outlined in the SGRQ-C manual (Jones, 2016). Missing data will be handled as detailed in the manual.

The SGRQ-C Total score will be converted to an SGRQ score as described in the manual (Meguro, 2007).

Change from baseline in SGRQ Total score will be calculated for the converted score.

If the language of the SGRQ-C assessed at a post-baseline visit is different from the language used at baseline (Day 1), all SGRQ-C scores at that visit and all subsequent visits will be set to missing.

SGRQ Responders
SGRQ responder analyses will be based on the resulting SGRQ Total scores (converted SGRQ-C scores). A participant will be considered a responder according to the SGRQ if his/her on-treatment SGRQ Total score has decreased at least 4 units from the baseline SGRQ Total score. A participant will be considered a non-responder if his/her on-treatment SGRQ Total score has decreased by fewer than 4 units, has not changed, or has increased compared to baseline. Handling of missing data for the responder analysis is detailed in Section 10.7.2. ("Handling of Missing Data").
COPD Assessment Test (CAT) Score
The CAT consists of eight items, each scored on a six-point differential scale, 0 (no impact) to 5 (high impact). A CAT score will be calculated by summing the non-missing scores of the eight items with a range of 0 to 40. If one item is missing, then the score for that item is set as the average of the non-missing items. If more than one item is missing, then the CAT score will be set to missing. Since the CAT score at Screening is a study entry criterion, screening CAT scores will be categorized as less than 10 and 10 or greater, and those categories summarised by treatment group. If the language of the CAT assessed at a post-baseline visit is different from the language used at baseline (Day 1), the CAT score at that visit and all subsequent visits will be set to missing.
CAT Responders
A participant will be considered a responder according to the CAT if his/her on-treatment CAT score has decreased at least 2 units from the baseline CAT score (Kon, 2014). A participant will be considered a non-responder if his/her on-treatment CAT score has decreased by fewer than 2 units, has not changed, or has increased compared to baseline. Handling of missing data for the responder analysis is detailed in Section 10.7.2. ("Handling of Missing Data").

COPD Exacerbations
Each COPD exacerbation will be categorized based on severity as follows: • Mild: exacerbations that were managed without oral/systemic corticosteroids and/or antibiotics (not involving hospitalization) • Moderate: exacerbations that required treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalization) • Severe: exacerbations that required in-patient hospitalization The duration of the exacerbation will be calculated as (exacerbation resolution date or date of death – exacerbation onset date +1). Exacerbation rate is event rate per 1000 subject-years, calculated as the number of events x 1000, divided by the total duration at risk (subject-years). A chest x-ray or CT scan is considered associated with a moderate/severe exacerbation if it is performed within the duration of the exacerbation or performed within -7 to +10 days (inclusive) of the date of onset.

10.6.4. Safety

Exposure
Extent of Exposure and Post-treatment Study Duration
Duration of exposure to randomized treatment will be calculated as: • Randomized treatment stop date – randomized treatment start date + 1 Duration of post-treatment time spent in the study will be calculated as: • Study conclusion date – randomized treatment stop date Duration of total time spent in the study will be calculated as: • Study conclusion date – randomized treatment start date + 1
Exposure Categories
The following exposure to randomized treatment categories will be derived: • ≥1 day, ≥4 weeks, ≥8 weeks, ≥12 weeks, 11-13 weeks

Adverse Events

Adverse Events of Special Interest

AESI have been defined as AEs which have specified areas of interest for FF, VI or UMEC or the overall COPD population. The following table presents the AESI 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.

AESI Group	AESI 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		

Bone Fracture Incidents

Details of bone fracture incidents will be collected on the Fracture Details eCRF page.

All bone fractures will be reported in aggregate. Traumatic and non-traumatic bone fractures will also be reported separately.

If a participant suffers fractures in multiple locations with the same date of fracture, this event is considered to be one fracture incident.

In the case of multiple fracture types (traumatic/non-traumatic) contributing to one fracture incident, the worst case fracture type (non-traumatic) will be assigned to the fracture incident (e.g., if a participant has a traumatic wrist fracture and a non-traumatic foot fracture on the same date, this will be considered to be one non-traumatic fracture incident).

Association of Chest Imaging (X-ray or CT Scan) with Pneumonia Events
Details of pneumonia events will be collected on the Pneumonia Details eCRF page. A chest x-ray or CT scan is considered associated with pneumonia if it is performed within the duration of the pneumonia or performed within -7 to +10 days (inclusive) of the date of onset.

Maximum/Minimum Post-Baseline	
Definition	**Reporting Details**
Maximum post-baseline (pulse rate, systolic and diastolic blood pressure)	Maximum on-treatment value over all timepoints
Minimum post-baseline (diastolic blood pressure)	Minimum on-treatment value over all timepoints

NOTES:

- The study phase definitions detailed in Section 10.4.1 ("Study Phases") will be used and only assessments within the on-treatment period will be considered in assessment of maximum/minimum post-baseline.
- Assessment of maximum/minimum post-baseline will include data from scheduled, unscheduled and study treatment discontinuation visits (if applicable). Vital signs (pulse rate, systolic blood pressure and diastolic blood pressure) collected at an assessment associated with a pneumonia event will also be included in derivation of a maximum/minimum post-baseline assessment. The pneumonia event related assessment (e.g., vital signs) dates will be assumed to be the same as the event date.

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 all phases of the study including screening, run-in, the randomised treatment phase and the safety follow-up. • Withdrawn participants will not be replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

10.7.2. Handling of Missing Data

Element	Reporting Detail

General	• Missing data occur when any requested data are not provided, leading to blank fields on the collection instrument.
	  ○ These data will be indicated by the use of a "blank" in subject listing displays, unless all data for a specific visit are missing in which case the data are excluded from the summary.
	  ○ Responses such as "Not applicable" and "Not evaluable" are not considered to be missing data and will be displayed as such.
	  ○ No imputation will be made for missing numerical data, except in the missing data sensitivity analyses and derivations described in Appendix 6: Derived and Transformed Data for efficacy assessments. Missing data will generally not be considered in the calculation of percentages (i.e., the denominator will not include participants who have missing data at a given time point).

Responder	• Participants with a missing baseline score will have responder status as missing. • Participants with missing post-baseline data at a timepoint and a subsequent non-missing on-treatment assessment will not be considered a responder or non-responder but will be left as missing at that timepoint. • Participants with a baseline score but all missing post-baseline on-treatment data will be considered a non-responder at all timepoints. • Participants with a baseline score but a missing post-baseline on-treatment score at a given timepoint with no subsequent on-treatment score will be considered a non-responder at that timepoint.

10.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events, (including Pneumonia)	• The eCRF does not allow partial dates to be captured for AEs. All dates will either be complete or missing. • Completely missing start or end dates will remain missing with no imputation applied. • Where AE onset dates are missing then the AE will be considered on-treatment.
Concomitant Medications	• The eCRF allows partial dates to be captured for concomitant medications. • Partial dates for any concomitant medications recorded in the eCRF will be imputed using the following convention:

Element	Reporting Detail
	○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month • The responses to the questions “Taken Prior to Study?” and “Ongoing?” which are recorded in the eCRF will also be taken into consideration to determine if the medication was started pre-treatment or continued post-treatment. In each case, should the answers suggest a different classification than the dates, the medication will be summarized in all possible classifications (pre-/on-/post-treatment) in which it could conceivably have been taken.
Exacerbations	• Exacerbations are treated in the same way as AEs.

10.8. Appendix 8: Abbreviations & Trade Marks

10.8.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
ASE	All Subjects Enrolled
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
BUD/FOR + TIO	Budesonide/Formoterol plus Tiotropium
CAT	COPD Assessment Test
CDISC	Clinical Data Interchange Standards Consortium
CDSB	Clinical Data Standards Board
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CSR	Clinical Study Report
CSV	Comma Separated Values
CT	Computerized (axial) Tomography
CV	Cardiovascular
DBF	Database Freeze
DBR	Database Release
DR	Dry Run
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 second
FF/UMEC/VI	Fluticasone Furoate/Umeclidinium/Vilanterol
GCSP	Global Clinical Safety and Pharmacovigilance
GOLD	Global Initiative on Obstructive Lung Disease
GSK	GlaxoSmithKline
HARP	Harmonized Analysis and Reporting Platform
hrs	Hours
IC	Informed Consent
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroid
IDSL	Integrated Data Standards Library
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
J2R	Jump to Reference
KR	Kenward and Roger
LABA	Long-Acting Beta-Agonist
LAMA	Long-Acting Muscarinic Antagonist

Abbreviation	Description
LRTI	Lower Respiratory Tract Infection
LS	Least Squares
MAR	Missing At Random
mcg	Microgram
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
mins	Minutes
mL	Milliliter
MMRM	Mixed Model Repeated Measures
mPP	Modified Per Protocol
OM	OBSMARGINS
PD	Protocol Deviation
PDE4	Phosphodiesterase Type 4
PDSF	Protocol Deviation Specification Form
PIFR	Peak Inspiratory Flow Rate
PT	Preferred Term
QD	Quaque Die (once daily)
R&D	Research and Development
RAP	Reporting and Analysis Plan
RMC	Respiratory Medication Class
RTF	Rich Text Format
RUCAM	Roussel Uclaf Causality Assessment Method
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SGRQ	St. George's Respiratory Questionnaire
SGRQ-C	St. George's Respiratory Questionnaire - COPD
SI	Special Interest
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SRT	Safety Review Team
WM	Weighted Mean

10.8.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
CAT and COPD Assessment Test
ELLIPTA

Trademarks not owned by the GlaxoSmithKline Group of Companies
Handihaler
SAS

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 1.49	1.1 to 1.2
Efficacy	2.1 to 2.33	2.1 to 2.13
Safety	3.1 to 3.36	3.1
Section	**Listings**	
ICH Listings	1 to 22	
Other Listings	23 to 49	

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. Output files in the following sections that use standard IDSL examples are identified in the "IDSL / Example Shell" column by their IDSL example format code.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAF_Fn	SAF_Tn	SAF_Ln

10.9.3. Deliverables

Delivery	Description
DR	Dry Run (prior to source data lock)
SAC	Final Statistical Analysis Complete (SAC)
Post-SAC	One week after SAC

10.9.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	ASE	POP_T01	Summary of Subject Populations and Reasons for Screen/Run-in Failure		DR, SAC
1.2.	ITT	POP_T02	Summary of Attendance at Each Visit		DR, SAC
1.3.	ITT	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		DR, SAC
1.4.	ITT	ES1	Summary of Study Status and Reasons for Study Withdrawal		DR, SAC
1.5.	ASE	DM11	Summary of Age Ranges		DR, SAC
1.6.	ASE	NS1	Summary of Number of Subjects by Geographical Region, Country and Centre		DR, SAC
1.7.	ITT	NS1	Summary of Number of Subjects by Geographical Region, Country and Centre		DR, SAC
1.8.	mPP	NS1	Summary of Number of Subjects by Geographical Region, Country and Centre		DR, SAC
1.9.	ASE	IE1	Summary of Inclusion/Exclusion Criteria Deviations for Screen Failures		DR, SAC
1.10.	ITT	IE1	Summary of Inclusion/Exclusion Criteria Deviations		DR, SAC
Protocol Deviations					
1.11.	ITT	POP_T03	Summary of Important Protocol Deviations		DR, SAC
Populations Analysed					
1.12.	ITT	POP_T04	Summary of Exclusion from the Modified Per Protocol Population	Refer to RAP Section 10.1.2 Table 2	DR, SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Demographic and Baseline Characteristics					
1.13.	ITT	DM1	Summary of Demographic Characteristics		DR, SAC
1.14.	mPP	DM1	Summary of Demographic Characteristics		DR, SAC
1.15.	ITT	DM1	Summary of Demographic Characteristics by Country		DR, SAC
1.16.	ITT	DM5	Summary of Race and Racial Combinations		DR, SAC
1.17.	mPP	DM5	Summary of Race and Racial Combinations		DR, SAC
1.18.	ITT	DM6	Summary of Race and Racial Combinations Details		DR, SAC
Medical Conditions					
1.19.	ITT	MH4	Summary of Current Medical Conditions		DR, SAC
1.20.	ITT	MH4	Summary of Past Medical Conditions		DR, SAC
1.21.	ITT	POP_T05	Summary of Cardiovascular Risk Factors		DR, SAC
1.22.	ITT	POP_T06	Summary of Family History of Cardiovascular Risk Factors		DR, SAC
Disease Characteristics					
1.23.	ITT	POP_T07	Summary of Smoking History at Screening		DR, SAC
1.24.	mPP	POP_T07	Summary of Smoking History at Screening		DR, SAC
1.25.	ITT	POP_T08	Summary of Smoking Status at Screening		DR, SAC
1.26.	mPP	POP_T08	Summary of Smoking Status at Screening		DR, SAC
1.27.	ITT	POP_T09	Summary of COPD History at Screening		DR, SAC
1.28.	ITT	POP_T10	Summary of COPD Exacerbation History at Screening		DR, SAC
1.29.	ITT	POP_T11	Summary of Screening Lung Function		DR, SAC
1.30.	mPP	POP_T11	Summary of Screening Lung Function		DR, SAC
1.31.	ITT	POP_T11	Summary of Screening Lung Function by Country		DR, SAC
1.32.	ITT	POP_T12	Summary of Reversibility and GOLD Grade (1 – 4) at Screening		DR, SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.33.	mPP	POP_T12	Summary of Reversibility and GOLD Grade (1 – 4) at Screening		DR, SAC
1.34.	ITT	POP_T13	Summary of Screening PIFR (L/min)		DR, SAC
1.35.	ITT	POP_T14	Summary of CAT Score and CAT Category at Screening		DR, SAC
Prior and Concomitant Medications					
1.36.	ITT	POP_T15	Summary of COPD Concomitant Medications Taken Prior to Screening		DR, SAC
1.37.	ITT	POP_T16	Summary of COPD Concomitant Medication Combinations Taken at Screening		DR, SAC
1.38.	mPP	POP_T16	Summary of COPD Concomitant Medication Combinations Taken at Screening		DR, SAC
1.39.	ITT	POP_T15	Summary of COPD Concomitant Medications Taken during Run-in for Reasons other than an Exacerbation		DR, SAC
1.40.	ITT	POP_T17	Summary of On-Treatment COPD Concomitant Medications Taken for Reasons other than an Exacerbation		DR, SAC
1.41.	ITT	POP_T17	Summary of Post-Treatment COPD Concomitant Medications Taken for Reasons other than an Exacerbation		DR, SAC
1.42.	ITT	POP_T15	Summary of Concomitant Medications Taken during Run-in for an Exacerbation		DR, SAC
1.43.	ITT	POP_T17	Summary of On-Treatment Concomitant Medications Taken for an Exacerbation		DR, SAC
1.44.	ITT	POP_T17	Summary of Post-Treatment Concomitant Medications Taken for an Exacerbation		DR, SAC
1.45.	ITT	POP_T18	Summary of On-Treatment Non-COPD Concomitant Medications		DR, SAC
1.46.	ITT	POP_T18	Summary of Post-Treatment Non-COPD Concomitant Medications		DR, SAC
Treatment Compliance					
1.47.	ITT	POP_T19	Summary of Treatment Compliance (%)		DR, SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Intercurrent Event					
1.48.	mPP	POP_T20	Summary of Intercurrent Events		DR, SAC
1.49.	ITT	POP_T21	Summary of Intercurrent Events		DR, SAC

10.9.5. Study Population Figures

Study Population Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	ITT	POP_F01	Kaplan-Meier Plot of Time to Study Withdrawal		DR, SAC
1.2.	ITT	POP_F01	Kaplan-Meier Plot of Time to Study Treatment Discontinuation		DR, SAC

10.9.6. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Spirometry					
2.1.	ITT	EFF_T01	Summary of Baseline FEV_1 (L)		DR, SAC
2.2.	mPP	EFF_T01	Summary of Baseline FEV_1 (L)		DR, SAC
2.3.	ITT	EFF_T01	Summary of Baseline FEV_1 (L) by Country		DR, SAC
2.4.	ITT	EFF_T02	Summary of Weighted Mean FEV_1 (0-24 hours) (L) – Hypothetical Estimand		DR, SAC
2.5.	mPP	EFF_T02	Summary of Weighted Mean FEV1 (0-24 hours) (L) – Hypothetical Estimand		DR, SAC
2.6.	ITT	EFF_T02	Summary of Weighted Mean FEV_1 (0-24 hours) (L) by Country – Hypothetical Estimand		DR, SAC
2.7.	ITT	EFF_T03	Analysis of Weighted Mean FEV_1 (0-24 hours) (L) – Hypothetical Estimand		DR, SAC
2.8.	mPP	EFF_T03	Analysis of Weighted Mean FEV_1 (0-24 hours) (L) – Hypothetical Estimand	Remove the p-values	DR, SAC
2.9.	ITT	EFF_T04	Significance Levels for Interactions of Treatment with Geographical Region and Baseline FEV_1 for Analysis of Weighted Mean FEV_1 (0-24 hours) (L) at Week 12– Hypothetical Estimand		DR, SAC
2.10.	mPP	EFF_T04	Significance Levels for Interactions of Treatment with Geographical Region and Baseline FEV_1 for Analysis of Weighted Mean FEV_1 (0-24 hours) (L) at Week 12 – Hypothetical Estimand		DR, SAC
2.11.	ITT	EFF_T05	Tipping Point Sensitivity Analysis: Two-Sided P-values after Imputing Week 12 Mean Changes from Baseline in Weighted Mean FEV_1 (0-24 hours) (L) – Hypothetical Estimand	Produced if superiority is achieved. Add * before each p-value that is less than 0.050	DR, Post-SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.12.	mPP	EFF_T06	Tipping Point Sensitivity Analysis: Lower Limit of 95% CIs after Imputing Week 12 Mean Changes from Baseline in Weighted Mean FEV_1 (0-24 hours) (L) – Hypothetical Estimand		DR, Post-SAC
2.13.	ITT	EFF_T07	Summary of Serial FEV_1 (L) – Hypothetical Estimand		DR, SAC
2.14.	ITT	EFF_T08	Summary of Change from Baseline in Serial FEV_1 (L) – Hypothetical Estimand		DR, SAC
2.15.	ITT	EFF_T09	Analysis of Serial FEV_1 (L) on Day 1 – Hypothetical Estimand		DR, SAC
2.16.	ITT	EFF_T09	Analysis of Serial FEV_1 (L) at Week 12 – Hypothetical Estimand		DR, SAC
2.17.	ITT	EFF_T02	Summary of Weighted Mean FEV_1 (0-24 hours) (L) – Treatment Policy Estimand	Produced if overall study treatment discontinuation rate is >5%	DR, SAC
2.18.	ITT	EFF_T03	Analysis of Weighted Mean FEV_1 (0-24 hours) (L) - Treatment Policy Estimand	Produced if overall study treatment discontinuation rate is >5%	DR, SAC
2.19.	ITT	EFF_T10	Tipping Point Sensitivity Analysis: Two-Sides P-values after Imputing Week 12 Mean Change from Baseline in Weighted Mean FEV1 (0-24 hours) (L) – Treatment Policy Estimand	Produced if overall study treatment discontinuation rate is >5% Add * before each p-value that is less than 0.050	DR, Post-SAC
2.20.	ITT	EFF_T11	Summary of Trough FEV_1 (L) – Hypothetical Estimand		DR, SAC
2.21.	ITT	EFF_T12	Analysis of Trough FEV_1 (L) – Hypothetical Estimand		DR, SAC
SGRQ					
2.22.	ITT	EFF_T13	Summary of Baseline SGRQ Total and Domain Scores		DR, SAC
2.23.	ITT	EFF_T14	Summary of SGRQ Total and Domain Scores – Hypothetical Estimand		DR, SAC
2.24.	ITT	EFF_T15	Analysis of SGRQ Total Score – Hypothetical Estimand		DR, SAC
2.25.	ITT	EFF_T16	Summary and Analysis of Proportion of Responders as Defined by SGRQ Total Score – Hypothetical Estimand		DR, SAC
CAT					
2.26.	ITT	EFF_T17	Summary of Baseline CAT Score		DR, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.27.	ITT	EFF_T18	Summary of CAT Score – Hypothetical Estimand		DR, SAC
2.28.	ITT	EFF_T15	Analysis of CAT Score – Hypothetical Estimand		DR, SAC
2.29.	ITT	EFF_T19	Summary and Analysis of Proportion of Responders as Defined by CAT Score – Hypothetical Estimand		DR, SAC
COPD Exacerbations					
2.30.	ITT	EFF_T20	Summary of On-Treatment COPD Exacerbations		DR, SAC
2.31.	ITT	EFF_T21	Summary of On-Treatment Details of COPD Exacerbations		DR, SAC
2.32.	ITT	EFF_T20	Summary of Post-Treatment COPD Exacerbations		DR, SAC
2.33.	ITT	EFF_T21	Summary of Post-Treatment Details of COPD Exacerbations		DR, SAC

10.9.7. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Spirometry					
2.1.	ITT	EFF_F01	Box Plot of Change from Baseline in Weighted Mean FEV_1 (0-24 hours) (L) at Week 12 – Hypothetical Estimand		DR, SAC
2.2.	mPP	EFF_F01	Box Plot of Change from Baseline in Weighted Mean FEV_1 (0-24 hours) (L) at Week 12 – Hypothetical Estimand		DR, SAC
2.3.	ITT	EFF_F02	Empirical Distribution Function Plot of Change from Baseline in Weighted Mean FEV_1 (0-24 hours) (L) at Week 12 – Hypothetical Estimand		DR, SAC
2.4.	mPP	EFF_F02	Empirical Distribution Function Plot of Change from Baseline in Weighted Mean FEV_1 (0-24 hours) (L) at Week 12 – Hypothetical Estimand		DR, SAC
2.5.	ITT	EFF_F03	Least Squares Mean (95% CI) Change from Baseline in Weighted Mean FEV_1 (0-24 hours) (L) – Hypothetical Estimand		DR, SAC
2.6.	mPP	EFF_F03	Least Squares Mean (95% CI) Change from Baseline in Weighted Mean FEV_1 (0-24 hours) (L) – Hypothetical Estimand		DR, SAC
2.7.	ITT	EFF_F04	Least Squares Mean (95% CI) Change from Baseline in Serial FEV_1 (L) Over Time at Day 1 and Week 12 – Hypothetical Estimand		DR, SAC
2.8.	ITT	EFF_F05	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Serial FEV_1 (L) Over Time at Day 1 and Week 12 – Hypothetical Estimand		DR, SAC
2.9.	ITT	EFF_F03	Least Squares Mean (95% CI) Change from Baseline in Trough FEV_1 (L) – Hypothetical Estimand		DR, SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
SGRQ					
2.10.	ITT	EFF_F02	Empirical Distribution Function Plot of Change from Baseline in SGRQ Total Score at Week 12 – Hypothetical Estimand		DR, SAC
2.11.	ITT	EFF_F03	Least Squares Mean (95% CI) Change from Baseline in SGRQ Total Score – Hypothetical Estimand		DR, SAC
CAT					
2.12.	ITT	EFF_F02	Empirical Distribution Function Plot of Change from Baseline in CAT Score at Week 12 – Hypothetical Estimand		DR, SAC
2.13.	ITT	EFF_F03	Least Squares Mean (95% CI) Change from Baseline in CAT Score – Hypothetical Estimand		DR, SAC

10.9.8. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Exposure					
3.1.	ITT	SAF_T01	Summary of Exposure		DR, SAC
Adverse Events					
3.2.	Run-in	AE1	Summary of Pre-Treatment Adverse Events		DR, SAC
3.3.	ITT	AE13	Overview of On-Treatment Adverse Events		DR, SAC
3.4.	ITT	AE1	Summary of On-Treatment Adverse Events		DR, SAC
3.5.	ITT	AE1	Summary of On-Treatment Adverse Events by Country		DR, SAC
3.6.	ITT	AE1	Summary of Post-Treatment Adverse Events		DR, SAC
3.7.	ITT	AE1	Summary of On-Treatment Drug-Related Adverse Events		DR, SAC
3.8.	ITT	AE15	Summary of On-Treatment Common (>=3% in Either Treatment Group) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		DR, SAC
3.9.	ITT	AE3	Summary of the 10 Most Frequent On-Treatment Adverse Events in each Treatment Group		DR, SAC
3.10.	ITT	AE5A	Summary of On-Treatment Adverse Events by System Organ Class and Maximum Intensity		DR, SAC
3.11.	ASE	AE2	Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text		DR, SAC
Serious and Other Significant Adverse Events					
3.12.	ASE	AE1	Summary of Pre-Treatment Serious Adverse Events		DR, SAC
3.13.	ITT	AE1	Summary of Pre-Treatment Serious Adverse Events		DR, SAC
3.14.	ITT	AE1	Summary of On-Treatment Serious Adverse Events		DR, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.15.	ITT	AE1	Summary of On-Treatment Fatal Serious Adverse Events		DR, SAC
3.16.	ASE	AE1	Summary of Pre-Treatment Serious Adverse Events Leading to Withdrawal from Study		DR, SAC
3.17.	ITT	AE1	Summary of On-Treatment Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study		DR, SAC
3.18.	ITT	AE1	Summary of Serious Adverse Events (Serious, Drug-Related Serious, Fatal and Drug-Related Serious) by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		DR, SAC
3.19.	ITT	AE1	Summary of On-Treatment Drug-Related Serious Adverse Events		DR, SAC
3.20.	ITT	AE1	Summary of On-Treatment Drug-Related Fatal Serious Adverse Events		DR, SAC
3.21.	ITT	AE1	Summary of On-Treatment Adverse Events of Special Interest		DR, SAC
3.22.	ITT	AE1	Summary of On-Treatment Serious Adverse Events of Special Interest		DR, SAC
3.23.	ITT	AE1	Summary of Post-Treatment Serious Adverse Events		DR, SAC
3.24.	ITT	AE1	Summary of Post-Treatment Serious Fatal Adverse Events		DR, SAC
Pneumonia					
3.25.	ITT	SAF_T02	Summary of On-Treatment Pneumonia Incidence		DR, SAC
3.26.	ITT	SAF_T03	Summary of On-Treatment Details of Pneumonia		DR, SAC
3.27.	ITT	SAF_T02	Summary of Post-Treatment Pneumonia Incidence		DR, SAC
3.28.	ITT	SAF_T03	Summary of Post-Treatment Details of Pneumonia		DR, SAC
Bone Fractures					
3.29.	ITT	SAF_T04	Summary of On-Treatment Bone Fractures		DR, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.30.	ITT	SAF_T04	Summary of Post-Treatment Bone Fractures		DR, SAC
Chest Imaging					
3.31.	ITT	SAF_T05	Summary of Chest Imaging (X-Ray or CT Scan)	Combine on- and post-treatment.	DR, SAC
Labs					
3.32.	ITT	SAF_T06	Summary of Chemistry Results at Screening		DR, SAC
3.33.	ITT	SAF_T06	Summary of Hematology Results at Screening		DR, SAC
Vital Signs					
3.34.	ITT	SAF_T07	Summary of Vital Signs		DR, SAC
3.35.	ITT	SAF_T07	Summary of Change from Baseline Vital Signs		DR, SAC
ECGs					
3.36.	ITT	SAF_T08	Summary of ECG Findings at Screening		DR, SAC

10.9.9. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Exposure					
3.1.	ITT	SAF_F01	Summary of Treatment Exposure		DR, SAC

10.9.10. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.	ASE	ES7	Listing of Reasons for Screen / Run-in Failure		DR, SAC
2.	ITT	TA1	Listing of Planned and Actual Treatments		DR, SAC
3.	ITT	SD2	Listing of Reasons for Study Treatment Discontinuation		DR, SAC
4.	ITT	ES2	Listing of Reasons for Study Withdrawal		DR, SAC
5.	ITT	BL1	Listing of Subjects for Whom the Treatment Blind was Broken		DR, SAC
Protocol Deviations					
6.	ITT	DV2	Listing of Important Protocol Deviations		DR, SAC
7.	ASE	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations for Screen Failures		DR, SAC
8.	ITT	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		DR, SAC
Populations Analysed					
9.	ITT	POP_L01	Listing of Exclusions from the Modified Per Protocol Population		DR, SAC
Demographic and Baseline Characteristics					
10.	ITT	DM2	Listing of Demographic Characteristics		DR, SAC
11.	ITT	DM9	Listing of Race		DR, SAC
Prior and Concomitant Medications					
12.	ITT	POP_L02	Listing of COPD Concomitant Medications		DR, SAC
13.	ITT	POP_L03	Listing of Non-COPD Concomitant Medications		DR, SAC
Exposure					
14.	ITT	SAF_L01	Listing of Exposure Data		DR, SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events					
15.	ASE	AE8	Listing of All Adverse Events		DR, SAC
16.	ASE	AE7	Listing of Subject Numbers for Individual Adverse Events		DR, SAC
Serious and Other Significant Adverse Events					
17.	ASE	AE8	Listing of Fatal Serious Adverse Events		DR, SAC
18.	ASE	AE8	Listing of Non-Fatal Serious Adverse Events		DR, SAC
19.	ASE	AE14	Listing of Reasons for Considering as a Serious Adverse Event		DR, SAC
20.	ASE	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment		DR, SAC
21.	ITT	AE8	Listing of Adverse Events of Special Interest		DR, SAC
Vital Signs					
22.	ITT	VS4	Listing of All Vital Signs Values		DR, SAC

10.9.11. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Study Population					
23.	ASE	POP_L04	Listing of Study Treatment Misallocations		DR, SAC
24.	ITT	POP_L05	Listing of Screening Lung Function, Reversibility Status, and GOLD Grade		DR, SAC
25.	ITT	POP_L06	Listing of Medical Conditions		DR, SAC
26.	ITT	POP_L07	Listing of Family History of Cardiovascular Risk Factors		DR, SAC
27.	ITT	POP_L08	Listing of COPD Exacerbation History		DR, SAC
28.	ITT	POP_L09	Listing of Smoking History and Smoking Status		DR, SAC
29.	ITT	POP_L10	Relationship between ATC Level 1, Ingredient and Verbatim Text for Non-COPD Medications		DR, SAC
30.	ITT	POP_L11	Listing of Treatment Compliance Data		DR, SAC
Spirometry					
31.	ITT	EFF_L01	Listing of Raw FEV_1 (L) and FVC (L) Data		DR, SAC
COPD Exacerbations					
32.	ITT	EFF_L02	Listing of COPD Exacerbations		DR, SAC
SGRQ					
33.	ITT	EFF_L03	Listing of SGRQ Scores		DR, SAC
CAT					
34.	ITT	EFF_L04	Listing of CAT Scores		DR, SAC
Adverse Events					
35.	ITT	SAF_L02	AE Terms of Special Interest		DR, SAC
36.	ITT	AE7	Listing of Subject Numbers for On-Treatment Adverse Events of Special Interest		DR, SAC
Pneumonia Incidence					
37.	ITT	SAF_L03	Listing of Pneumonia Data		DR, SAC
Bone Fractures					
38.	ITT	SAF_L04	Listing of Bone Fracture Data		DR, SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Chest Imaging (X-ray or CT Scan)					
39.	ITT	SAF_L05	Listing of Chest Imaging (X-ray or CT scan) Data		DR, SAC
Liver Events					
40.	ITT	SAF_L06	Listing of Liver Event Results and Time of Event Relative to Treatment		DR, SAC
41.	ITT	SAF_L07	Listing of Medical Conditions for Subjects with Liver Stopping Events		DR, SAC
42.	ITT	SAF_L08	Listing of Substance Use for Subjects with Liver Stopping Events		DR, SAC
43.	ITT	SAF_L09	Listing of Liver Event Information for RUCAM Scores		DR, SAC
44.	ITT	SAF_L10	Listing of Liver Biopsy Details		DR, SAC
45.	ITT	SAF_L11	Listing of Liver Imaging Details		DR, SAC
Inhaler Malfunctions					
46.	ITT	SAF_L12	Listing of Inhaler Malfunctions		DR, SAC
Hepatitis B and C Tests					
47.	ITT	SAF_L14	Listing of Hepatitis B and C Test Results		DR, SAC
ECG					
48.	ITT	SAF_L15	Listing of ECG Data		DR, SAC
Labs					
49.	ITT	LB14	Listing of Laboratory Data with Character Results		DR, SAC

10.10. Appendix 10: Example Mock Shells for Data Displays

Available Upon Request