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

Title	:	Reporting and Analysis Plan for 200812: A phase IIIB, 24-week randomised, double-blind study to compare 'closed' triple therapy (FF/UMEC/VI) with 'open' triple therapy (FF/VI + UMEC), in subjects with chronic obstructive pulmonary disease (COPD)
Compound Number	:	GSK2834425 (GW685698, GSK573719, GW642444)
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TABLE OF CONTENTS

PAGE

1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	• This RAP details all planned analyses and outputs required for the final Clinical Study Report (CSR) of study 200812
Protocol	• This RAP is based on the protocol amendment (Dated: 29-June-2016) of study 200812 (GSK Document Number. 2015N261999_03) and eCRF Version 2.1
Primary Objective	• To compare the effect of FF/UMEC/VI with FF/VI + UMEC on lung function after 24 weeks of treatment in COPD subjects
Primary Endpoint	• Change from baseline in trough FEV1 at Week 24 • The primary treatment comparison of FF/UMEC/VI with FF/VI+UMEC will be performed on trough FEV1 at Week 24, for the mPP Population.
Secondary Objectives	• To compare the effects of FF/UMEC/VI with FF/VI + UMEC on health related quality of life and dyspnoea after 24 weeks of treatment • To compare the effect of FF/UMEC/VI with FF/VI + UMEC on time to first moderate or severe exacerbation during 24 weeks of treatment
Secondary Endpoints	• Proportion of Responders based on the St George Respiratory Questionnaire (SGRQ) Total Score at Week 24 • Change from baseline in SGRQ Total Score at Week 24 • Proportion of Responders based on Transitional Dyspnoea Index (TDI) focal score at Week 24 • TDI focal score at Week 24 • Time to first moderate/severe exacerbation
Study Design	• This is a phase IIIB, 24-week, randomised, double-blind, parallel group, multicenter study evaluating FF/UMEC/VI (100/62.5/25mcg) delivered via a single ELLIPTA ('closed' triple) plus matching placebo ELLIPTA versus FF/VI (100/25mcg) + UMEC (62.5mcg) delivered via two ELLIPTAs ('open' triple), all taken once daily. • Subjects will be randomized 1:1 to either FF/UMEC/VI or FF/VI+UMEC. The randomisation will be stratified based on long-acting bronchodilator usage during the run-in (none, one or two long-acting bronchodilators per day). • A study with 816 evaluable subjects for the primary analysis will have 90% power to determine non-inferiority of FF/UMEC/VI to FF/VI+UMEC based on trough FEV1 at Week 24 , an estimate of residual standard deviation (SD) for trough FEV1 at Week 24 of 220mL, at the one-sided 2.5% significance level when the margin of non-inferiority is 50mL and the true mean treatment difference is assumed to be 0mL. • Based on approximately 20% of subjects who are randomized discontinuing study treatment or being excluded from the mPP population at Week 24, approximately 1020 subjects will be randomised
Planned Analyses	• No interim analyses are planned for this study.

Overview	Key Elements of the RAP
	• All decisions regarding final analysis, as defined in this RAP document, will be made by Source Data Lock (SDL) prior to Study Data Tabulation Model (SDTM) Database Freeze (DBF) of the study data except for the identification of protocol deviation (PD) that require treatment details. The PD of taking incorrect treatment and treatment non-compliance (based on active treatment) will be identified following DBF.

Analysis Populations	• All Subjects Enrolled (ASE) population includes all subjects, for whom a record exists in the study database, including screen failures and any subject who was not screened but experienced an SAE between the date of informed consent and the planned date of the Screening visit. All Subjects Enrolled population (ASE) will be used for subject disposition, reason for withdrawal prior to randomisation, inclusion, exclusion and randomisation criteria deviations and SAEs for non randomised subjects.
	• Intent-to-treat (ITT) population, which comprises all randomized subjects, excluding those who were randomized in error. A subject who is recorded as a screen or run-in failure and also randomized will be considered to be randomized in error. Any other subject who receives a randomisation number will be considered to have been randomized. Intent-to-treat (ITT) population will be used for study population, efficacy and safety endpoints.
	• Modified Per-Protocol (mPP) population includes all subjects in the ITT Population who do not have a full protocol deviation considered to impact efficacy.
	  • Data following a moderate or severe COPD exacerbation or pneumonia will be excluded from analysis due to the potential impact of the exacerbation or the medications used to treat it
	  • Subjects 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
	  • mPP population will be used for the primary treatment comparison of the primary endpoint only.

Hypothesis	The null hypothesis is that the difference in trough FEV1 between treatment groups is less than or equal to a pre-specified non-inferiority margin -Δ: H_0: T1 – T2 ≤ -Δ The alternative hypothesis is that the difference between treatment groups is greater than the margin. H1: T1 – T2 > -Δ where T1 and T2 are the treatment means for FF/UMEC/VI and FF/VI+UMEC, respectively. The non-inferiority margin has been set at 50mL, which is half the generally accepted minimal clinically important difference (MCID) for trough FEV1. If the lower bound of the two-sided 95% confidence interval around the

Overview	Key Elements of the RAP
	(FF/UMEC/VI vs. FF/VI+UMEC) treatment difference is above -50mL then FF/UMEC/VI will be considered non-inferior to FF/VI+UMEC.
Primary Analyses	The primary endpoint of change from baseline in trough FEV1 at Week 24 will be analyzed in the mPP population, using a mixed model repeated measures (MMRM) analysis, including trough FEV1 recorded at each of Week 4, 12 and 24. The model will include covariates of stratum (number of long-acting bronchodilators per day during the run-in, baseline FEV1, Visit, geographical region, treatment 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. The variance-covariance matrix will be assumed unstructured.
Other Efficacy Analyses	The MMRM analysis will be repeated for the ITT Population

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There was one change to the originally planned statistical analysis specified in the protocol.

The Adherent population in the originally planned statistical analysis specified in the protocol is now referred to as the Modified Per Protocol (MPP) population. This is simply a change of the name of population. The definition remains the same.

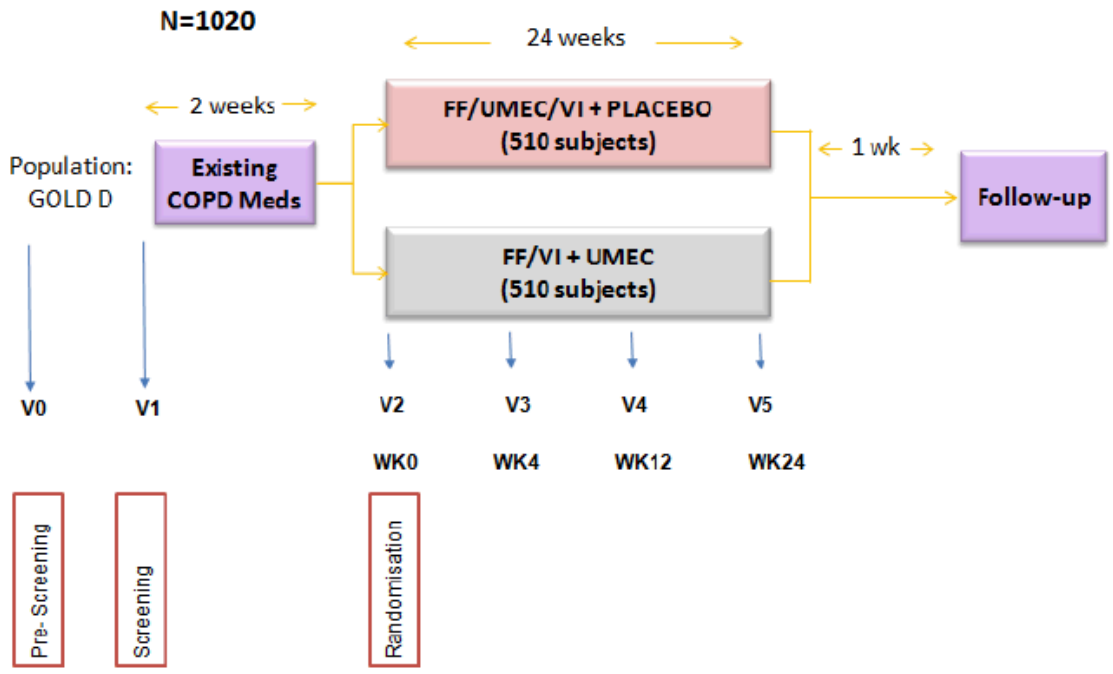
2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
• To compare the effect of FF/UMEC/VI with FF/VI + UMEC on lung function after 24 weeks of treatment	• Change from baseline in trough FEV1 at Week 24
	Other Endpoints
	• Change from baseline in trough FEV1 on Week 4 and 12 • Change from baseline in trough FVC on Week 4,12 and 24
Secondary Objective	**Secondary Endpoint**
• To compare the effects of FF/UMEC/VI with FF/VI + UMEC on health related quality of life and dyspnoea after 24 weeks of treatment • To compare the effect of FF/UMEC/VI with FF/VI + UMEC on time to first moderate or severe exacerbation	• Proportion of Responders based on the St George Respiratory Questionnaire (SGRQ) Total Score at Week 24 • Change from baseline in SGRQ Total Score at Week 24 • Proportion of Responders based on Transitional Dyspnoea Index (TDI) focal score at Week 24 • TDI focal score at Week 24

Objectives	Endpoints
during 24 weeks of treatment	• Time to first moderate or severe exacerbation
	Other Endpoints
	• Proportion of Responders based on the St George Respiratory Questionnaire (SGRQ) Total Score at Week 12 • Change from baseline in SGRQ Total Score at Week 12 • Proportion of Responders based on TDI focal score at Week 12 • TDI focal score at Week 12
PK	
• To compare the PK of FF, UMEC and VI when given as FF/UMEC/VI or FF/VI+UMEC in a subset of subjects	• Population PK (in a subset of approximately 180 subjects) (note: Population PK analysis is subject to a separate RAP)
Safety	
• To compare the safety profile of FF/UMEC/VI with FF/VI + UMEC over 24 weeks of treatment	• Incidence of adverse events • Incidence of adverse events of special interest • ECG measurements • Vital signs • Haematological and clinical chemistry parameters

2.3. Study Design

Overview of Study Design and Key Features



Overview of Study Design and Key Features	
Design Features	• This is a phase IIIB, 24-week, randomised, double-blind, parallel group, multicenter study evaluating FF/UMEC/VI delivered via a single ELLIPTA ('closed' triple) plus matching placebo ELLIPTA versus FF/VI + UMEC delivered via two ELLIPTAs ('open' triple), all taken once daily. • Subjects will be randomized 1:1 to either FF/UMEC/VI or FF/VI+UMEC. The randomisation will be stratified based on long-acting bronchodilator usage during the run-in (none, one or two long-acting bronchodilators per day). • Subjects will run-in on their existing COPD medications for 2 weeks and in addition will be provided with short acting albuterol/salbutamol to be used on an as-needed basis (rescue medication) throughout the study. Subjects will discontinue all existing COPD medications at the start of the randomised treatment period but may continue their study-supplied rescue albuterol/salbutamol. • A subject will be considered to have completed the study when they have completed all phases of the study including screening, run-in, the randomised treatment phase, and safety follow-up. Subjects who stop study treatment early will complete an Early Withdrawal Visit, followed by a Safety Follow-Up a week later and be withdrawn from the study. • Approximately 180 subjects, in selected sites, will be asked to participate in PK research. There will be two PK groups (subset A and subset B). Approximately 120 subjects will be assigned to subset A and approximately 60 subjects will be assigned to subset B. Subjects in subset A will provide a blood sample at two time-points at Week 12 (V4) and at Week 24 (V5). Subjects in subset B will provide bloodsamples at seven time points at Week 12 (V4). • A subset of subjects in selected countries (Russia, Japan and Germany) providing PK samples for subset A will also be asked to take part in a hair sample scalp & finger secretion PK Sub-Study. Hair sample scalp & finger secretion PK data is subject to a separate RAP.
Dosing	• The ELLIPTA contains 30 doses (FF/UMEC/VI, FF/VI, UMEC or placebo) and subjects will be instructed to administer one dose from each ELLIPTA once daily in the morning.
Treatment Assignment	• Following the run-in period, subjects who fulfil the randomisation criteria will be randomised (1:1) to one of the following double-blind treatment groups for 24 weeks: FF/UMEC/VI 100/62.5/25mcg and placebo, both via the ELLIPTA once daily in the morning or, FF/VI 100/25mcg and UMEC 62.5mcg, both via the ELLIPTA once daily in the morning

Overview of Study Design and Key Features	
	• GSK RandAll NG used to generate randomisation schedules. • Country based randomisation for treatment allocation. • The randomisation is stratified based on long-acting bronchodilator usage during the run-in (none, one or two long-acting bronchodilators per day).
Interim Analysis	• No interim analysis is planned for the study.

2.4. Statistical Hypotheses

The primary objective of this study is to compare FF/UMEC/VI with FF/VI+UMEC in COPD subjects. The primary endpoint is change from baseline in trough FEV1 at Week 24. The primary analysis is the comparison of this endpoint for FF/UMEC/VI vs. FF/VI+UMEC.

The null hypothesis is that the difference in change from baseline trough FEV1 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 treatments is greater than the margin:

H_1: $T_1 - T_2 > -\Delta$

where T_1 and T_2 are the treatment means for FF/UMEC/VI and FF/VI+UMEC, respectively.

The non-inferiority margin has been set at 50mL, which is half the generally accepted minimal clinically important difference (MCID) for trough FEV1.

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

3. PLANNED ANALYSES

3.1. Final Analyses

No interim analysis is planned for this study. The final planned analyses will be performed after the completion of the following sequential steps (for this Clinical Data Interchange Standards Consortium [CDISC] study):

1. All subjects have completed the study or been withdrawn as defined in the protocol.
2. All required database cleaning activities have been completed and final database release (SDL) has been declared by Data Management on System Independent (SI) datasets.

3. SI data to SDTM data conversion has completed by Conversion Service and quality control of SDTM has completed by DM.
4. Study is unblinded by Clinical Statistician in Randall NG.
5. Clinical Programmer extracts unblinded randomization and container codes from Randall NG and SMS2000 file from SMS2000 and then unblinds relevant SDTM datasets (Example: DM, EX, SE, PC etc) as per Clinical Statistics & Programming Study and Subject Treatment Unblinding Guideline document.
6. Database freeze on SDTM datasets has been declared by DM.

Note: following database frozen (*i.e.,* treatment unblinding), protocol deviations for subject received incorrect treatment and for non-compliance based on active treatment will be identified and flagged as PP exclusionary. These protocol deviations will be flagged as PP exclusionary in ADaM DV dataset.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Subjects Enrolled (ASE)	• All subjects for whom a record exists in the study database, including screen failures and any subject who was not screened but experienced an SAE between the date of informed consent and the planned date of the Screening visit.	• Subject Disposition • Reason for withdrawal prior to randomisation • Inclusion, exclusion and randomisation criteria deviations • SAEs for non-randomised subjects
Intent-to-Treat (ITT)	• All randomized subjects, excluding those who were randomized in error. A subject who is recorded as a screen or run-in failure and also randomized will be considered to be randomized in error. Any other subject who receives a randomization number will be considered to have been randomized.	• Study Population • Efficacy • Health-related Quality of Life • Inhaler Assessments • Safety
Modified Per Protocol (mPP)	• All subjects in the ITT Population who do not have a full protocol deviation considered to impact efficacy. • Data following a moderate/severe COPD exacerbation or pneumonia will be excluded from analysis due to the potential impact of the exacerbation or the medications used to treat it • Subjects with partial protocol deviations considered to impact efficacy will be included	• Primary treatment comparison of the primary endpoint only

Population	Definition / Criteria	Analyses Evaluated
	in the mPP Population but will have their data excluded from analyses from the time of deviation onwards.	

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

In the event one or more investigators are withdrawn from the study due to concerns over protocol deviation then a further population will be defined which will consist of all subjects in the ITT population excluding subjects from those investigative sites. This population will be used to perform additional sensitivity analysis for the primary efficacy endpoint only, and will only be defined if the combined enrolment at these sites exceeds ≥ 2% of the overall ITT study enrolment.

4.1. Protocol Deviations

- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.
- Exclusions from the mPP analysis population will also be summarised and listed. (Please refer to Appendix 1: Protocol Deviation Management and Definitions for mPP Population).
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
    - Data will be reviewed prior to SDTM DBF to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
    - This dataset will be the basis for the summaries and listings of protocol deviations.
- Subjects who received an incorrect container will be captured as an important protocol deviation. Whether or not the incorrect container contains incorrect treatment will be identified following DBF in the Analysis Data Model (ADaM) dataset. Overall treatment non-compliance based on active treatment will also be identified following DBF and will be flagged as PP exclusionary in 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

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

Table 1 Overview of Appendices

Section	Component
10.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
10.2	Appendix 2: Time & Events
10.3	Appendix 3: Assessment Windows
10.4	Appendix 4: Treatment States and Phases
10.5	Appendix 5: Data Display Standards & Handling Conventions
10.6	Appendix 6: Derived and Transformed Data
10.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
10.8	Appendix 8: Multicenter Studies
10.9	Appendix 9: Examination of Covariates, Subgroups & Other Strata
10.10	Appendix 10: Multiple Comparisons & Multiplicity
10.11	Appendix 11: Model Checking and Diagnostics for Statistical Analyses.
10.12	Appendix 12: Abbreviations & Trade Marks
10.13	Appendix 13: List of Data Displays

5.1. Handling of Missing Data

The primary estimand for this study is a 'de jure' estimand. The primary analysis will use an 'MPP' population, using only data collected on-treatment and excluding data following protocol deviation or other event considered to impact the primary efficacy endpoint of change from baseline in trough FEV1 (as detailed in Section 10.1.2). This will evaluate the treatment difference if all subjects had taken the treatment as directed in the protocol which is considered the appropriate estimand for a determination of non-inferiority.

All data excluded from the primary efficacy analysis will be assumed to be missing at random. The sensitivity of the results to this assumption will be investigated by use of a 'tipping point' analysis as described in Section 7.1.2. This will evaluate various assumptions for the mean change from baseline in trough FEV1 for data excluded from the primary analysis, including scenarios where the response to treatment on FF/UMEC/VI is worse than that on FF/VI + UMEC and vice versa.

An alternative estimand will be evaluated. This will use the ITT population using all data collected on-treatment, for the change from baseline in trough FEV1. (No off-treatment

data for trough FEV1 were collected in this study.) All missing data will be assumed to be missing at random. This will evaluate the treatment difference in all randomized subjects, regardless of adherence to the protocol but assuming the treatment effect for subjects who discontinued treatment was similar to that for those who completed treatment.

5.2. Handling of Data from Additional Subset Populations

Approximately 180 subjects, in selected sites, will be asked to participate in the PK analysis. There will be two PK groups (subset A and subset B). Approximately 120 subjects will be assigned to subset A and approximately 60 subjects will be assigned to subset B. Subjects in subset A will provide a blood sample at two time-points at Week 12 (V4) and at Week 24 (V5). Subjects in subset B will provide blood samples at seven time points at Week 12 (V4).

Population PK analysis population (including subjects provided blood PK samples from this study and other studies in Closed Triple Program) will be described in a separate RAP.

A subset of subjects in selected countries (Russia, Japan and Germany) providing PK samples for subset A will also be asked to take part in a hair sample scalp & finger secretion PK Sub-Study. Separate analysis populations will be defined for the hair sample scalp & finger PK and analysis will be described in a separate RAP.

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses generally will be based on the ITT population unless otherwise specified. Displays which use the ASE population or mPP population are identified below.

Table 2 provides an overview of the planned study population analyses, with the detailed list of data displays being presented in Section 10.13.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Study Populations and Reasons for Screen/Run-in Failures	Y[1]		Y
Attendance at Clinic Visits	Y		
Study Treatment Status	Y		Y
End of Study Record	Y	Y[2]	Y
Number of Subjects	Y[3]		
Inclusion and Exclusion Criteria Deviations	Y[4]		Y[4]
Important Protocol Deviations	Y		Y
Exclusion from Modified Per Protocol Population	Y		Y
Reasons for study withdrawal			Y
Demography			
Demographic Characteristics	Y[5,7]		Y
Race and Racial Combination	Y[7]		Y
Medical Conditions			
Medical Conditions (Current/Past)	Y		Y
Cardiovascular Risk Factors	Y		
Family History of Cardiovascular Risk Factors	Y		Y
Smoking History at Screening	Y		Y
Smoking Status	Y		Y
Disease Characteristics			
COPD Exacerbation History	Y		Y
Screening Lung Function	Y[5,7]		Y
Reversibility and GOLD Grade(1-4) at Screening	Y[7]		Y
CAT Score at Screening	Y		Y
Concomitant Medications			
COPD Medications	Y[6]		Y
COPD Medication Combination at Screening	Y[7]		
Non-COPD Medications	Y[8]		Y
Relationship between ATC Level1/Ingredient/Verbatim Text for Non-COPD Medications			Y
Long-acting Bronchodilator Usage Per Day During Run-in (Randomisation Strata)	Y[7,9]		Y

Display Type	Data Displays Generated		
	Table	Figure	Listing
Treatment Compliance			
Treatment Compliance	Y		Y
Study Population Listings			
Randomized and Actual Treatments			Y
Treatment Blind Broken During Study			Y
Treatment Misallocations			Y
Randomisation Strata (Derived and from eCRF)			Y
Percent Oxygen in Blood			Y
Inhaler Malfunction			Y

NOTES :

Y = Yes display generated.

1. ASE population
2. Kaplan-Meier plot
3. By country (ASE population); by age category (ASE population); by geographical region, country and centre (ITT population)
4. Screen failures (ASE population) and ITT population separately
5. Repeat by country (ITT population)
6. Run-in/On-treatment/Post-treatment and Given for Reasons other than an Exacerbation, given for an exacerbation, separately
7. ITT population and mPP population separately
8. On-treatment and Post-treatment, separately
9. None, one or two long acting bronchodilator

6.1.1. Disposition

The study population summary will show the number of subjects overall who were enrolled, the number of pre-screen failures, the number of screen and run-in failures and the number with each reason for screen or run-in failure, the number of subjects in each treatment group and overall who were randomized, in the ITT population and the number of subjects in the mPP population.

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

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

6.1.2. Concomitant Medications

COPD concomitant medications that have been stopped prior to Screening and non-COPD concomitant medications that have been stopped prior to randomization will be listed and not be included in any summary tables.

Non-COPD medication tables will report by Anatomical Therapeutic Chemical (ATC) level 1 and ingredient. COPD medication tables will report by respiratory medication class (RMC) and ingredient (See Section 10.6.2).

Multi-ingredient medications will be presented according to their combination ATC classification rather than the classification of the ingredients.

The number and percentage of subjects taking each medication in the RMC categories ICS, LABA, LAMA, PDE4 inhibitors, Xanthines and combinations of these RMCs on the day of the Screening visit will be presented.

The number of long-acting bronchodilator used per day during the run-in (none, one or two long-acting bronchodilators per day) will be summarised.

6.1.3. Treatment Compliance

Treatment compliance will be determined as discussed in Section 10.6.2. Note that the ELLIPTA inhaler used to dispense FF/UMEC/VI, FF/VI, UMEC or placebo has a counter that shows exactly the number of doses remaining. Compliance will be calculated based on the count recored on the dose counter and will be calculated overall and separately for each ELLIPTA inhaler (the inhaler contains FF/UMEC/VI or FF/VI and the inhaler contains placebo or UMEC).

6.1.4. Disease Characteristics

The screening lung function summary will include pre-bronchodilator and post-salbutamol FEV1, FVC, FEV1/FVC ratio, FEV1 as a percentage of predicted normal, and FEV1 reversibility to salbutamol (expressed in milliliters [mL] and as a percentage).

6.1.5. Inhaler Malfunction

Device malfunction occurs during the study will be recorded in eCRF with container numbers. This data will be listed.

7. PRIMARY STATISTICAL ANALYSES

7.1. Efficacy Analyses

7.1.1. Overview of Planned Efficacy Analyses

The primary efficacy analyses for change from baseline in Trough FEV1 will be on the mPP population. All outputs produced for the primary endpoint will be repeated on the ITT population.

Table 3 provides an overview of the planned efficacy analyses for Trough FEV1, with full details of data displays being presented in Section 10.13, List of Data Displays.

Other endpoints of trough FEV1 at Weeks 4 and 12, and trough FVC at Weeks 4, 12 and 24 are also included in this section as they are related to the primary endpoint.

Table 3 Overview of Planned Efficacy Analyses

	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Spirometry														
Baseline FEV1				Y[1]			Y[2]							
Trough FEV1 (MMRM analysis)	Y[1]			Y[1]			Y[2]	Y[1]	Y[4]		Y[1]	Y[4,5]		Y[2]
Trough FVC				Y[3]			Y[2]				Y[3]			Y[2]

NOTES :

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

1. For mPP population and ITT population, separately.
2. ITT population only and include a flag for mPP population.
3. ITT population only
4. MPP population only
5. empirical distribution function plot

7.1.1.1. Spirometry data

Spirometry is assessed pre-treatment on Week 0, and pre-dose at Weeks 4, 12 and 24.

Spirometry data including FEV1 and FVC will be transferred from the vendor to GSK. When spirometry has been performed but the reading was unacceptable, a record in the database will indicate that the spirometry was performed but all data will be missing and will not be included in listings or summary displays.

The definition of baseline FEV1 and FVC is in Section 10.5.2.1 and of trough FEV1 and FVC is in Section 10.6.4.

7.1.2. Planned Efficacy Statistical Analyses

Primary Statistical Analyses
Endpoint(s)
○ Trough FEV1
Model Specification
○ The primary endpoint of change from baseline in trough FEV1 will be analyzed in the mPP population, using a mixed model repeated measures (MMRM) analysis, including trough FEV1 recorded at each of Week 4, 12 and 24. The model will include covariates of baseline FEV1, stratum (number of long-acting bronchodilators per day during the run-in), Visit, geographical region, treatment 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. ○ The variance-covariance matrix will be assumed unstructured. ○ Two models will be fitted; one with a response variable of trough FEV1, and one with a response variable of change from baseline in trough FEV1.
Handling of Missing Data for Analysis
○ No data were collected for subjects who prematurely discontinued study treatment. All missing and excluded data will be assumed to be Missing at Random (MAR). Sensitivity analyses to investigate the impact of this assumption will be conducted as described below.
Model Checking & Diagnostics
○ Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
○ Least Square (LS) mean and LS mean change from baseline with their corresponding standard errors (SEs) will be presented for each treatment by Visit, together with estimated treatment differences (FF/UMEC/VI vs. FF/VI+UMEC) and the corresponding 95% confidence intervals (CIs). ○ A plot of LS means change from baseline and 95% CIs from the model will be generated for each treatment by Visit.
Example SAS Code
proc mixed data=<dataset>; *class treatment visit cengroup stratum subjid;* *model endpoint=baseline stratum visit cengroup treatment visit*baseline visit*treatment / ddfm=kr;* *repeated visit/ subject=subjid type=un;* *lsmeans visit*treatment / cl diff e om=OMdset at (baseline)=(&blm.);* *ods output lsmeans=lsmeans;* *ods output diffs=diffs;* *run;* where OMdset is a dataset with a row for every subject-visit combination that contains all of the covariates and blm is a macro variable containing the mean baseline for the subjects used in the analysis. This is used to derive the LS means using coefficients which are based on the subjects used in the analysis.

Sensitivity and Supportive Statistical Analyses
○ The above will be repeated for the ITT population. LS mean and LS mean change from

Sensitivity and Supportive Statistical Analyses

baseline with their corresponding SEs will be presented for each treatment by Visit, together with estimated treatment differences and the corresponding 95% CIs.

- A "tipping point" sensitivity analysis of trough FEV1 at Week 24 will be conducted for the mPP Population. This will explore the impact of missing data by using differing assumptions regarding the mean treatment effect in subjects who discontinue study treatment or have data excluded from the mPP Population analyses. Mean treatment effects 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 FF/VI+UMEC will be investigated; thus including scenarios where subjects who discontinue FF/UMEC/VI have a lower treatment effect than those who discontinue FF/VI+UMEC 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 subject with missing or excluded data at Week 24, 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 the Week 24 visit. Data for subjects with missing baseline values will not be imputed. Analysis of the complete Week 24 dataset will be carried out using an ANCOVA model with covariates of treatment group, stratum (number of long-acting bronchodilators per day during the run-in), geographical region and baseline.
  - The seed will be set using the following SAS code:

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

proc print;
run;
```

    The seeds generated and assigned to each analysis will be documented separately prior to DBF.

    A table will be produced displaying the 95% CI for the treatment difference at Week 24 under the above assumptions for the mean changes from baseline for each of the treatment arms.

- Interactions between treatment and other factors will be investigated as follows by adding interaction terms to the specified model:
  - An assessment of whether the effect of treatment on trough FEV1 is modified by number of long-acting bronchodilators per day during the run-in, geographic region, or baseline will be made by fitting separate repeated measures models, identical to the primary analysis models described above but also including additional terms as described below.
  - For the factors of number of long-acting bronchodilators per day during the run-in and

Sensitivity and Supportive Statistical Analyses
geographical region, the primary analysis model will be used with additional terms for the factor by treatment by Visit interaction. The p-value for the treatment by factor interaction at Week 24 will be obtained using contrast statements. If that p-value is ≥ 0.10 the interaction will be considered not significant. If the p-value is < 0.10, further investigation will be performed, for example running the analysis by each stratum or geographic region. ○ For baseline FEV1, the primary analysis model will be used with additional terms for the baseline value by treatment by Visit interaction. The p-value for the treatment by baseline interaction at Week 24 will be obtained using contrast statements. If that p-value is ≥ 0.10 the interaction will be considered not significant. If the p-value is < 0.10, further investigation will be performed, for example running the analysis by dichotomous categories of baseline values (values above and below the median).

8. SECONDARY STATISTICAL ANALYSES

8.1. Other Efficacy Analyses

8.1.1. Overview of Planned Efficacy Analyses

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

Table 4 provides an overview of the planned efficacy analyses, with further details of data displays being presented in Section 10.13, List of Data Displays.

Table 4 Overview of Planned Efficacy Analyses

	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
SGRQ														
Baseline SGRQ Scores				Y			Y							
SGRQ Domain Scores				Y			Y				Y			
SGRQ Total Score (MMRM Analysis)	Y			Y			Y	Y	Y		Y	Y[2]		Y
Proportion of Responders according to SGRQ Total Score	Y			Y			Y							
Baseline Dyspnea Index (BDI)/Transitional Dyspnea Index (TDI)														
BDI				Y			Y							
TDI	Y	Y		Y			Y							
Proportion of Responders according to TDI Focal Score	Y			Y			Y							
COPD Exacerbations														
Exacerbation Occurrence and Details				Y[1]			Y							

	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Time to First On-treatment Moderate/Severe Exacerbation	Y	Y[3]		Y			Y							

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modeling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
  1. Number and percent reporting COPD exacerbation and summary of details regarding the exacerbation. Repeat for post-treatment exacerbations.
  2. empirical distribution function plot
  3. Kaplan -Meier Plot

8.1.1.1. St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C)

The SGRQ-C is completed at Week 0, Week 12, and Week 24. The calculation for the SGRQ-C, including how to handle missing values, is detailed in the SGRQ-C manual (Jones, 2016). The conversion of the SGRQ-C scores to SGRQ scores is as described in the manual and as detailed in Section 10.6.4.

Subjects will be classified as responders/non-responders based on SGRQ total score as described in Section 10.6.4

8.1.1.2. COPD Exacerbations

The definition of moderate and severe exacerbations is provided in Section 10.6.4. The definition of on- and post-treatment exacerbations is provided in Section 10.4.2.

For summary of on-treatment COPD exacerbations, details of the event to be summarized include the number and percent of subjects reporting an exacerbation (any severity, mild, moderate, severe and moderate/severe), number and percent subjects with each number of moderate/severe exacerbations (0, 1, ≥2), outcome, severity, duration, whether treatment with systemic or oral steroids was required, whether treatment with antibiotics was required, whether hospitalization was required, and whether the exacerbation resulted in a visit to the emergency room. Post-treatment exacerbations will be similarly summarized. The total number of exacerbations will be included. For derivation of time to first on treatment moderate or severe exacerbation, see Section 10.6.4.

8.1.1.3. Baseline Dyspnea Index (BDI)/Transitional Dyspnea Index (TDI) Focal Score

BDI is assessed at Week 0. TDI is assessed at Week 12 and Week 24. The BDI and TDI focal scores [Mahler, 2004] will be calculated as shown in Section 10.6.4.

8.1.2. Planned Other Efficacy Statistical Analyses

8.1.2.1. SGRQ Total Score

Secondary Statistical Analyses
Endpoint(s)
○ SGRQ total score
Model Specification, Model Checking & Diagnostics, Model Results Presentation
○ Same as for trough FEV1, see Section 7.1.2 ○ Visit includes week 12 and 24.

8.1.2.2. TDI

Secondary Statistical Analyses
Endpoints
• TDI focal score
Model Specification, Checking, Results Presentation and SAS code
• Same as for trough FEV1, see Section 7.1.2 • BDI will be used in place of baseline. • Visit includes week 12 and 24.

8.1.2.3. Proportion of Responders according to SGRQ Total Score and Responders according to TDI

Endpoints
• Proportion of Responders according to SGRQ total score • Proportion of Responders according to TDI
Model Specification
• Generalized Linear Mixed Model • Terms in the model: Dependent Variable: Response (Yes/No) Categorical : treatment group, stratum, geographical region, visit Continuous : Baseline (for SGRQ total score) or BDI Interaction : baseline*Visit, treatment*Visit Repeated : Visit • The model will be fit with an unstructured variance-covariance matrix • One single model to include all visits ○ SGRQ: include Week 12 and 24 ○ TDI: include Week 12 and 24
Handling of Missing Data for Analysis
• Subjects with missing on-treatment data and a subsequent non-missing on-treatment scheduled assessment will not be considered as a responder/non-responder but will be left as missing. • Subjects that have withdrawn from the study prior to the visit in question will be imputed as

non-responders at all visits post-withdrawal where the assessment was expected to be performed.

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

Model Results Presentation

- Number and percentage of responders and non-responders for each treatment at each Week
- Odds ratio for comparison between FF/UMEC/VI and FF/VI+UMEC with associated 95% CI

Example SAS Code

```
proc glimmix data=filename ;
   class treatment stratum visitnum  subjid centgroup;
   model respond(event="1") = treatment base stratum visitnum centgrp visitnum*base
                  visitnum*treatment
      / dist=binary link=logit ddfm=kr solution;
   lsmeans  visitnum*treatment / cl diff or om ;
   random visitnum / subject=subjid residual type=un;
   ods output diffs=differs;
run;
```

8.1.2.4. COPD Exacerbations

Secondary Statistical Analyses

Endpoints

- Time to first on-treatment moderate/severe COPD exacerbation

Model Specification

- Cox's proportional hazards model

Terms in the model:

Dependent variable: time to first on-treatment moderate/severe exacerbation
Categorical: treatment group, gender, exacerbation history (0, 1, >=2 moderate/severe exacerbations in the last 12 month at screening), smoking status (screening), stratum and geographical region.
Continuous: % predicted FEV1 at Baseline

- Use the 'exact' method for handling ties. (If the analysis will not run using the 'exact' method, then the 'Efron' method for handling ties will be used instead.)

Handling of Missing Data for Analysis

- Subjects who withdrew from the study prior to experiencing a COPD exacerbation will be considered censored at random.

Model Checking & Diagnostics

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

Model Results Presentation

- Hazard ratio for comparison between FF/UMEC/VI and FF/VI+UMEC with associated 95% CI

Example SAS Code

Secondary Statistical Analyses
proc phreg data=<dataset> ; *model timeto1*eventflag(0)=treatment fevpred stratum cengroup smokehis hxf_exac / risklimits ties=exact;* *run;*

Secondary Statistical Analyses
Endpoints
• Time to first on-treatment moderate/severe COPD exacerbation
Model Specification
○ A Kaplan-Meier analysis will also be performed for figure showing Kaplan-Meier survivor functions of the proportion of subjects with a first exacerbation over time for each treatment group separately plotted on the same figure.
Example SAS code
proc lifetest data=destin outsurv=survest; *time timeto1*eventflag(0);* *strata treatment;* *run;*
Model Results Presentation
○ Probability of having an event, 95% CI and first quartile time to exacerbation (estimate of the time at which 25% of subjects in each treatment group would have had an exacerbation) ○ Figure showing Kaplan-Meier survivor functions of the proportion of subjects with a first exacerbation over time for each treatment group separately plotted on the same figure.

8.2. Safety Analyses

8.2.1. Overview of Planned Analyses

The safety analyses generally will be based on the ITT population.

Table 5 provides an overview of the planned analyses, with the detailed list of data displays being presented in Section 10.13.

Table 5 Overview of Planned Safety Analyses

	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Exposure								
Exposure Data	Y		Y	Y				
Adverse Events (AEs)								
Overview of On-Treatment AEs	Y							
On-Treatment AEs	Y[10]							
Post-Treatment AEs	Y							
On-Treatment Drug-Related AEs	Y							
Pre-Treatment SAEs	Y[1,2]							

	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
On-Treatment SAEs	Y							
Post-Treatment SAEs	Y							
On-Treatment Fatal SAEs	Y							
On-Treatment Drug-Related SAEs	Y							
Pre-Treatment SAEs Leading to Withdrawal from Study	Y[1]							
On-Treatment AEs Leading to Withdrawal from Study	Y							
On-Treatment AEs of Special Interest	Y							
On-Treatment SAEs of Special Interest	Y							
Relationship of AE System Organ Class, Preferred Term and Verbatim Text	Y[1]							
On-treatment Common Non-Serious AEs (3% or More of Subjects in Any Treatment Group)	Y							
10 Most Frequent On-treatment Adverse Event in Each Treatment Group	Y							
On-treatment Adverse Events by System Organ Class and Maximum Intensity	Y							
Subject Numbers for Individual AEs				Y[1]				
All AEs				Y[1]				
Non-Fatal Serious AEs				Y[1]				
Fatal AEs				Y[1]				
AEs Leading to Withdrawal from Study				Y				
Subject Numbers for On-Treatment AEs of Special Interest				Y				
Reasons for Considering as a Serious Adverse Event				Y				

	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Pneumonia								
On-Treatment Pneumonias Incidence	Y[9]			Y[3]				
Details of on-treatment Pneumonia	Y[9]			Y[3]				
Post-Treatment Pneumonias Incidence	Y[9]			Y[3]				
Details of Post-treatment Pneumonia	Y[9]			Y[3]				
Bone Fractures								
On-Treatment Bone Fractures	Y			Y[3]				
Post-Treatment Bone Fractures	Y			Y[3]				
Radiography (Chest Imaging including X-Rays and CT Scan)								
On-Treatment Chest Imaging	Y			Y[3]				
Post-Treatment Chest Imaging	Y			Y[3]				
Liver Events								
Medical conditions for subjects with liver stopping events				Y				
Liver Event Results and Time of Event Relative to Treatment				Y				
Liver Event Substance Use				Y				
Liver Event Information for RUCAM Score				Y				
Liver Biopsy Details				Y				
Liver Imaging Details				Y				
On Treatment Laboratory Parameters								
Liver Function Tests		Y[6]						
Chemistry Values for Subjects with at Least One Value Outside the Normal Range				Y				
Chemistry Data	Y	Y[4]			Y	Y[5]		
Chemistry Data Outside the Normal Range	Y							
Chemistry Changes from Baseline Relative to the Normal Range	Y							
Hematology Values for Subjects with at Least One Value Outside the				Y				

	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Normal Range								
Hematology Data	Y	Y[4]			Y	Y[5]		
Hematology Data Outside the Normal Range	Y							
Hematology Changes from Baseline Relative to the Normal Range	Y							
On Treatment Vital Signs								
Vital Sign Data (Pulse Rate, Sys BP, Dia BP)	Y			Y	Y			
12-Lead ECGs								
ECG Values	Y			Y[7]	Y		Y[8]	
ECG Findings	Y							
ECG Findings Shifts from Baseline	Y							
QTcF Categories	Y				Y			
ECG Abnormalities	Y			Y[7]			Y[8]	
ECG Abnormalities Occurring in at least 3% of Subjects in Either Treatment Group	Y							
Maximum Post-Baseline QTcF		Y[8]				Y[8]		

NOTES :

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

1. ASE Population
2. ITT Population
3. Combined listing for on-treatment and post-treatment.
4. Separate box plots of change from baseline in maximum and minimum post-baseline values
5. Separate scatter plots for maximum and minimum post-baseline versus baseline divided by ULN for maximum and LLN for minimum
6. Trellis Display of Maximum Post-baseline Liver Function Test Values Versus Baseline Liver Function Test Values
7. Listing of data only for subjects with any abnormal ECG finding.
8. Empirical Distribution Function Plot
9. Pneumonia are the cases recorded in Pneumonia Details CRF form
10. Repeat for by country
11. Trellis plot baseline vs post baseline

8.2.1.1. Adverse Events of Special Interest

Adverse events (AEs) of special interest (AESI) have been defined as AEs which have specified areas of interest for FF, VI, or UMEC or for the COPD population. A list of Standardized Medical Dictionary for Regulatory Affairs (MedDRA) Queries (SMQs) and other groupings for AESI is provided in Section 10.6.3.

8.2.1.2. Pneumonia

Summaries of pneumonia will include data from the Pneumonia Details CRF form.

8.2.1.3. Vital Signs

Vital signs are collected at Screening (Visit 1) and pre-dose at Week 4, Week 24 or at the Early Withdrawal Visit. Vital signs collected at Early Withdrawal and at the onset of a pneumonia event will be included in 'minimum/maximum post-baseline' (see Section 10.6.3 for the definition) summaries but will not be summarized separately.

8.2.1.4. ECGs

12-Lead ECGs are collected at Screening (Visit 1) and approximately 15-45 min after dosing at Week 24 or at the Early Withdrawal Visit. All ECG data present in the database will be considered valid and will be reported (even if the ECG had a technical error). ECGs collected at Study Treatment Discontinuation will be included in summary of ECG finding where 'worst case post-baseline' summarized but will not be summarized separately.

8.2.1.5. Pregnancy

Any pregnancies reported during the study will be summarized in 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

Aguis R and Kintz P (2010) Drug and alcohol testing in hair, collection and analysis. European workplace drug testing society, version 1.0, 1-18

Barbosa, J, Faria, J, Carvalho, F, Pedro, M, Queiros, O, Moreira, R and Dinis-Oliveira RJ (2013) Hair as an alternative matrix in bioanalysis. Bioanalysis 5 (8):

GlaxoSmithKline Document Number 2015N261999_03, 200812, A phase IIIB, 24-week randomised, double-blind study to compare 'closed' triple therapy (FF/UMEC/VI) with 'open' triple therapy (FF/VI + UMEC), in subjects with chronic obstructive pulmonary disease (COPD), 26-JUN-2016

GOLD. Global Initiative for Chronic Obstructive Lung Disease (Updated 2015).http://www.goldcopd.org.

Jones, PW and Forde Y (2016). St. Georges Respiratory Questionnaire for COPD Patients Manual, version 1.3.

Mahler DA, Ward J, Fierro-Carrion G, Waterman LA, Lentine TF, Mejia-Alfaro R, Baird JC (2004). Development of Self-Administered Versions of Modified Baseline and Transition Dyspnea Indexes in COPD. COPD Journal of Chronic Obstructive Pulmonary Disease 1(2), pp. 165-172.

Meguro M, Barley EA, Spencer S et al. Development and validation of an improved COPD-Specific Version of the St. George Respiratory Questionnaire. Chest.2007;132:456-463

10. APPENDICES

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

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

10.1.1. Exclusion of Data from the ITT Analyses

In general, all data recorded for subjects 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 are excluded from ITT analyses if the actual time of assessment is after the time of dosing on that day or if albuterol/salbutamol was used within 4h of the assessment on that day.

10.1.2. Exclusions from mPP Population

The full list of protocol deviations collected on the eCRF is in the PDMP.

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

- Full exclusion: subjects who have a full protocol deviation considered to impact primary endpoint (trough FEV1)
  - Eligibility criteria (those that impacts primary endpoint as listed in PDMP, Appendix 2) not met
  - Treatment non-compliance (overall compliance <80% or >120% over the 24-week treatment period, based on active treatment)
  - Randomisation criteria not met
    - Pneumonia or moderate/severe COPD exacerbation during run-in
    - Any change to COPD maintenance medications (including dosage and regimen) during the run-in
    - Antibiotics for respiratory tract infections during the run-in
- Partial exclusion: subjects who have a protocol deviation considered to impact primary endpoint. Trough FEV1 assessments collected after the incidence of the protocol deviation will be excluded from primary analysis.
  - Subject received incorrect container which contains incorrect study treatment.
  - Subjects took prohibited medication during treatment period, as detailed in PDMP Appendix 3 Prohibited Medication.

- Partial exclusion: other events (not a protocol deviation) considered to impact the primary endpoint. Trough FEV1 assessments collected on or after the event start date will be excluded from primary analysis.
    - Subjects had a moderate/severe COPD exacerbation
    - Subjects had pneumonia.
    - Subjects who were unblinded by GCSP due to safety concerns.

Note: Subjects who received incorrect treatment and non-compliance based on active treatment will be identified as important PDs and flagged as PP exclusionary following treatment unblinding. These PDs will be flagged as PP exclusionary in ADaM DV dataset and will be included in summary of exclusion from mPP population table.

10.2. Appendix 2: Time & Events

Protocol Activity	Pre-Screen	Screen	Treatment				Follow Up	
	Visit 0 Pre-screen	Visit 1 Screening	Visit 2 Randomisation	Visit 3	Visit 4	Visit 5	Early Withdrawal Visit	Safety Follow-up Contact
Study Week		**Week -2**	**Week 0**	**Week 4**	**Week 12**	**Week 24**		**1 week Fw-up**
Window		**-3/+8d**		**-4/+2d**	**-8/+6d**	**-8/+6d**		**-1/+4d**
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	X
Inclusion/Exclusion Criteria		X						
Randomisation Criteria			X					
Smoking History		X						
Smoking status		X				X	X	
Smoking Cessation Counselling		X				X	X	
Register Visit in IRT/ RAMOS NG [d]		X	X	X	X	X	X	
Reversibility Testing [e]		X						
Spirometry			X[f]	X[f]	X[f]	X[f]		
Device training and registration		X	X					
Exacerbation Assessment		X	X	X	X	X	X	X
SGRQ-C [g]			X		X	X		
BDI [g]			X					
TDI [g]					X	X		
CAT [g]		X						
eDevice close out [h]			X			X	X	
Physical examination [i]		X				X	X	
Adverse Events Assessment		X	X	X	X	X	X	X
Vital signs [j]		X		X		X	X	
ECG		X				X[k]	X[k]	
Chest X-ray [l]		X						
Pulse oximetry [m]			X					
Blood draw for PK					X[n]	X[o]		
Blood Draw for Genetics research						X[p]		

Protocol Activity	**Pre-Screen**	**Screen**	**Treatment**				**Follow Up**	
	Visit 0 Pre-screen	**Visit 1 Screening**	**Visit 2 Randomisation**	**Visit 3**	**Visit 4**	**Visit 5**	**Early Withdrawal Visit**	**Safety Follow-up Contact**
Study Week		**Week -2**	**Week 0**	**Week 4**	**Week 12**	**Week 24**		**1 week Fw-up**
Window		**-3/+8d**		**-4/+2d**	**-8/+6d**	**-8/+6d**		**-1/+4d**
Haematology/biochemistry [q]		**X**				**X**	**X**	
Urine Pregnancy Test [r]		**X**		**X**	**X**	**X**	**X**	
Hepatitis B and C tests		**X**						
Dispense study treatment			**X**	**X**	**X**			
Administer study treatment in clinic [s]			**X**	**X**	**X**	**X**	**X**	
Assess study treatment compliance				**X**	**X**	**X**	**X**	
Collect study treatment				**X**	**X**	**X**	**X**	
Dispense albuterol/salbutamol		**X**	**X**	**X**	**X**			
Collect albuterol/salbutamol			**X**	**X**	**X**	**X**	**X**	
Issue/review paper diary [t]		**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 (IC) may be given at Screening Visit 1 if the subject does not take or has not taken any protocol excluded medications.
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.
c. Demography may be captured at either the Pre-screen Visit or Screening Visit (for subjects who do not have a Pre-screen Visit).
d. The IRT will be used for randomisation, emergency unblinding and study treatment supply management (Please refer RAMOS NG IRT manual for more information)
e. At Screening Visit 1 both pre and post-bronchodilator spirometry will be conducted. Pre-bronchodilator spirometry will be performed prior to the subject taking their morning dose of their usual COPD treatment, between 6am and 11am and after withholding rescue albuterol/salbutamol for ≥4 hours.
f. At Visits 2-5 (and the Early Withdrawal Visit), pre-bronchodilator spirometry will be performed prior to taking the morning dose of study treatment, between 6am and 11am and after withholding rescue albuterol/salbutamol for ≥4 hours.
g. Patient reported assessments should be conducted in the following order and before other study assessments: SGRQ-C, BDI/TDI.
h. Close out eDevice for any subject who fails to randomize, withdraws early, or completes Visit 5.
i. Physical examination may include height, weight, blood pressure, temperature, heart rate.
j. Vital signs must be performed prior to spirometry and prior to taking morning dose of study mediation.
k. ECG to be obtained 15 - 45 minutes post-dose at treatment Visit 5 and Early Withdrawal Visit (if possible).If a subject is not dosed at Early Withdrawal, then an ECG can be taken at any time during the visit
l. Chest X-ray **(**PA and lateral) is required at Screening (or historical x-ray obtained within 3 months prior to Screening) and at anytime there is a suspected pneumonia or a mod/severe exacerbation.
m. Pulse oximetry must be performed at V2 and anytime there is a suspected pneumonia or a moderate or severe exacerbation.
n. PK subset A: PK samples of 120 subjects at selected sites, to be obtained at two time points at Visit 4: pre-dose and in the window 5 to15 minutes post-dose.
   PK subset B: PK samples of 60 subjects at selected sites, to be obtained and Visit 4: pre-dose, 5-15min, 45-90min, 2.5-4h, 6-8h, 10-12h, 23-24h post-dose.
o. PK subset A: PK samples of 120 subjects at selected sites, to be obtained at two time points at Visit 5: 5 to 15 minutes post–dose and 45 to 90 minutes post-dose.
p. The genetics blood sample should be taken at V5 or at any visit after Randomisation (V2).
q. Haematology and chemistry panels will include liver chemistry, and potassium and glucose levels.
r. All female subjects of child bearing potential will have a urine pregnancy test at each visit except Visits 2 and follow-up.
s. Subjects must withhold their morning dose of study treatment at each clinic visit and not take their study treatment dose until instructed to do so by study staff.
t. Subjects will be issued a paper diary, at screening and other clinic visits (if required) in order to note any changes to concomitant medications and/or incidence of adverse events that may have occurred between clinic visits.

10.3. Appendix 3: Assessment Windows

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

Subjects that permanently stop study medication early between scheduled clinic visits should undergo all assessments listed for the Early Withdrawal Visit. Data collected at this visit will be listed and used in summary or analysis tables as part of the 'worst case post baseline' summary/analysis if appropriate.

Subjects that permanently stop study medication early at the time of a scheduled study visit will have data collected in the eCRF as part of the scheduled study visit.

10.4. Appendix 4: Treatment States and Phases

Assessments and events will be classified according to time of occurrence relative to the start and/or stop date of the study treatment. The 'worst case-post baseline' derivation for summaries of data up to Week 24 will consider all scheduled and unscheduled measurements that have been assigned a treatment phase of 'On-treatment'.

10.4.1. Treatment Phase for Concomitant Medication Data

COPD medication combinations taken at screening will include all COPD medications that were taken on the day of the screening visit, excluding medications that stopped on the day of the screening visit. Calculation of stratum, i.e. long-acting bronchodilator usage per day during the run-in (none, one or two long-acting bronchodilators per day), will also be based on the COPD medication taken on the day of the screening visit. If the calculated stratum is different to the randomized stratum, the calculated stratum will be used as a covariate in all analyses, but both values will be listed. Treatment phases for summaries of COPD and non-COPD concomitant medications will be defined as follows:

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

Definition	Treatment Phase		
	Run-in	On-treatment	Post-treatment
goingmed is Yes)			
Conmed start≥treatment stop date and treatment start date ≠ treatment stop date			Y

NOTES:

- A concomitant medication will be classed in every period of the study in which it was taken (e.g., run-in, on-treatment or post-treatment).
- See Section 10.7.2.1 for handling of partial dates.
- If the study treatment stop date is missing, it will be imputed as described in Section 10.6.1.
- Medications that stopped prior to Screening will not be assigned a treatment phase and will not be summarized.

10.4.2. Treatment Phase for Other Data

Treatment phases for assessments scheduled at a set time will be defined according to the planned relative time of the assessment.

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

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

Treatment Phase	Definition
Pre-treatment	Event onset date/time or assessment date/time < treatment start date/time.
On-treatment	Treatment start date/time ≤ event onset date/time or assessment date/time ≤ treatment stop date + 1 day, 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 ≥treatment stop date + 2 and event onset date/time or assessment date/time ≤ study conclusion date Note: the study conclusion date reflects the safety F/U contact for study treatment completers.

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

Treatment Phase	Definition
Pre-treatment	Event onset date or assessment date < treatment start date.
On-treatment	Treatment start date ≤ event onset date or assessment date ≤ treatment stop date + 1 day 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 ≥treatment stop date + 2 and event onset date or assessment date ≤ study conclusion date Note: the study conclusion date reflects the safety F/U contact for study treatment completers.

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
1	FF/UMEC/VI 100mcg/62.5mcg/25mcg + Placebo	FF/UMEC/VI 100/62.5/25	1
2	FF/VI 100mcg/25mcg + UMEC 62.5mcg	FF/VI 100/25 + UMEC 62.5	2

NOTES:

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

10.5.2. Baseline Definition & Derivations

10.5.2.1. Baseline Definitions

Parameter	Study Assessments Collected prior to dosing		Baseline Definition
	Screening	Week 0 (Pre-Dose)	
Efficacy			
Trough FEV1, Trough FVC	X	X	Week 0 pre-dose.
SGRQ total and domain scores		X	Week 0 pre-dose
Safety			
Vitals, Labs, ECGs	X		Most recent individual value prior to first dose (generally Screening but could be a test repeat).

NOTES :

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

10.5.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS and TCSG software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Area	: /arenv/arprod/gsk2834425/mid200812/final
QC Spreadsheet	: /arenv/arwork/gsk2834425/mid200812/documents
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM Implementation Guide Version 3.1.3 or higher & AdaM Implementation Guide Version 1.0 or higher). • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files will be generated for the final reporting effort for use in writing the CSR.	

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics
Formats
• All data will be reported according to the treatment to which the subject was randomized unless otherwise stated. However, there may be additional adhoc displays for individual subjects using the actual treatment received. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places will be adopted for reporting of data based on the raw data collected. • All data (including data collected post-study treatment discontinuation) will be reported according to the treatment to which the subject was randomized unless otherwise stated. However, there may be additional adhoc displays for individual subjects using the actual treatment received. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places will be adopted for reporting of eCRF 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. • 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%. . • Numeric data will be reported at the precision collected on the eCRF.

Reporting Standards	
• 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.	
Planned and Actual Time	
• Reporting for tables, figures and statistical analyses : o Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. Actual time will be used for calculation of times to events and Kaplan-Meier plots. • Reporting for listings: o Planned and actual time relative to study drug dosing will be shown in listings (refer to IDSL Statistical Principle 5.05.1). o Unscheduled or unplanned readings will be presented within the subject's listings.	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables except as part of a 'worst case post-baseline' assessment. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous data	Refer to IDSL Statistical Principle 6.06.1
Categorical data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

10.6. Appendix 6: Derived and Transformed Data

10.6.1. General

Study Day

- Calculated as the number of days from treatment start date :
  - 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

Study Treatment Stop Date

If overall treatment stop date is missing it will be imputed as follows:

- For subjects who attended an Early Withdrawal visit, use the date of the Early Withdrawal visit
- For subjects who attended the last on-treatment visit, use the Visit 5 (Week 24) date
- For subjects who died and did not attend an Early Withdrawal visit or the last on-treatment visit, use the date of death
- For all other subjects, use the last recorded exposure start or stop date

Study and Treatment Completion Definitions

- A subject is considered to have completed the treatment period if they have not prematurely discontinued IP and attended Visit 5.
- A subject is considered to have completed the study if they either attended Visit 5 or had a phone contact at Visit 5.

10.6.2. Study Population

Demographics

Age

- Age will be calculated based on the Pre-screening visit date
- Birth date will be imputed as follows:
  - Any subject with a missing day will have this imputed as day '15'.
  - Any subject with a missing date and month will have this imputed as '30JUN'.
- Birth date will be presented in listings as 'YYYY'.

Age Category

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

Demographics
Body Mass Index
• Calculated as weight (kg) / [height (m)]^2

Subject Disposition
Subject Withdrawal
• For Kaplan-Meier plots of subject withdrawal over time, censoring will be performed as follows: For subject withdrawal, subjects are represented from their Week 0 date to the date of early withdrawal from the study. Subjects that completed the study are censored at the earliest of the date of completion and day 168.
Smoking Status
At Screening, subjects who were identified as former smokers but who last smoked within 6 months prior to Screening will be re-classified as current smokers prior to summarizing. Subject listings will include original and re-classified status.
Compliance

• ELLIPTA™ inhaler A contains FF/UMEC/VI (for subjects in FF/UMEC/VI treatment group) or FF/VI (for subjects in FF/VI+UMEC treatment group) and has container number with prefix 3.
• ELLIPTA™ inhaler B contains placebo (for subjects in FF/UMEC/VI treatment group) or UMEC (for subjects in FF/VI+UMEC treatment group) and has container number with prefix 4.
• If a dose counter start count is missing then it will be assumed to be 30. If any dose counter stop is missing then the treatment compliance will be set to missing for that subject and for that inhaler.
• Number of doses of study drug taken by each subject from each inhaler = Dose counter start-dose counter stop.
• Compliance are calculated as follows:
  • Compliance for Ellipta inhaler A =(dose counter start – dose counter stop for inhaler A) x 100 / (exposure stop date – exposure start date +1)
  • Compliance for Ellipta Inhaler B=(dose counter start – dose counter stop for Inhaler B) x 100 / (exposure stop date – exposure start date +1)
  • Overall Compliance = (compliance for Inhaler A + compliance for inhaler B with active treatment)/2. That is:
  ○ For subject in FF/UMEC/VI treatment group, Overall Compliance = compliance for Inhaler A
  ○ For subject in FF/VI + UMEC treatment group, Overall Compliance = (compliance for Inhaler A + compliance for inhaler B)/2
• Overall compliance and compliance for each inhaler will be categorized as follows:
< 80 %
≥ 80 % to < 95 %
≥ 95 % to ≤105 %
>105 % to ≤120 %
>120 %.
• If a subject received a treatment other than the randomized treatment during the study, the

Subject Disposition
compliance will still be calculated using data from all containers received and overall exposure start and stop dates.
Long-acting Bronchodilator Usage During the Run-in (Randomisation Stratum)
Randomization stratum, long-acting bronchodilator usage during the run-in, will be derived based on the RMC classification and will be grouped into the following 3 categories: • None • One long-acting bronchodilator per day • Two long-acting bronchodilators per day Long-acting bronchodilator is defined as any COPD medication in Respiratory Medication Class (MRC) under 'Long-acting beta-2 agonist – Group 2' or 'Long-acting beta-2 agonist – Group 3' or 'Long-acting anticholinergic'. Based on RAMOS NG record, the number of subjects used none long-acting bronchodilator during run-in is very small (ie. <1% of randomized subjects). Therefore, the combined stratum with 2 categories will be used in the statistical analysis, ie, none and one long-acting bronchodilator per day will be combined into one category in analysis. Ranodmisation stratum is also collected at randomization in RAMOS NG. Both randomization stratum (derived and collected) will be listed.

Medical Conditions and Concomitant Medications
Cardiovascular Risk Factors
Subjects with at least one of the following current or past medical conditions at Screening will be classed as having a cardiovascular (CV) risk factor at screening. 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 • Carotid or aorto-femoral vascular disease, • Diabetes mellitus • Hypercholesterolemia
COPD Concomitant medications
COPD concomitant medications will be grouped into the following RMCs based on pre-defined code lists derived from ATC classifications: • Antiinfectives (antibiotics, antifungals, antivirals, antiseptics) • Short-acting anticholinergic

Medical Conditions and Concomitant Medications
• Short-acting beta-2 agonist • Long-acting anticholinergic • Long-acting beta-2 agonist • Xanthine • PDE4 Inhibitor • Corticosteroid - inhaled • Corticosteroid - depot • Corticosteroid - systemic oral parenteral and intra-articular • Corticosteroid - other • Leukotriene receptor antagonist • Nedocromil or cromolyn sodium • Mucolytic • Oxygen • Other medication given for exacerbation • Other COPD medication
COPD medication combination
COPD medications taken on the day of the Screening visit 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

Medical Conditions and Concomitant Medications
COPD Exacerbation History

- Individual exacerbations during the 12 months prior to Screening and during the study were to be collected on the eCRF by the Investigator.
- COPD exacerbations with onset date on or after the date of Screening will not be included in the counts of number of exacerbations in the past year; all other exacerbations recorded on the eCRF will be included in the counts, even if onset/resolution dates are missing or earlier than the start of the exact 12 month period prior to Screening.
- COPD exacerbations reported in the past 12 months will be categorized as 0, 1, 2, ≥3
- Number of COPD exacerbations reported in the past 12 months prior to Screening will be summarized according to three categories: moderate COPD exacerbations, severe COPD exacerbations and moderate/severe COPD exacerbations.
    - Moderate COPD exacerbations are defined as exacerbations that required treatment with systemic/oral corticosteroids and/or antibiotics (not involving hospitalization).
    - Severe COPD exacerbations are defined as exacerbations that required in-patient hospitalization.
- Total number of moderate/severe COPD exacerbations are defined as total numbers of moderate and severe COPD exacerbations for each subject.
- Summaries of moderate/severe exacerbations by treatment course are defined as exacerbations treated with systemic/oral corticosteroids (with or without antibiotics), and exacerbations treated with antibiotics (with or without systemic/oral corticosteroids).

Medical Conditions and Concomitant Medications
COPD Assessment Test (CAT) at Screening
CAT Score
The CAT consists of eight items each formatted as a six-point differential scale: 0 (no impact) to 5 (high impact). A CAT score will be calculated by summing the non-missing scores on the eight items with a range from 0 to 40. If one item is missing, then the score for that item is set as the average of the non-missing items. If more than one item is missing, then the CAT score will be set to missing. The CAT score at screening will be summarized.
CAT Category
Subject will be classified into the following CAT category based on the CAT score at Screening: • CAT <10 • CAT≥10 The CAT category at screening will be summarised

Baseline Lung Function
Reversibility
The reversibility to salbutamol status of a subject is calculated at Screening and is based on the difference (absolute change and % change) between a subject's pre-salbutamol assessment of FEV1 and their post-salbutamol assessment FEV1 and is defined as follows: • Reversible, if they had a difference in FEV1 of ≥ 12% and ≥ 200 mL, or • Non-reversible, if they had a difference in FEV1 of < 200 mL or a ≥ 200 mL difference that was < 12 % of the pre-salbutamol FEV1.
GOLD Grade 1-4 at Screening
Subjects will be classified into Global Initiative on Obstructive Lung Disease (GOLD) Grades 1-4 using the post-salbutamol percent predicted FEV1 assessment at Screening: • GOLD Grade 1 (Mild): percent predicted FEV1 ≥ 80% • GOLD Grade 2 (Moderate): 50%≤ percent predicted FEV1 < 80% • GOLD Grade 3 (Severe): 30%≤ percent predicted FEV1 < 50% • GOLD Grade 4 (Very Severe): percent predicted FEV1 < 30%

10.6.3. Safety

Exposure
Exposure Duration
Duration of exposure to study treatment is calculated as: • treatment stop date – treatment start date +1.

Exposure

Exposure Duration

Exposure Categories

- For the ITT population, the following exposure categories will be derived:

  ≥1 day, ≥4 weeks, ≥8 weeks, ≥12 weeks, ≥16 weeks, ≥20 weeks and ≥24 weeks

Adverse Events

AEs 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.

AE of special interest group	AE special interest subgroup	Sub-SMQ
Adrenal suppression		
Anticholinergic syndrome (SMQ)		
Asthma/bronchospasm (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)	
Ocular effects	Glaucoma (SMQ)	
	Lens Disorder (SMQ)	
Decreased bone mineral density and associated fractures		
Effects on potassium		
Gastrointestinal obstruction (SMQ)		

Hyperglycaemia/new onset diabetes mellitus (SMQ)		
Hypersensitivity		
Local steroid effects		
Pneumonia		
LRTI excluding pneumonia		
Tremor		
Urinary retention		

Bone Fracture Incidents
If a subject suffers fractures in multiple locations with the same date of fracture, this is considered to be one fracture incident. All bone fractures will be reported; and separately by traumatic and non-traumatic bone fractures.

Maximum/Minimum Post-Baseline and Worst-Case Post-Baseline	
Definition	**Reporting Details**
Maximum post-baseline; (QTcF, QTcB, PR interval, ECG heart rate, pulse rate, systolic BP, diastolic BP and laboratory tests.)	Maximum on-treatment value over all timepoints.
Minimum post-baseline; (Diastolic BP and laboratory tests that do not have a lower limit = 0.)	Minimum on-treatment value over all timepoints.
Worst case post-baseline (ECG findings)	• 'Abnormal' if any on-treatment assessment is evaluated as 'Abnormal' • 'Unable to evaluate' if all on-treatment assessments are 'Unable to evaluate' • 'Normal' if any on-treatment assessment is evaluated as 'Normal' and there are no on-treatment assessments evaluated as 'Abnormal'

NOTES :

- The treatment phase definitions specified in Section 10.4.2 will be used and only assessments within the on-treatment period will be considered in assessment of minimum/maximum/worst-case post-baseline.
- Assessment of minimum/maximum/worst-case post-baseline will include data from scheduled, unscheduled and study treatment discontinuation visits (if applicable). Vital signs (heart 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 'minimum/maximum post-baseline' assessment.

Laboratory Parameters
• Non-quantifiable laboratory results will be treated as missing in summary displays. However, the results will be listed as received (e.g. '<x' or '>x'). • An 'any visit post-baseline' classification will be derived, in which subjects will be counted in the 'low' and 'high' categories if they reported a low or high value at any scheduled or

Laboratory Parameters
unscheduled on-treatment visit during the treatment phase being summarized (see Section 10.4.1 for the definition of treatment phases). • Change from baseline values will be classified relative to the normal range as 'to low', 'to normal or no change' or 'to high'. Subjects who do not change categories or move from out-of-range to normal will be classified as 'to normal or no change'. • An 'any visit post-baseline' change classification will be derived, in which subjects will be counted in the 'to low' and 'to high' categories if they reported a change from a 'normal' baseline to a value below or above the normal range (respectively) at any scheduled or unscheduled on-treatment visit during the treatment phase being summarized (see Section 10.4.1 for the definition of treatment phases). Subjects who did not report a change to a value outside the normal range at any visit after the start of study treatment will be counted in the 'to normal or no change' category.
Multiple Measurements for Post-Baseline Visits for Safety
• Subjects having both High and Low values relative to Normal Ranges at post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables.

ECG

QTcF and QTcF change from baseline results will be reported in categories as below:

ECG Parameter	Units	Ranges	
		Lower	Upper
Absolute			
Absolute QTcF Interval	msec	0	≤ 450
		> 450	≤ 480
		> 480	≤ 500
		> 500	≤ 530
		> 530	

ECG			
Change from Baseline			
Change from Baseline QTcF	msec		<-60
		≥-60	<-30
		≥-30	<0
		≥0	< 30
		≥ 30	<60
		≥ 60	

Association of Chest Imaging (X-ray or CT scan) with Pneumonia Event
• A chest X-ray is considered associated with pneumonia if it is performed within -7 to +14 days of the date of onset of pneumonia or the date of resolution, whichever the latter. Pneumonia is considered to be supported by a chest X-ray if there is an associated X-ray which shows the presence of infiltrates. • Details of pneumonia events are collected on the Pneumonia Details eCRF page. As there may not be a one-to-one correspondence between these events and pneumonia AESI events, a cross-tabulation will be provided for the association of pneumonia AESI events and those recorded on the Pneumonia Details eCRF page.

10.6.4. Efficacy and Health Outcomes

Spirometry
Predicted FEV1, Predicted FVC, Absolute and Percent Reversibility in FEV1, Percent Predicted FEV1, Percent Predicted FVC, and Pre-salbutamol and Post-salbutamol FEV1/FVC Ratio
• These derived items will be delivered in a dataset from the vendor for central spirometry, except for post-salbutamol FEV1/FVC ratio, and no recalculation will be performed. Post-salbutamol FEV1/FVC ratio will be calculated as the ratio of post-salbutamol FEV1 and FVC values.
Trough
• The trough value for FEV1 and FVC at Weeks 4, 12 and 24 is the value of the pre-dose assessment. • If the actual time of assessment is after the time of dosing on that day, the value for FEV1 and FVC will not be used. • Change from baseline in trough FEV1 and FVC will be calculated.

St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C)
General
• The SGRQ-C contains 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). This includes details on how to handle missing data. • SGRQ-C domain and total score will be converted to SGRQ scores as described in the manual. • Changes from baseline in domain and total score will be calculated for the converted scores. • If the language of the SGRQ-C conducted at a post-treatment visit is different to the language used at Day 1, all SGRQ scores at that visit and all subsequent visits will be set to missing.
Responder Status according to SGRQ Total Score
• A subject will be a considered a responder according to SGRQ total score if their on-treatment SGRQ total score has decreased at least 4 units from baseline SGRQ total score. • A subject will be considered a non-responder if their on-treatment SGRQ total score has decreased by less than 4 units, has not changed, or has increased compared to baseline. • Missing data will be handled as detailed in Section 10.7.2

COPD Exacerbations

• Each COPD exacerbation will be categorized based on severity as follows:
  ○ Mild: no treatment with systemic/oral corticosteroids and/or antibiotics and no hospitalization
  ○ Moderate: required treatment with systemic/oral corticosteroids and/or antibiotics (not involving hospitalization)
  ○ Severe: required in-patient hospitalization
• The duration of the exacerbation will be calculated as (exacerbation resolution date or date of death - exacerbation onset date + 1).
• The time to the first on-treatment exacerbation will be calculated as (exacerbation onset date of first on-treatment exacerbation – date of start of treatment + 1).
• Subjects will be represented from their Week 0 date to the earliest of the event or censoring. For subjects who do not experience the event will be censored at the earliest of the date of their treatment stop date +1 day or the date of death.

Association to Chest Imaging (X-ray or CT Scan)
• A chest X-ray or CT scan is considered associated with a moderate/severe exacerbation if it is performed within 0 to +14 days of the exacerbation start date.

SAC BDI/TDI
General
• The BDI focal score will be calculated as the sum of the ratings recorded for each of the three individual scales (Functional Impairment, Magnitude of Task, Magnitude of Effort). Each of these scales has five possible scores ranging from 0 to 4 (with lower scores indicating more impairment), so the range of the BDI focal score is 0 to 12. If a score is missing for any of the three scales, then the BDI focal score will be set to missing. BDI is assessed at baseline (Week 0). • The SAC TDI focal score will be calculated as the sum of the ratings recorded for each of the three individual scales (Functional Impairment, Magnitude of Task, Magnitude of Effort). Each of these scales has a possible score ranging from -6 to +6 . SAC TDI focal score is calculated as the sum of the three individual scores and then divided by 2 (so the range of the TDI focal score is -9 to +9). If a score is missing for any of the three scales, then the SAC TDI focal score will be set to missing. • If the language of the SAC TDI conducted at a visit is different to the language for the BDI, all TDI scores at that visit and all subsequent visits will be set to missing
Responder Status according to SAC TDI Focal Score
• A subject will be a responder if the on-treatment SAC TDI focal score was at least 1 unit at that visit. • A subject will be considered a non-responder if their on-treatment SAC TDI focal score was less than 1 unit. • Missing data will be handled as detailed in Section 10.7.2

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

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	• For reporting purposes, subject study completion (*i.e.* as specified in the protocol) was defined as a subject will be considered to have completed the study when they have completed all phases of the study including screening, run-in, randomization, the randomized treatment phase up to visit 5 and safety follow-up visit. Withdrawn subjects will not be replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.
Vitals/Lab/ECG	• Vitals/Lab/ECG data collected as part of the early withdrawal at a scheduled visit, or at a standalone EW visit will be used in the summary of absolute values and change from baseline as part of the 'minimum post baseline', 'minimum change from baseline', 'maximum post-baseline' and 'maximum change from baseline' for diastolic and 'maximum post-baseline' and 'maximum change from baseline' for pulse rate and systolic blood pressure

10.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument : o These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such. o No imputation will be made for any missing numerical data, except in the sensitivity analysis of the primary endpoint to assess the impact of missing data on study results. Missing data will generally not be considered in the calculation of percentages (i.e., the denominator will not include subjects who have missing data at a given time point).
Responder	• Subjects with a missing baseline will have responder status as missing. • Subjects with missing post-baseline data and a subsequent non-missing assessment will not be considered a responder or non-responder but will be left as missing. • Subjects with a baseline but all missing post-baseline data will be considered a non-responder at all time points.

10.7.2.1. Handling of Missing or Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays. • Dates which are completely missing will not be imputed, with the exception of the treatment stop date. Details around imputation of the treatment stop date are provided in Section 10.6.1
Concomitant Medications	• Partial dates for any concomitant medications will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.
Adverse Events, Exacerbation, Pneumonia	• Any partial dates will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month. ○ However, if these results in a date prior to Week 0 and the event could possibly have occurred during treatment from the partial information, then the Week 0 date will be assumed to be the start date. ○ The event will then be considered to start on-treatment (worst case). ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. ○ The recorded partial date will be displayed in listings.

10.7.2.2. Handling of Missing Data for Statistical Analysis

A "tipping point" sensitivity analysis of trough FEV1 at Week 24 will be conducted for the mPP Population. This will explore the impact of missing data by using differing assumptions regarding the mean treatment effect in subjects who discontinue study treatment or have data excluded from the mPP Population analyses. Further details are given Section 7.1.2.

10.8. Appendix 8: Multicenter Studies

10.8.1. Methods for Handling Centers

It is likely that many centers will enroll a very small number of subjects and so rather than adjusting for center in the statistical analyses, a geographical region will be used in analyses where specified. The center group will be created based on geographical region and number of randomized subjects in a country, in order to define groups of roughly similar size. The table below shows (most up to date) the numbers in each reagion and the breakdown by stratum.

Region	Countries	Number of subjects in each region	Number of subjects in each strata and each region
Europe 1	Russia, Poland Romania	398	0: 9
			1: 195
			>=2: 194
Europe 2	France, Germany, Italy, Spain	252	0: 15
			1: 75
			>=2: 162
Asia	Australia, Japan, S. Korea	215	0: 6
			1: 49
			>=2: 160
America	Argentina, Mexico	194	0: 3
			1: 139
			>=2: 52

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

10.9.1. Handling of Covariates, Subgroups & Other Strata

- Randomisation is stratified based on long-acting bronchodilator usage during the run-in (none, one or two long-acting bronchodilators per day). The stratum (with none and one combined into the same category based on derived strata) will be fitted as a covariate in all statistical models.
- Other covariates will be included for specific analyses as detailed in model specifications in Section 7 and Section 8.

10.10. Appendix 10: Multiple Comparisons & Multiplicity

10.10.1. Handling of Multiple Comparisons & Multiplicity

Treatment comparisons will not be adjusted for multiplicity. No p-values for treatment comparisons will be displayed.

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

10.11.1. Statistical Analysis Assumptions

Endpoints	• Trough FEV1 • SGRQ total score • TDI focal score
Analysis	MMRM

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

Endpoints	• Proportion of responders according to SGRQ total score, TDI focal score
Analysis	• Generalized Linear Model

- Computation of confidence intervals for the odds ratios is based on the individual Wald tests
- FF/VI+UMEC will be used as the reference level for treatment
- Pearson residuals will be plotted by using PLOTS=PEARSONPANEL option for the model statement in SAS.

Endpoints	• Time to first on-treatment moderate/severe COPD exacerbation •
Analysis	• Cox's proportional hazard method

- The proportional hazards assumption for this method of analysis will be examined by obtaining the Kaplan-Meier estimates of the survival function S(t) over time separately for treatment group. Under the assumption of proportional hazard between the treatment groups, $\ln\{-\ln[S(t)]\}$ for the two groups should be parallel to each other and the distance between them constant. If the curves are approximately parallel, then the proportional hazard assumption is not violated. If these curves cross each other or diverge greatly from the assumption of parallel lines, then the assumption is not met.

10.12. Appendix 12: Abbreviations

ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ASE	All Subjects Enrolled
ATC	Anatomical Therapeutic Chemical Classification
BDI	Baseline Dyspnoea Index
BMI	Body Mass Index
BP	Blood Pressure
Bpm	Beats Per Minute
CAT	COPD Assessment Test
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Intervals
COPD	Chronic Obstructive Pulmonary Disease
CRT	Case Report Tabulation
CSR	Clinical Study Report
CRF	Case Report Form
CV	Cardiovascular
DBF	Database Freeze
DM	Data Management
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FEV1	Forced Expiratory Volume in One Second
FF	Fluticasone Furoate
FVC	Forced Vital Capacity
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
GSK573719	Umeclidinium (UMEC)
GW642444	Vilanterol Trifenatate (VI)
GW685698	Fluticasone Furoate (FF)
HRQoL	Health Related Quality of Life
IB	Investigator Brochure
ICS	Inhaled Corticosteroid
IDMC	Independent Data Monitoring Committee
ITT	Intent-to-Treat
LABA	Long Acting Beta-Agonist
LAMA	Long-acting Muscarinic Receptor Antagonists
MACE	Major Adverse Cardiac Event
mcg	Microgram
mL	Milliliter
MMRM	Mixed Models Repeated Measures
mPP	Modified Per-Protocol
PD	Protocol Deviation
PDMP	Protocol Deviation Management Plan

QD	Once daily
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
RAMOS	Randomization & Medication Ordering System
RANDALL-NG	GSK Randomization System – Next Generation
RAP	Reporting and Analysis Plan
RMC	Respiratory Medication Class
SABAs	Short-acting β2-adrenergic receptor agonists
SAE	Serious Adverse Event
SD	Standard Deviation
SDL	Source Data Lock
SDTM	Study Data Tabulation Model
SE	Standard Error
SGRQ	St Georges Respiratory Questionnaire
SGRQ-C	SGRQ for COPD patients
SI	System Independent
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TDI	Transitional Dyspnoea Index
TFL	Tables, Figures & Listings
TSCG	Tibco Spotfire Clinical Graphics software
UMEC	Umeclidinium
VI	Vilanterol Trifenatate

10.12.1. Trademarks

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

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10.13. Appendix 13: List of Data Displays

10.13.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.41	1.1
Efficacy	2.1 to 2.24	2.1 to 2.10
Safety	3.1 to 3.47	3.1 to 3.14
Section	**Listings**	
ICH Listings	1 to 17	
Other Listings	17 to 50	

10.13.2. Programming Note

Unless otherwise stated all listings will be produced by country, treatment, center, and subject. Present Country as a subheading/by variable in listing. In addition, where applicable, listings will include a flag to indicate if the record is on-treatment or post-treatment and a flag to indicate if the subject is in the mPP population.

10.13.3. Study Population Tables

Study Population Tables			
No.	**Population**	**Title**	**Deliverable**
Subject Disposition			
1.1.	ASE	Summary of Subject Populations and Reason for Screen/Run-in Failure	SAC
1.2.	ITT	Summary of Attendance at Each Visit	SAC
1.3.	ITT	Summary of Completion and Premature Discontinuation of Study Treatment	SAC
1.4.	ITT	Summary of Study Completion and Withdrawal	SAC
1.5.	ASE	Summary of Number of Subjects Enrolled By Country	SAC
1.6.	ASE	Summary of Age ranges	SAC
1.7.	ITT	Summary of Number of Subjects By Geographical Region, Country and Center	SAC
1.8.	MPP	Summary of Number of Subjects By Geographical Region, Country and Center	SAC
1.9.	ASE	Summary of Inclusion/Exclusion Criteria Deviations For Screen Failures	SAC
1.10.	ITT	Summary of Inclusion/Exclusion Criteria Deviations	SAC
1.11.	ITT	Summary of Important Protocol Deviations	SAC
1.12.	ITT	Summary of Exclusions from Modified Per Protocol Population	SAC
Demography			
1.13.	ITT	Summary of Demographic Characteristics	SAC
1.14.	MPP	Summary of Demographic Characteristics	SAC
1.15.	ITT	Summary of Demographic Characteristics by Country	SAC
1.16.	ITT	Summary of Race and Racial Combinations	SAC
1.17.	MPP	Summary of Race and Racial Combinations	SAC
Medical Conditions			
1.18.	ITT	Summary of Current Medical Conditions	SAC
1.19.	ITT	Summary of Past Medical Conditions	SAC
1.20.	ITT	Summary of Cardiovascular Risk Factors	SAC
1.21.	ITT	Summary of Family History of Cardiovascular Risk Factors	SAC
1.22.	ITT	Summary of Smoking History at Screening	SAC
Disease Characteristics			
1.23.	ITT	Summary of COPD Exacerbation History at Screening	SAC
1.24.	ITT	Summary of Screening Lung Function	SAC
1.25.	MPP	Summary of Screening Lung Function	SAC
1.26.	ITT	Summary of Screening Lung Function by Country	SAC
1.27.	ITT	Summary of Reversibility and GOLD Grade (1-4) at Screening	SAC
1.28.	MPP	Summary of Reversibility and GOLD Grade (1-4) at Screening	SAC
1.29.	ITT	Summary of CAT Score and CAT Category at Screening	SAC
Concomitant Medications			
1.30.	ITT	Summary of Long-acting Bronchodilator Usage during the Run-in (Randomization Strata)	SAC
1.31.	MPP	Summary of Long-acting Bronchodilator Usage during the Run-in (Randomization Strata)	SAC
1.32.	ITT	Summary of COPD Concomitant Medication Combinations Taken at Screening	SAC

Study Population Tables			
No.	**Population**	**Title**	**Deliverable**
1.33.	ITT	Summary of COPD Concomitant Medications Taken in the Run-in, Medications Given for Reasons other than an Exacerbation	SAC
1.34.	ITT	Summary of On-Treatment COPD Concomitant Medications, Medications Given for Reasons other than an Exacerbation	SAC
1.35.	ITT	Summary of Post-Treatment COPD Concomitant Medications, Medications Given for Reasons other than an Exacerbation	SAC
1.36.	ITT	Summary of Concomitant Medications Taken in the Run-in Given for An Exacerbation	SAC
1.37.	ITT	Summary of On-Treatment Concomitant Medications Given for an Exacerbation	SAC
1.38.	ITT	Summary of Post-Treatment Concomitant Medications Given For an Exacerbation	SAC
1.39.	ITT	Summary of On-Treatment Non-COPD Concomitant Medications	SAC
1.40.	ITT	Summary of Post-Treatment Non-COPD Concomitant Medications	SAC
Treatment Compliance			
1.41.	ITT	Summary of Treatment Compliance (%)	SAC

10.13.4. Study Population Figures

Study Population figures			
No.	**Population**	**Title**	**Deliverable**
1.1.	ITT	Kaplan-Meier Plot of Time to Study Withdrawal	SAC

10.13.5. Efficacy Tables

Efficacy: Tables			
No.	**Population**	**Title**	**Deliverable**
Spirometry			
2.1	ITT	Summary of Baseline FEV1 (L)	SAC
2.2	MPP	Summary of Baseline FEV1 (L)	SAC
2.3.	ITT	Summary of Baseline FEV1 (L) by Country	SAC
2.4.	ITT	Summary of Trough FEV1 (L)	SAC
2.5.	MPP	Summary of Trough FEV1 (L)	SAC
2.6.	ITT	Summary of Trough FEV1 (L) by Country	SAC
2.7.	ITT	Analysis of Trough FEV1 (L)	SAC
2.8.	MPP	Analysis of Trough FEV1 (L)	SAC
2.9.	ITT	Significance Levels for Interactions of Treatment with Number of Long-acting Bronchodilators per Day During the Run-in, Geographical Region, and Baseline for Analysis of Trough FEV1 (L)	SAC
2.10.	mPP	Significance Levels for Interactions of Treatment with Number of Long-acting Bronchodilators per Day During the Run-in, Geographical Region, and Baseline for Analysis of Trough FEV1 (L)	SAC

Efficacy: Tables			
No.	**Population**	**Title**	**Deliverable**
2.11.	MPP	Trough FEV1 (L) Tipping Point Sensitivity Analysis: 95%CIs after Imputing Varying Week 24 Mean Change from Baseline Trough FEV1 (L)	SAC
2.12.	ITT	Summary of Baseline FVC (L)	SAC
2.13.	ITT	Summary of Trough FVC (L)	SAC
SGRQ			
2.14.	ITT	Summary of Baseline SGRQ Scores	SAC
2.15.	ITT	Summary of SGRQ Scores	SAC
2.16.	ITT	Analysis of SGRQ Total Score	SAC
2.17.	ITT	Summary and Analysis of Proportion of Responders According to SGRQ Total Score	SAC
COPD Exacerbations			
2.18.	ITT	Summary of On-Treatment COPD Exacerbations	SAC
2.19.	ITT	Summary of Post-Treatment COPD Exacerbations	SAC
2.20.	ITT	Summary and Analysis of Time to First On-treatment Moderate or Severe Exacerbation (days)	SAC
SACBDI/TDI			
2.21.	ITT	Summary of SAC BDI Focal Score	SAC
2.22.	ITT	Summary of SAC TDI Focal Score	SAC
2.23.	ITT	Analysis of SAC TDI Focal Score	SAC
2.24.	ITT	Summary and Analysis of Proportion of Responders According to SAC TDI Focal Score	SAC

10.13.6. Efficacy Figures

Efficacy: Figures			
No.	**Population**	**Title**	**Deliverable**
Spirometry			
2.1	ITT	Box Plot of Change from Baseline in Trough FEV1 (L) at Week 24	SAC
2.2	MPP	Box Plot of Change from Baseline in Trough FEV1 (L) at Week 24	SAC
2.3	ITT	Empirical Distribution Function Plot of Change from Baseline in Trough FEV1 (L) at Week 24	SAC
2.4	MPP	Empirical Distribution Function Plot of Change from Baseline in Trough FEV1 (L) at Week 24	SAC
2.5	ITT	Least Squares Mean (95% CI) Change from Baseline in Trough FEV1 (L)	SAC
2.6	MPP	Least Squares Mean (95% CI) Change from Baseline in Trough FEV1 (L)	SAC
SGRQ			
2.7	ITT	Least Squares Mean (95% CI) Change from Baseline in SGRQ Total Score	SAC
2.8	ITT	Empirical Distribution Function Plot of Change from Baseline in SGRQ Total Score at Week 24	SAC
COPD Exacerbations			
2.9	ITT	Kaplan-Meier Plot of Time to First Moderate/Severe COPD Exacerbation (Days)	SAC

Efficacy: Figures			
No.	**Population**	**Title**	**Deliverable**
BDI/TDI			
2.10	ITT	Least Squares Means (95% CI) TDI Focal Score	SAC

10.13.7. Safety Tables

Safety Tables			
No.	**Population**	**Title**	**Deliverable**
Exposure			
3.1	ITT	Summary of Exposure	SAC
Adverse Events			
3.2	ITT	Overview of On-Treatment Adverse Events	SAC
3.3	ITT	Summary of On-Treatment Adverse Events	SAC
3.4	ITT	Summary of On-Treatment Adverse Events by Country	SAC
3.5	ITT	Summary of Post -Treatment Adverse Events	SAC
3.6	ITT	Summary of On-treatment Drug-Related Adverse Events	SAC
3.7	ITT	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)	SAC
3.8	ITT	Summary of On-treatment Serious Adverse Events	SAC
3.9	ITT	Summary of On-treatment Fatal Serious Adverse Events	SAC
3.10	ASE	Summary of Pre-treatment Serious Adverse Events	SAC
3.11	ITT	Summary of Pre-treatment Serious Adverse Events	SAC
3.12	ASE	Summary of Pre-treatment Serious Adverse Events Leading to Withdrawal from Study	SAC
3.13	ITT	Summary of On-treatment Drug-Related Serious Adverse Events	SAC
3.14	ITT	Summary of On-treatment Drug-Related Fatal Serious Adverse Events	SAC
3.15	ITT	Summary of On-treatment Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study	SAC
3.16	ITT	Summary of On-treatment Adverse Events of Special Interest	SAC
3.17	ITT	Summary of On-treatment Serious Adverse Events of Special Interest	SAC
3.18	ASE	Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text	SAC
3.19	ITT	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)	SAC
3.20	ITT	Summary of the 10 Most Frequent On-treatment Adverse events in each Treatment Group	SAC

Safety Tables			
No.	**Population**	**Title**	**Deliverable**
3.21	ITT	Summary of On-Treatment Adverse Events by System Organ Class and Maximum Intensity	SAC
Pneumonia			
3.22	ITT	Summary of On-treatment Pneumonias Incidence	SAC
3.23	ITT	Summary of On-treatment Details of Pneumonia	SAC
3.24	ITT	Summary of Post-treatment Pneumonias	SAC
3.25	ITT	Summary of Post-treatment Details of Pneumonia	SAC
Bone Fractures			
3.26	ITT	Summary of On-treatment Bone Fractures	SAC
3.27	ITT	Summary of Post-treatment Bone Fractures	SAC
Radiography (Chest Imaging : X-Rays or CT Scan)			
3.28	ITT	Summary of On-treatment Chest Imaging (X-Ray or CT Scan	SAC
3.29	ITT	Summary of Post-treatment Chest Imaging (X-Ray or CT Scan)	SAC
Laboratory Parameters			
3.30	ITT	Summary of Chemistry Data	SAC
3.31	ITT	Summary of Change from Baseline in Chemistry Data	SAC
3.32	ITT	Summary of Chemistry Data Outside the Normal Range	SAC
3.33	ITT	Summary of Chemistry Changes from Baseline Relative to the Normal Range	SAC
3.34	ITT	Summary of Hematology Data	SAC
3.35	ITT	Summary of Change from Baseline in Hematology Data	SAC
3.36	ITT	Summary of Hematology Data Outside the Normal Range	SAC
3.37	ITT	Summary of Hematology Changes from Baseline Relative to the Normal Range	SAC
Vitals Signs			
3.38	ITT	Summary of Vital Signs	SAC
3.39	ITT	Summary of Change from Baseline Vital Signs	SAC
ECGs			
3.40	ITT	Summary of ECG Values	SAC
3.41	ITT	Summary of Change from Baseline in ECG Values	SAC
3.42	ITT	Summary of QTc(F) (msec) Categories	SAC
3.43	ITT	Summary of Change From Baseline in QTc(F) (msec) Categories	SAC
3.44	ITT	Summary of ECG Findings	SAC
3.45	ITT	Summary of ECG Findings Shifts from Baseline	SAC
3.46	ITT	Summary of ECG Abnormalities	SAC

Safety Tables			
No.	**Population**	**Title**	**Deliverable**
3.47	ITT	Summary of ECG Abnormalities Occurring in at Least 3% of Subjects in Either Treatment Group	SAC

10.13.8. Safety Figures

Safety : Figures			
No.	**Population**	**Title**	**Deliverable**
Exposure			
3.1	ITT	Plot of Exposure to Study Drug	SAC
Laboratory Parameters			
3.4	ITT	Trellis Display of Maximum Post-baseline Liver Function Test Values, Versus Baseline Liver Function Test Values	SAC
3.5	ITT	Scatter Plots of Maximum Post-baseline Versus Baseline For Chemistry Data	SAC
3.6	ITT	Box Plots of Change from Baseline to Maximum Post-baseline Values for Chemistry Data	SAC
3.7	ITT	Scatter Plots of Minimum Post-baseline Versus Baseline For Chemistry Data	SAC
3.8	ITT	Box Plots of Change from Baseline to Minimum Post-baseline Values for Chemistry Data	SAC
3.9	ITT	Scatter Plots of Maximum Post-baseline Versus Baseline For Hematology Data	SAC
3.10	ITT	Box Plots of Change from Baseline to Maximum Post-baseline Values for Hematology Data	SAC
3.11	ITT	Scatter Plots of Minimum Post-baseline Versus Baseline For Hematology Data	SAC
3.12	ITT	Box Plots of Change from Baseline to Minimum Post-baseline Values for Hematology Data	SAC
12-Lead ECGs			
3.13	ITT	Empirical Distribution Function Plot of Maximum Post-baseline QTcF (msec)	SAC
3.14	ITT	Empirical Distribution Function Plot of Change from Baseline in Maximum Post-baseline QTcF (msec)	SAC

10.13.9. ICH Listings

ICH : Listings			
No.	**Population**	**Title**	**Deliverable**
Study population			
1.	ITT	Listing of Randomized and Actual Treatments	SAC
2.	ITT	Listing of Study Treatment Discontinuation Record	SAC
3.	ITT	Listing of Reasons for Study Withdrawal	SAC
4.	ASE	Listing of Subjects with Inclusion and Exclusion Criteria Deviations for Screen Failures	SAC
5.	ITT	Listing of Subjects with Inclusion and Exclusion Criteria Deviations	SAC
6.	ITT	Listing of Subjects for Whom the Treatment Blind was Broken during the Study	SAC
7.	ITT	Listing of Demographic Characteristics	SAC
8.	ITT	Listing of Race	SAC
Spirometry			
9.	ITT	Listing of Raw FEV1 (L) and FVC (L) Data	SAC
Exposure			
10.	ITT	Listing of Exposure	SAC
Adverse Events			
11.	ASE	Listing of Subject Numbers for Individual Adverse Events	SAC
12.	ASE	Listing of All Adverse Events	SAC
13.	ASE	Listing of Non-Fatal Serious Adverse Events	SAC
14.	ASE	Listing of Fatal Adverse Events	SAC
15.	ITT	Listing of Adverse Events leading to Withdrawal from the Study	SAC

ICH : Listings			
No.	**Population**	**Title**	**Deliverable**
Laboratory Parameters			
16.	ITT	Listing of Chemistry Values for Subjects with at Least One Value outside the Normal Range	SAC
17.	ITT	Listing of Hematology Values for Subjects with at Least One Value outside the Normal Range	SAC

10.13.10. Non-ICH Listings

Non-ICH : Listings			
No.	**Population**	**Title**	**Deliverable**
Study Population			
18.	ASE	Listing of Reason for Screen/Run-in Failure	SAC
19.	ITT	Listing of Important Protocol Deviations	SAC
20.	ITT	Listing of Exclusion from Modified Per Protocol Population	SAC
21.	ASE	Listing of Study Treatment Misallocations	SAC
22.	ITT	Listing of Screening Lung Function, Reversibility Status, GOLD Grade and CAT Score	SAC
23.	ITT	Listing of Medical Conditions	SAC
24.	ITT	Listing of Family History of Cardiovascular Risk Factors	SAC
25.	ITT	Listing of COPD Exacerbation History	SAC
26.	ITT	Listing of Smoking History and Smoking Status	SAC
27.	ITT	Listing of Percent Oxygen in Blood	SAC
28.	ITT	Listing of COPD Concomitant Medications	SAC
29.	ITT	Listing of Non-COPD Concomitant Medications	SAC
30.	ITT	Listing of Randomisation Strata (Derived and from eCRF)	SAC
31.	ITT	Relationship between ATC Level 1, Ingredient and Verbatim Text for Non-COPD Medications	SAC
32.	ITT	Listing of Treatment Compliance Data	SAC

Non-ICH : Listings			
No.	**Population**	**Title**	**Deliverable**
Adverse Events			
33.	ITT	Listing of Subject Numbers for On-Treatment Adverse Events of Special Interest	SAC
34.	ITT	Listing of Reasons for Considering as a Serious Adverse Event	SAC
COPD Exacerbations			
35.	ITT	Listing of COPD Exacerbations	SAC
SGRQ			
36.	ITT	Listing of SGRQ Scores	SAC
BDI/TDI			
37.	ITT	Listing of BDI/TDI Focal Scores	SAC
CAT			
38.	ITT	Listing of CAT Scores	SAC
Pneumonia Incidence			
39.	ITT	Listing of Pneumonia Data	SAC
Bone Fractures			
40.	ITT	Listing of Bone Fracture Data	SAC
Chest Imaging (X-Rays or CT Scan)			
41.	ITT	Listing of Chest Imaging (X-Ray or CT Scan) Data	SAC
Liver Events			
42.	ITT	Listing of Liver Event Results and Time of Event Relative to Treatment	SAC
43.	ITT	Listing of Medical Conditions for Subjects with Liver Stopping Events	SAC
44.	ITT	Listing of Substance Use for Subjects with Liver Stopping Events	SAC
45.	ITT	Listing of Liver Event Information for RUCAM Score	SAC
46.	ITT	Listing of Liver Biopsy Details	SAC
47.	ITT	Listing of Liver Imaging Details	SAC

Non-ICH : Listings			
No.	**Population**	**Title**	**Deliverable**
12-Lead ECGs			
48.	ITT	Listing of ECG Values for Subjects with Any Abnormal ECG Finding	SAC
49.	ITT	Listing of ECG Abnormalities	SAC
Inhaler malfunctions			
50.	ITT	Listing of Inhaler Malfunctions	SAC