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

Title	:	Reporting and Analysis Plan for a phase III, 52 week, randomized, double-blind, 3-arm parallel group study, comparing the efficacy, safety and tolerability of the fixed dose triple combination FF/UMEC/VI with the fixed dose dual combinations of FF/VI and UMEC/VI, all administered once-daily in the morning via a dry powder inhaler in subjects with chronic obstructive pulmonary disease
Compound Number	:	GSK2834425 (GSK573719+GW642444+GW685698)
Effective Date	:	14-JUL-2017

Description :

- The purpose of this Reporting and Analysis Plan (RAP) is to describe the planned analyses and output to be included in the Clinical Study Report (CSR) for Protocol CTT116855.
- This RAP is intended to describe the planned efficacy, safety and health outcomes analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	• This Reporting and Analysis Plan (RAP) details planned analyses and outputs required for the final Clinical Study Report (CSR) of study CTT116855.
Protocol	• This RAP is based on the following protocol and protocol amendments: • Original protocol [Dated: 17MAR2014, GlaxoSmithKline Document Number 2013N176913_00] • Protocol amendment 01 [Dated: 31MAR2014, GlaxoSmithKline Document Number 2013N176913_01] • Protocol amendment 02 [Dated: 10APR2014, GlaxoSmithKline Document Number 2013N176913_02] • Protocol amendment 03 [Dated: 05DEC2014, GlaxoSmithKline Document Number 2013N176913_03] • Protocol amendment 04 [Dated: 12MAY2015, GlaxoSmithKline Document Number 2013N176913_04] • Protocol amendment 05 [Dated: 30JUN2016, GlaxoSmithKline Document Number 2013N176913_05] • Protocol amendments 3 and 4 are for China only.
Primary Objective	• To evaluate the efficacy of fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) to reduce the annual rate of moderate/severe exacerbations compared with dual therapy of FF/VI or UMEC/VI in subjects with chronic obstructive pulmonary disease (COPD)
Secondary Objectives	• To evaluate the long term safety and other efficacy assessments of FF/UMEC/VI compared with dual therapy of FF/VI or UMEC/VI • To evaluate the efficacy of FF/UMEC/VI to reduce exacerbations compared with UMEC/VI in the subset of subjects with a blood eosinophil count ≥ 0.15 10^9/L
Primary Endpoint and Co-primary Treatment Comparisons	• Annual rate of on-treatment moderate/severe exacerbations comparing FF/UMEC/VI with UMEC/VI • Annual rate of on-treatment moderate/severe exacerbations comparing FF/UMEC/VI with FF/VI
Secondary Endpoints and Treatment Comparisons	• Change from baseline in trough forced expiratory volume in 1 second (FEV1) at Week 52 comparing FF/UMEC/VI with FF/VI • Change from baseline in St. George's Respiratory Questionnaire (SGRQ) Total Score at Week 52 comparing FF/UMEC/VI with FF/VI • Time to first on-treatment moderate/severe exacerbation comparing FF/UMEC/VI with FF/VI and with UMEC/VI • Annual rate of on-treatment moderate/severe exacerbations comparing FF/UMEC/VI with UMEC/VI in the subset of subjects with a blood

Overview	Key Elements of the RAP
	eosinophil count ≥ 0.15 10^9/L • Time to first on-treatment moderate/severe exacerbation comparing FF/UMEC/VI with UMEC/VI in the subset of subjects with a blood eosinophil count ≥ 0.15 10^9/L • Annual rate of on-treatment severe exacerbations comparing FF/UMEC/VI with FF/VI and with UMEC/VI

Study Design	• This is a phase IIIa, randomized, double-blind, 3-arm parallel group, global multicenter study evaluating FF/UMEC/VI (100/62.5/25 mcg) inhalation powder versus FF/VI (100/25 mcg) inhalation powder and UMEC/VI (62.5/25 mcg) inhalation powder all given once daily in the morning. The target enrollment is 10,000 randomized subjects at approximately 1,000 study centers globally.
	• Eligible subjects will be randomized (2:2:1) to one of the following double-blind treatment groups:
	  • FF/UMEC/VI 100/62.5/25 mcg (n=4,000)
	  • FF/VI 100/25 mcg (n=4,000)
	  • UMEC/VI 62.5/25 mcg (n=2,000)
	• The total duration of subject participation will be approximately 55 weeks, consisting of a 2-week run-in period, up to 52-week treatment period and a 1-week safety follow-up period.
	• Subjects who have permanently discontinued study treatment are not required to withdraw from the study. Subjects who have permanently discontinued study treatment and have not withdrawn consent may continue in the study and complete all remaining protocol specified visits by telephone contact to collect exacerbations, SAEs and concomitant medications. This off-treatment data will be used in sensitivity analyses for assessing the effect of missing data on study conclusions.

Planned Analyses	• An Independent Data and Monitoring Committee (IDMC) will review unblinded safety data (including exacerbation data) during the conduct of this study. Blinded review of exacerbation data for potential sample size adjustment will be performed by GSK during the recruitment period of the study. • No interim analysis of unblinded data is planned. One final statistical analysis will be conducted. • 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. Identification of taking incorrect treatment will be identified following DBF.
Analysis Populations	• Intent-to-Treat (ITT) population, which comprises all randomized subjects, excluding those who were randomized in error and did not receive a dose of study medication. A subject who is recorded as a screen or run-in failure and also randomized, but did not receive a dose of study treatment, will be considered to be randomized in error. Any other subject who receives a

Overview	Key Elements of the RAP
	randomization number will be considered to have been randomized. • All Subjects Enrolled (ASE) population includes all subjects for whom a record exists on the study database, both screened subjects and subjects who were not screened but signed an informed consent form (ICF). • Pre-dose Electrocardiogram (ECG) population will comprise all subjects in the ITT population from sites included in the ECG substudy who performed an on-treatment pre-dose ECG assessment at Week 4. • Transitional Dyspnea Index (TDI) population will comprise all subjects in the ITT population who completed a pre-dose Baseline Dyspnea Index (BDI) at Day 1.
Hypothesis	• The primary purpose of this study is to evaluate the efficacy of FF/UMEC/VI to reduce the annual rate of on-treatment moderate/severe exacerbations compared with dual therapy of FF/VI or UMEC/VI in subjects with COPD over a 52-week period. • The co-primary treatment comparison will be the pairwise comparisons of FF/UMEC/VI with FF/VI and FF/UMEC/VI with UMEC/VI for the primary endpoint, the annual rate of on-treatment moderate/severe exacerbations. • The hypotheses (two-sided) associated with the statistical test of the primary endpoint are: H_0: $\lambda_T/\lambda_D=1$ versus H_A: $\lambda_T/\lambda_D\neq 1$, where λ_T is the annual rate for triple therapy (FF/UMEC/VI) and λ_D is the annual rate for the respective dual therapies (FF/VI and UMEC/VI).
Primary Analyses	• The primary analyses will be performed using a generalized linear model (GLM) assuming the negative binomial distribution. The primary analyses will be based on a two-sided hypothesis testing approach and will use data for the ITT population collected while subjects were on study treatment. • To account for multiplicity of the co-primary treatment comparisons, the truncated Hochberg method [Dmitrienko, 2008] with a truncation parameter of $\gamma=0.6$ will be used to control overall type I error at $\alpha=0.05$. Using this approach, both comparisons will be declared statistically significant if the unadjusted p-value for both comparisons is significant at the 0.04 level. Should the largest p-value for the two comparisons be above 0.04, the other comparison will be declared statistically significant if the smaller unadjusted p-value is below 0.025.
Secondary Analyses	• Pairwise comparisons of FF/UMEC/VI versus FF/VI and FF/UMEC/VI versus UMEC/VI will be performed for the secondary efficacy and other endpoints. If at least one of the co-primary treatment comparisons is considered statistically significant, inferences will be drawn from p-values for the treatment comparisons on secondary and other endpoints. If neither of the co-primary treatment comparisons is considered statistically significant, testing on the secondary and other endpoints will be performed and presented for descriptive purposes only. • If both co-primary treatment comparisons are statistically significant, these secondary and other treatment comparisons will be declared significant if the unadjusted p-value is <0.05. If only one co-primary treatment comparison is

Overview	Key Elements of the RAP
	statistically significant, these secondary and other treatment comparisons will be declared significant if the unadjusted p-value is <0.01. • Where strong control of type I error is required for selected secondary endpoints, multiplicity will be controlled using a hierarchical, closed testing procedure. The secondary hypothesis tests will be grouped sequentially in two blocks of two comparisons each, grouped according to specific clinical concepts (lung function and health-related quality of life, and time to first exacerbation event). • Each block of comparisons will also be adjusted for multiplicity using the truncated Hochberg method as described for the primary endpoint analysis with a truncation parameter of γ=0.6 for the first block and a truncation parameter of γ=1 for the second block. • Within each block, at least one endpoint must be considered statistically significant in order to make inferences in the subsequent block. • Pairwise comparisons of FF/UMEC/VI versus FF/VI and FF/UMEC/VI versus UMEC/VI on other endpoints will not be adjusted for multiplicity. • Pairwise comparisons of UMEC/VI versus FF/VI will not be adjusted for multiplicity for any endpoint.
Secondary and Other Analyses	• Pairwise comparisons of FF/UMEC/VI versus FF/VI and FF/UMEC/VI versus UMEC/VI will be performed for the secondary efficacy and other endpoints. • If at least one of the co-primary treatment comparisons is considered statistically significant, inferences will be drawn from p-values for the secondary and other treatment comparisons. • If both co-primary treatment comparisons are statistically significant, these secondary and other treatment comparisons will be declared significant if the unadjusted p-value is <0.05. If only one co-primary treatment comparison is statistically significant, these secondary and other treatment comparisons will be declared significant if the unadjusted p-value is <0.01. • If neither of the co-primary treatment comparisons is considered statistically significant, testing on the secondary and other endpoints will be performed and presented for descriptive purposes only. • No adjustment for multiplicity will be made across these secondary and other treatment comparisons.
Secondary and Other Analyses where strong control of type I error is required	• Where strong control of type I error is required, multiplicity will be controlled across selected secondary endpoints and treatment comparisons using a hierarchical, closed testing procedure. The secondary hypothesis tests will be grouped sequentially in two blocks of two comparisons each, grouped according to specific clinical concepts (lung function and health-related quality of life, and time to first exacerbation event). • Each block of comparisons will also be adjusted for multiplicity using the truncated Hochberg method as described for the primary endpoint analysis with a truncation parameter of γ=0.6 for the first block and a truncation parameter of γ=1 for the second block.

Overview	Key Elements of the RAP
	• Within each block, at least one endpoint must be considered statistically significant in order to make inferences in the subsequent block. • If at least one endpoint is statistically significant in the final block, inferences will be drawn from p-values for the remaining secondary and other treatment comparisons. The reference level for declaring statistical significance will depend on the results obtained from tests within the hierarchy. • If neither of the treatment comparisons in the final block is considered statistically significant, testing on the remaining secondary and other endpoints will be performed and presented for descriptive purposes only. • No adjustment for multiplicity will be made across the remaining secondary and other treatment comparisons. • In addition, pairwise comparisons of UMEC/VI and FF/VI will be performed for all endpoints. These are not adjusted for multiplicity.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were changes to the originally planned statistical analysis specified in the protocol amendment 05 (Dated: 30JUN2016) of study CTT116855 [GlaxoSmithKline Document Number 2013N176913_05].

The protocol only states that comparisons of FF/UMEC/VI with FF/VI and with UMEC/VI will be performed. In addition, comparisons of UMEC/VI with FF/VI will also be performed for all endpoints.

Additional endpoints to those mentioned in the protocol will be analyzed as listed below. These are related to protocol-defined endpoints and will be used to further characterize the effects of FF/UMEC/VI, FF/VI and UMEC/VI.

COPD Exacerbations:

- Time to first on-treatment moderate/severe exacerbation by Eosinophil subgroup (comparing FF/UMEC/VI with FF/VI)
- Time to each on-treatment moderate/severe exacerbationTime to first on-treatment severe exacerbation by Eosinophil subgroup
- Time to first on-treatment mild/moderate/severe exacerbation
- Time to first on-treatment moderate exacerbation
- Time to first on-treatment exacerbation requiring systemic/oral corticosteroids
- Time to first on-treatment exacerbation requiring antibiotics

Spirometry:

- Change from baseline in trough FEV1 by Eosinophil subgroup
- FEV1 reversibility
- Percentage of subjects with an increase from baseline in trough FEV1 ≥100mL
- Percentage of subjects with an increase from baseline in trough FEV1 ≥100mLby Eosinophil subgroup
- Change from baseline in trough Forced Vital Capacity (FVC)
- Change from baseline in post-bronchodilator FVC

All Cause Mortality:

- Time to death from any cause (on and off treatment)

SGRQ:

- Change from baseline in SGRQ Total score by Eosinophil subgroup
- Proportions of responders according to the SGRQ Total score by Eosinophil subgroup

TDI:

- TDI focal score comparing FF/UMEC/VI with UMEC/VI (note, the comparison of FF/UMEC/VI with FF/VI is in the protocol)
- TDI Focal Score by Eosinophil subgroup
- Proportion of responders according to TDI
- Proportion of responders according to TDI by Eosinophil subgroup

CAT:

- Change from baseline in COPD Assessment Test (CAT) score by Eosinophil subgroup
- Proportion of responders according to CAT score by Eosinophil subgroup

Daily Diary:

- Change from baseline in mean nighttime awakenings per night due to COPD symptoms
- Change from baseline in the percentage of days symptoms stopped usual activities

Composite Endpoints:

- Time to first event in the pneumonia AESI group and moderate/severe COPD exacerbation composite
- Time to first event in the pneumonia AESI group resulting in hospitalization, prolonged hospitalization or death and severe COPD exacerbation composite
- Time to first event in the pneumonia AESI group resulting in hospitalization, prolonged hospitalization or death, event in the CV AESI group resulting in hospitalization, prolonged hospitalization or death and severe COPD exacerbation composite

Even though some endpoints only state one treatment comparison, all treatment comparisons (FF/UMEC/VI compared with FF/VI, FF/UMEC/VI compared with UMEC/VI and UMEC/VI compared with FF/VI) will be performed and displayed for completeness for all endpoints except for J2R sensitivity analyses.

The Safety Analyses section of the protocol includes reference to analyses of time to first pneumonia and time to first hospitalization for pneumonia. The analyses are clarified in this RAP as time to first event in the 'Pneumonia' Adverse Event of Special Interest (AESI) group and time to first event in the 'Pneumonia' AESI group resulting in hospitalization, prolonged hospitalization or death.

2.2. Study Objectives and Endpoints

Objectives
Primary Objective
• To evaluate the efficacy of FF/UMEC/VI to reduce the annual rate of moderate/severe exacerbations compared with dual therapy of FF/VI or UMEC/VI in subjects with COPD
Secondary Objectives
• To evaluate the long term safety and other efficacy assessments of FF/UMEC/VI compared with dual therapy of FF/VI or UMEC/VI • To evaluate the efficacy of FF/UMEC/VI to reduce exacerbations compared with UMEC/VI in the subset population of subjects with a screening eosinophil count ≥0.15 10^9/L
Other Objectives
• To evaluate the patient perspective of the efficacy of FF/UMEC/VI in subjects with COPD • To evaluate the population pharmacokinetic (PK) profiles of FF, UMEC and VI in subjects with COPD • To collect blood samples for a genetics research study

Note: PK and genetics analyses as well as any analysis performed on the single biomarker (fibrinogen) data collected for this study will be detailed in separate RAPs.

Endpoints
Co-Primary Treatment Comparisons on the Primary Efficacy Endpoint
• Annual rate of on-treatment moderate/severe exacerbations comparing FF/UMEC/VI with UMEC/VI • Annual rate of on-treatment moderate/severe exacerbations comparing FF/UMEC/VI with FF/VI
Secondary Efficacy Endpoints and Treatment Comparisons
• Change from baseline in trough FEV1 at Week 52 comparing FF/UMEC/VI with FF/VI • Change from baseline in SGRQ Total Score at Week 52 comparing FF/UMEC/VI with FF/VI • Time to first on-treatment moderate/severe exacerbation comparing FF/UMEC/VI with FF/VI and with UMEC/VI • Annual rate of on-treatment moderate/severe exacerbations comparing FF/UMEC/VI with UMEC/VI in the subset of subjects with a blood eosinophil count ≥0.15 10^9/L • Time to first on-treatment moderate/severe exacerbation comparing FF/UMEC/VI with

Endpoints
UMEC/VI in the subset of subjects with a blood eosinophil count ≥0.15 10^9/L • Annual rate of on-treatment severe exacerbations comparing FF/UMEC/VI with FF/VI and with UMEC/VI
Other Efficacy Endpoints
• Annual rate of all on-treatment exacerbations (mild, moderate, severe) • Annual rate of on-treatment moderate exacerbations • Annual rate of on-treatment exacerbations requiring systemic/oral corticosteroids • Annual rate of on-treatment exacerbations requiring antibiotics • Annual rate of on-treatment severe exacerbations by Eosinophil subgroup (note, annual rate of on-treatment moderate/severe exacerbations comparing FF/UMEC/VI with UMEC/VI in the subset of subjects with a blood eosinophil count ≥0.15 10^9/L is a secondary endpoint) • Time to first on-treatment mild/moderate/severe exacerbation • Time to first on-treatment moderate exacerbation • Time to first on-treatment COPD exacerbation requiring systemic/oral corticosteroids • Time to first on-treatment exacerbations requiring antibiotics • Time to first on-treatment severe exacerbation • Time to first on-treatment moderate/severe exacerbation by Eosinophil subgroup (note: time to first on-treatment moderate/severe exacerbation comparing FF/UMEC/VI with UMEC/VI in the subset of subjects with a blood eosinophil count ≥0.15 10^9/L is a secondary endpoint) • Time to first on-treatment severe exacerbation by Eosinophil subgroup • Time to each on-treatment moderate/severe exacerbation • Time to each on-treatment severe exacerbation • Time to death from any cause (on-treatment only) • Time to death from any cause (on and off treatment) • Change from baseline in trough FEV1 (note, comparing FF/UMEC/VI with FF/VI at Week 52 is a secondary endpoint) • Change from baseline in trough FEV1 by Eosinophil Subgroup • Percentage of subjects with an increase from baseline in trough FEV1 ≥100mL • Percentage of subjects with an increase from baseline in trough FEV1 ≥100mL by Eosinophil Subgroup • Change from baseline in post-bronchodilator FEV1 • FEV1 reversibility • Change from baseline in trough FVC • Change from baseline in post-bronchodilator FVC • Change from baseline in SGRQ Total score (note, comparing FF/UMEC/VI with FF/VI at Week 52 is a secondary endpoint)

Endpoints

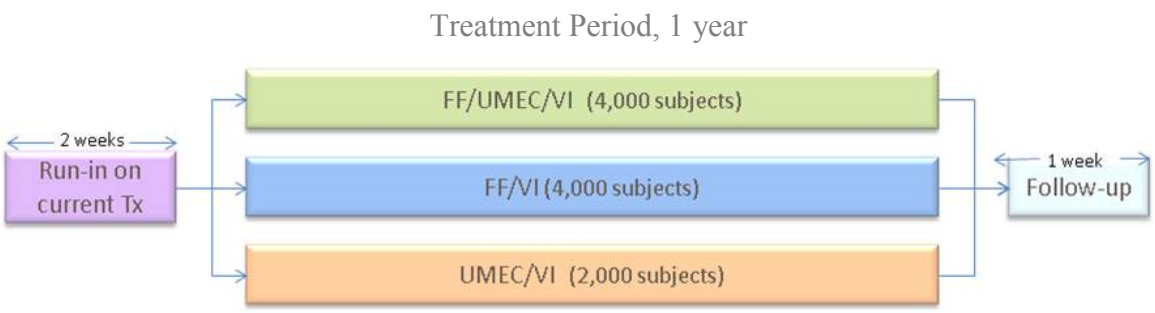
- Change from baseline in SGRQ Total score by Eosinophil Subgroup
- Proportion of responders according to the SGRQ Total score
- Proportion of responders according to the SGRQ Total score by Eosinphil Subgroup
- Change from baseline in CAT score
- Change from baseline in CAT score by Eosinophil Subgroup
- Proportion of responders according to the CAT score
- Proportion of responders according to the CAT score by Eosinophil Subgroup
- TDI focal score (in a subset of subjects)
- TDI focal score by Eosinophil Subgroup
- Proportion of responders according to TDI
- Proportion of responders according to TDI by Eosinophil Subgroup
- Subject global rating of activity limitation and subject global impression of change in activity limitation
- Subject global rating of severity of COPD and change in COPD severity
- Change from baseline in use of rescue albuterol/salbutamol (occasions/day)
- Change from baseline in percentage of rescue-free days
- Change from baseline in mean number of nighttime awakenings per night due to COPD symptoms
- Change from baseline in the percentage of days symptoms stopped usual activities

Safety Endpoints

- Incidence of adverse events (AEs). To include:
    - AEs collected on the eCRF page
    - SAEs collected on the eCRF page
    - AEs of Special Interest
    - SAE's of Special Interest
    - Fatal On-treatment AE's of Special Interest
- Adjudicated Serious Adverse Reports
- Incidence of pneumonia. To include:
    - Pneumonia details collected on the eCRF page
    - Events in the Pneumonia AEs of Special Interest Group
    - Serious events in the Pneumonia AE's of Special Interest Group
- Incidence of cardiovascular events. To include:
    - MACE
    - Events in the Cardiovascular AEs of Special Interest Group

Endpoints
• Events in the pneumonia AESI group and moderate/severe exacerbations composite • Events in the pneumonia AESI group leading to hospitalization, prolonged hospitalization or death and severe exacerbations • Events in the pneumonia AESI group resulting in hospitalization, prolonged hospitalization or death, severe exacerbation and event in the cardiovascular AESI group resulting in hospitalization, prolonged hospitalization or death • ECG measurements • Vital signs • Hematological and clinical chemistry parameters • Oropharyngeal examinations (reported as part of the AEs) • Incidence of bone fractures
• **Health Outcome Endpoints**
• EuroQol Questionnaire (EQ-5D-5L) • Healthcare resource utilization (all-cause and COPD related)

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	• This is a phase IIIa, randomized, double-blind, 3-arm parallel group, global multicenter study evaluating FF/UMEC/VI (100/62.5/25 mcg) inhalation powder versus FF/VI (100/25 mcg) inhalation powder and UMEC/VI (62.5/25 mcg) inhalation powder all given once daily in the morning. The target enrollment is 10,000 randomized subjects at approximately 1,000 study centers globally. • The total duration of subject participation will be approximately 55 weeks, consisting of a 2-week run-in period, 52-week treatment period and a 1-week safety follow-up period. • Subjects who have permanently discontinued study treatment are not required to withdraw from the study. Subjects who have permanently discontinued study treatment and have not withdrawn consent may continue in the study and complete all remaining protocol specified visits by telephone contact. This off-treatment data will be used in an assessment of the sensitivity of primary analyses to missing data as described in Section 7.3, Section 8.2.2 and Section 8.3.2. Data collected after discontinuation of study treatment may include exacerbations, serious adverse events (SAEs) and concomitant medications.
Dosing	• Study treatment will be delivered by the ELLIPTA Dry Powder Inhaler (DPI). The ELLIPTA DPI will contain 30 doses (FF/UMEC/VI or FF/VI or UMEC/VI). Subjects will be instructed to administer the ELLIPTA DPI once daily in the morning for the duration of the 52 week treatment period.

Treatment Assignment	• Following the run-in period, eligible subjects are to be randomized (2:2:1) to one of the following double-blind treatment groups for 52 weeks:
	  • FF/UMEC/VI 100/62.5/25 mcg (n=4,000)
	  • FF/VI 100/25 mcg QD (n=4,000)
	  • UMEC/VI 62.5/25 mcg QD (n=2,000)
	• The randomization schedule was generated using GlaxoSmithKline (GSK) software (RANDALL NG). The study

Overview of Study Design and Key Features	
	will use site-based randomization to allocate treatments. • Subjects will be assigned to study treatment in accordance with the randomization schedule using an Interactive Voice Response System (IVRS) (RAMOS).
Interim Analysis	• No interim analysis of unblinded data will be performed. • An IDMC will review unblinded safety data (including exacerbation data) during the conduct of the study. • Blinded review of exacerbation data for potential sample size adjustment will be performed during the recruitment period of the study.

2.4. Statistical Hypotheses

The primary purpose of this study is to evaluate the efficacy of FF/UMEC/VI to reduce the annual rate of moderate/severe exacerbations compared with dual therapy of FF/VI or UMEC/VI in subjects with COPD over a 52 week period.

The aim of this study is to demonstrate the contribution of the inhaled corticosteroid (ICS (FF)) when used in combination with a fixed dose of a long-acting beta-agonist / long-acting muscarinic receptor antagonist (LABA/LAMA (UMEC/VI)), and the contribution of the LAMA (UMEC) above the efficacy of an ICS/LABA (FF/VI) combination, in reducing the rate of on-treatment moderate/severe exacerbations in subjects with COPD.

The primary endpoint is the annual rate of on-treatment moderate/severe exacerbations (calculated from the number of moderate and severe exacerbations during the treatment period).

The primary analyses will be the pairwise comparisons of FF/UMEC/VI with FF/VI and FF/UMEC/VI with UMEC/VI, with inferences adjusted for multiplicity as described in Section 11.9. The primary analyses will be based on a two-sided hypothesis testing approach.

The hypotheses associated with the statistical test of the primary efficacy endpoint are:

H_0: $\lambda_T/\lambda_D=1$ versus H_A: $\lambda_T/\lambda_D\neq1$

where λ_T is the annual rate for triple therapy (FF/UMEC/VI) and λ_D is the annual rate for the respective dual therapies (FF/VI and UMEC/VI).

In addition the comparison of UMEC/VI with FF/VI will be presented on all analysis tables with the exception of the Jump to Reference sensitivity analyses.

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analyses will be performed.

3.2. Final Analyses

No interim analysis of unblinded data is planned for this study.

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

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final System Independent (SI) Source Data Lock has been declared by Data Management (DM).
3. Unblinded randomization schedules, container data and PK data (SI PC) are released to conversion service by Randomization coordinator
4. SI data to SDTM data conversion has been completed by the Conversion Service including unblinding activities as per Temporary Treatment Process and quality control (QC) of unblinded SDTM has been completed by DM.
5. Database freeze on unblinded SDTM datasets has been declared by DM.
6. Study is unblinded
    - Randomization schedules and container data are released in RANDALL NG.
    - SMS2000 data is released in HARP

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Subjects Enrolled (ASE)	• Comprised of all subjects for whom a record exists on the study database, including screened subjects and subjects who were not screened but signed an ICF.	• Subject disposition • SAEs for non-randomized subjects
Intent-to-Treat (ITT)	• Comprised of all randomized subjects, excluding those who were randomized in error who did not receive a dose of study medication. A subject who is recorded as a screen or run-in failure and also randomized, but did not receive a dose of study treatment, 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 • Safety • Health outcomes
Pre-dose ECG	• Comprised of all subjects in the ITT	• Study Population

Population	Definition / Criteria	Analyses Evaluated
(ECG)	population from sites included in the ECG substudy who performed an on-treatment pre-dose ECG assessment at Week 4.	• ECG
TDI (TDI)	• Comprised of all subjects in the ITT population who completed a pre-dose BDI assessment at Day 1.	• Study Population • BDI/TDI

NOTES :
- Refer to Section 11.12 which details the population to be used for each data display 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

- PDs will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (PDMP) and updated throughout the course of the study.
- Data will be reviewed prior to SDL to ensure all important deviations are captured and categorized in the protocol deviations dataset.
- Subjects who received an incorrect treatment container will be captured as an important protocol deviation. Whether or not the incorrect container contained incorrect treatment will be identified following DBF in the Analysis Data Model (ADaM) dataset and the PD will be flagged accordingly.
- Important protocol deviations (as identified in the PDMP) will be summarized and listed.
- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the electronic case report form (eCRF).

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Handling of Data from Subset Populations

Certain subsets of subjects will undergo the following additional procedures during the study: BDI/TDI, PK blood draws, and/or an additional pre-dose ECG at Week 4. These subsets are not mutually exclusive.

In addition, a blood eosinophil subgroup will be derived based on the baseline blood eosinophil count (detailed in Section 11.4.1.3).

Separate populations will be defined for the TDI and pre-dose ECG analysis as described in this RAP in Section 4. The PK analysis population will be described in a separate RAP. Any analysis performed on the pharmacogenetic or single biomarker data collected for this study will be detailed in a separate analysis plan.

5.2. Handling of Data Collected After Study Treatment Discontinuation

Subjects who have permanently discontinued study treatment are not required to withdraw from the study. Subjects who have permanently discontinued study treatment and have not withdrawn consent may continue in the study and complete all remaining protocol specified visits by telephone contact. Data collected after discontinuation of study treatment may include exacerbations (off-treatment efficacy data), SAEs (post-treatment safety data) and concomitant medications (post-treatment study population data). Subjects who have permanently discontinued study treatment and are continuing in the study are allowed to use any medications prescribed by the Investigator or their treating physician.

This off-treatment exacerbation data will be used in the exacerbation sensitivity analyses for assessing the effect of missing data on study conclusions and in summaries of off-treatment exacerbation data. A detailed description of the sensitivity analyses for exacerbations is provided in Section 7.3 and Section 8.3.2.

Post-treatment study population and safety data will be summarized as described in Section 6 and Section 9.2.

5.3. Overview of Appendices

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
11.1	Appendix 1: Time & Events
11.2	Appendix 2: Assessment Windows
11.3	Appendix 3: Treatment States and Phases
11.4	Appendix 4: Data Display Standards and Handling Conventions
11.5	Appendix 5: Derived and Transformed Data
11.6	Appendix 6: Handling of Missing Data
11.7	Appendix 7: Multicenter Studies
11.8	Appendix 8: Examination of Covariates, Subgroups & Other Strata
11.9	Appendix 9: Handling Multiple Comparisons and Multiplicity
11.10	Appendix 10: Model Checking and Diagnostics for Statistical Analysis
11.11	Appendix 11: Abbreviations & Trademarks
11.12	Appendix 12: List of Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population outputs will be based on the ITT population unless otherwise stated.

Table 2 provides an overview of the planned study population outputs, with the detailed list of data displays being presented in Section 11.12.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Study Populations and Reasons for Screen Failures	Y[1]		Y[1]
Clinic Visits (Clinic Attendance/Phone Contact)	Y		
Study Treatment Status	Y	Y[5]	Y
End of Study Record	Y	Y[5]	Y
Number of Subjects Enrolled	Y[6]		
Inclusion and Exclusion Criteria Deviations	Y[7]		Y[7]
Important Protocol Deviations	Y		Y
Demography			
Demographic Characteristics	Y[2,3,4,8]		Y
Race and Racial Combinations	Y[2,3,4]		Y
Medical Conditions			
Medical Conditions (Current/Past)	Y[2,3]		
Cardiovascular Risk Factors	Y[2,3]		
Family History of Cardiovascular Risk Factors	Y[2,3]		
Smoking History at Screening	Y[2,3]		
Smoking Status	Y[2,3]		
Pneumonia Risk Factors at Screening	Y[2]		
Disease Characteristics			
COPD Duration	Y[2]		Y
COPD Exacerbation History	Y[2,8]		Y
Screening Lung Function	Y[2,8]		
Reversibility and GOLD Grade(1-4) at Screening	Y[2,8]		
CAT Score at Screening	Y[2]		
Shift in CAT Score Category from Screening to Baseline	Y[2]		
Pulse Oximetry			
Percent Oxygen in Blood	Y		
Concomitant Medications			
COPD Medications	Y[9]		Y
COPD Medication Combination at Screening	Y[2,8]		
COPD Medication Combination at IP Discontinuation	Y		
COPD Medication Combination at IP Discontinuation for those Subjects Providing Off-treatment Information	Y		
Pneumonia and Influenza Vaccines Taken at Any Time up to the End of Study Treatment	Y		
Non-COPD Medications	Y[10]		

Display Type	Data Displays Generated		
	Table	Figure	Listing
Treatment Compliance			
Treatment Compliance	Y		
Study Population Listings			
Randomized and Actual Treatments by Country and Center			Y
Treatment Blind Broken During Study			Y
Study Treatment Misallocations			Y

NOTES :

Y = Yes display generated.

1. ASE population
2. Repeat for Eosinophil subgroup
3. Repeat for ECG population
4. Repeat for TDI population
5. Kaplan-Meier plot displaying FF/UMEC/VI, FF/VI and UMEC/VI and repeated displaying FF/VI and UMEC/VI only.
6. By country (ASE population); by age category (ASE population); by geographical region, country and center (ITT, ECG and TDI)
7. Screen failures (ASE population) and ITT population separately
8. Repeat by country (ITT population)
9. Prior to screening and then also Run-in/On-treatment/Post-treatment given for reasons other than an exacerbation and On-treatment/Post-treatment given for an exacerbation separately.
10. On-treatment/Post-treatment

6.1.1. Disposition

The study population summary will show the number of subjects who were enrolled, pre-screen failures, screen failures and the number with each reason for screen failure. In addition it will also show the number of subjects in each treatment group and overall who were randomized, in the ITT population, pre-dose ECG population, TDI population and each level of the Eosinophil subgroup.

The end of study record summary will show 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 will show 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 treatment discontinuation.

6.1.2. Disease Characteristics

The screening lung function summary will include pre-bronchodilator and post-bronchodilator 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). These assessments, with the exception of pre-bronchodilator FEV1/FVC ratio and pre-bronchodilator FEV1 as a percentage of predicted normal, will be collected in the eCRF and no recalculation of these values will be performed. Pre-bronchodilator FEV1/FVC ratio and pre-bronchodilator FEV1 as a percentage of predicted normal will be derived as

defined in Section 11.4.2 and Section 11.5.2.9. The reversibility to salbutamol status (Reversible or Non-reversible) will also be summarized as defined in Section 11.5.2.9.

COPD exacerbation history at screening (see Section 11.5.2.8) will be summarized with frequency distributions (0, 1, 2, ≥3 and ≥2) of the number of moderate exacerbations, the number of severe exacerbations, the number of moderate/severe exacerbations, the number of exacerbations treated with systemic/oral corticosteroids (with or without antibiotics), and the number of exacerbations treated with antibiotics (with or without systemic/oral corticosteroids). For each moderate/severe exacerbation the severity, duration, whether the exacerbation led to hospitalization, systemic/oral corticosteroids being taken and antibiotics being taken will be summarized. See Section 11.5.2.8 for the definition of exacerbation severity.

6.1.3. Concomitant Medications

COPD concomitant medications that have been stopped greater than three months prior to Visit 1 and non-COPD concomitant medications that have been stopped prior to randomization will not be included in any summary tables with the exception of the concomitant medications included in the summary of influenza and/or pneumonia vaccines.

A summary of the number and percentage of subjects having received an influenza and/or pneumonia vaccine anytime on or before the study treatment stop date will also be presented.

Non-COPD medication tables will report by Anatomical Therapeutic Chemical (ATC) level 1 classification and ingredient. COPD medication tables will report by respiratory medication class (RMC) and ingredient (See Section 11.5.2.6).

Multi-ingredient non-COPD medications will be presented according to their combination ATC classification rather than the classifications 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 and IP discontinuation (for all subjects and separately for subjects that provide post-study treatment information and defined in Section 11.3.1 and Section 11.5.2.6) will be presented.

6.1.4. Treatment Compliance

Calculation of treatment compliance will be based on the ELLIPTA DPI dose counter (which displays the number of doses remaining) as described in Section 11.5.2.3. Percentage of compliance will be summarized categorically and with descriptive statistics.

6.1.5. Percent Oxygen in Blood

Percent oxygen in blood will be measured pre-dose at Visit 2 and will be summarized with descriptive statistics.

7. PRIMARY EFFICACY STATISTICAL ANALYSES

7.1. Overview of Planned Efficacy Analyses for the Primary Endpoint

The co-primary treatment comparisons are the pairwise treatment comparisons of FF/UMEC/VI against FF/VI and FF/UMEC/VI against UMEC/VI for the annual rate of on-treatment moderate/severe exacerbations. The primary analyses detailed below will be based on the ITT population using data collected on-treatment.

Table 3 provides an overview of the planned primary efficacy analyses, with the detailed list of data displays presented in Section 11.12.

Table 3 Overview of Planned Efficacy Analyses

	Absolute						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
COPD Exacerbations							
Primary Analyses: Annual Rate of on-treatment Moderate/Severe Exacerbations	Y[3]	Y[4]		Y[1]	Y[5]		
On-treatment Moderate/Severe Exacerbations Details				Y			Y[2]
Supportive Analysis: On-treatment Moderate/Severe Exacerbations – Negative Binomial Analysis with Interaction Terms	Y						
Sensitivity Analyses: Moderate/Severe Exacerbations, Including Off-treatment Data – Negative Binomial Analysis	Y	Y[4]					
Sensitivity Analyses: On-treatment Moderate/Severe Exacerbations, imputing data following FF/UMEC/VI discontinuation using jump to reference assumption– Negative Binomial Analysis	Y[6]	Y[4]					
Sensitivity Analyses: On and Off-treatment Moderate/Severe Exacerbations, imputing data following FF/UMEC/VI discontinuation using jump to reference assumption– Negative Binomial Analysis	Y[6]	Y[4]					

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. Repeat by country for the summary of exacerbation data only.
2. Listing will include all reported exacerbations
3. Negative binomial regression model; repeat with Poisson regression model
4. Plot of moderate/severe adjusted exacerbation rate ratios as a separate plot for the primary analyses. Rate ratios from both the primary and all sensitivity analyses to be included as a forest plot.
5. Box plot of annual exacerbation raw rates (see Section 11.5.3.1 for derivations of individual subject raw COPD exacerbation rate)

6. This analyses will be performed twice; once using FF/VI as the reference group and a second time using UMEC/VI as the reference group

7.1.1. COPD Exacerbations

The definition of exacerbation severity (mild, moderate, severe) is provided in Section 11.5.3.1. The classification of on-treatment and off-treatment exacerbation is also provided in Section 11.3.3.

For the primary analysis of moderate/severe exacerbations, missing data will not be imputed. For statistical analysis, the response variable will be the number of recorded, on-treatment, moderate and severe exacerbations. The number and severity of exacerbations will be based on assessments as recorded in the eCRF. Symptom data recorded on the daily eDiary and concomitant medication use will not be used to determine exacerbations. The method of statistical analysis will also incorporate the length of time that each subject was at risk of an exacerbation.

Summaries of recorded, on-treatment exacerbations will be provided. Details of the exacerbations to be summarized overall and by country includes the number and percent of subjects reporting an exacerbation (by severity; moderate, severe and moderate/severe), number and percent of subjects with each number of moderate/severe exacerbations (0, 1, 2, ≥3), the number of subjects with ≥2 moderate/severe exacerbations, the total number of exacerbations per treatment and annual raw exacerbation rate. For each exacerbation, the outcome, severity, duration, whether the exacerbation led to hospitalization, systemic/oral corticosteroids being taken, antibiotics being taken, and emergency room visit will be summarized. For calculation of the raw exacerbation rate, see Section 11.5.3.1.

7.2. Planned Primary Statistical Analyses for Primary Endpoint

Primary Statistical Analyses
Endpoint(s)
• Annual rate of on-treatment moderate/severe exacerbations comparing FF/UMEC/VI with FF/VI • Annual rate of on-treatment moderate/severe exacerbations comparing FF/UMEC/VI with UMEC/VI
Model Specification

• Generalized linear model assuming a negative binomial distribution
• Terms in the model:
  • **Response**: number of recorded, on-treatment, moderate/severe exacerbations experienced per subject.
  • **Categorical**: treatment group, gender, exacerbation history (≤1, ≥2 moderate/severe), smoking status (screening), geographical region
  • **Continuous**: post-bronchodilator % predicted FEV1 (Screening)
  • **Offset**: As defined in Section 11.5.3.1

Model Checking & Diagnostics
• Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analysis

Primary Statistical Analyses
Model Results Presentation
• Treatment group model estimated exacerbation rates and associated 95% confidence intervals (CI), pairwise treatment rate ratios and associated 95% CIs will be presented. The pairwise treatment percent reductions in annual exacerbation rate and associated 95% CIs will also be presented in the same table. • Both adjusted (accounting for the Hochberg multiplicity adjustment, see Section 11.9) and unadjusted p-values will be presented for the pairwise treatment comparisons of FF/UMEC/VI versus FF/VI, FF/UMEC/VI versus UMEC/VI. Unadjusted p-values will be presented for UMEC/VI versus FF/VI. • The pairwise treatment rate ratios and associated 95% CIs for FF/UMEC/VI versus FF/VI and FF/UMEC/VI versus UMEC/VI will also be presented graphically
Example of SAS Code
proc genmod data=dsetin; *class trtcd gender exachis smk region;* *model no_exac = trtcd gender exachis smk pctpredFEV region* */ dist=negbin link=log offset=log_tm wald type3;* *[note: both contrast and estimate statements will be used for the pairwise comparisons]* *lsmeans trtcd / cl diff om;* *run;*

7.3. Planned Supportive and Sensitivity Statistical Analyses

7.3.1. Supportive Analyses

7.3.1.1. Poisson Model

A supportive analysis will be performed whereby the number of on-treatment moderate/severe exacerbations will be analyzed using a Poisson regression model with deviance over-dispersion correction. The model specification and presentation of results will be the same as that with the negative binomial regression analysis.

Supportive Statistical Analyses – Poisson Model
Endpoint(s)
• Annual rate of on-treatment moderate/severe exacerbations comparing FF/UMEC/VI with FF/VI • Annual rate of on-treatment moderate/severe exacerbations comparing FF/UMEC/VI with UMEC/VI
Model Specification
• Generalized linear model assuming a Poisson distribution • As defined in Section 7.2
Model Checking & Diagnostics
• Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analysis
Model Results Presentation
• As defined in Section 7.2. • Note, only unadjusted p-values will be displayed.
Example SAS code
• Poisson regression:

Supportive Statistical Analyses – Poisson Model
proc genmod data=dsetin; class trtcd gender exachis smk region subjid; model no_exac = trtcd gender exachis smk pctpredFEV region / dist=poisson link=log offset=log_tm type3 lrci; [note: both contrast and estimate statements will be used for the pairwise comparisons] lsmeans trtcd /cl diff om; run;

7.3.1.2. Investigation of Interactions

The interactions between treatment and other factors (gender, exacerbation history, smoking status, region, percent predicted FEV1) will be investigated.

Supportive Statistical Analyses – Interactions
Endpoint(s)
• Annual rate of on-treatment moderate/severe exacerbations
Model Specification
• The interactions between treatment and other factors will be investigated as follows by adding interaction terms to the negative binomial regression model as defined in Section 7.2 • Separate negative binomial models will be fitted to investigate the effect of treatment by covariate interactions: (i) with the addition of an interaction term for treatment by gender; (ii) with the addition of an interaction term for treatment by exacerbation history; (iii) with the addition of an interaction term for treatment by smoking status; (iv) with the addition of an interaction term for treatment by geographical region and (v) with the addition of an interaction term for treatment by post-bronchodilator percent predicted FEV1 (Screening).
Model Checking & Diagnostics
• Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analysis
Model Results Presentation
• The p-value for each interaction test will be presented. • If any interaction p-value is less than 0.10 further investigations will be carried out, for example running the analysis by each category of the subgroup. Interaction p-values and any output from interaction investigation will be presented.

7.3.2. Sensitivity Analyses – Investigating Missing Data

7.3.2.1. Including both On and Off-treatment Data

The negative binomial regression model will be rerun to include both on- and off-treatment moderate/severe exacerbations as the response variable. The analysis will include all post-randomization (on-treatment and off-treatment, see Section 11.3.3) moderate/severe exacerbations.

Supportive Statistical Analyses – Including Both On and Off-treatment Data
Endpoints
• Annual rate of moderate/severe exacerbations comparing FF/UMEC/VI with FF/VI • Annual rate of moderate/severe exacerbations comparing FF/UMEC/VI with UMEC/VI

Supportive Statistical Analyses – Including Both On and Off-treatment Data
Model Specification
• As defined in Section 7.2
Model Checking & Diagnostics
• Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analysis
Model Results Presentation
• As defined in Section 7.2 • Note, only unadjusted p-values will be displayed.

7.3.2.2. Jump to Reference (J2R) - Using On-treatment Data

On-treatment exacerbations will be analysed in a sensitivity analysis to examine the robustness of the exacerbation analysis to departures from the implicit assumption that missing data is missing-at-random (MAR).

Subjects that have prematurely withdrawn from study treatment will have their "missing" data from the date of the end of study treatment up to their projected Week 52 date (see Section 11.5.1.4) imputed and analysed.

The (unconditional) jump-to-reference (J2R) multiple imputation method is based on pattern mixture models [Keene et al, 2014], and uses two assumptions about the imputed exacerbations during the "unobserved" period: 1) exacerbations in all treatment groups during the "unobserved" period are imputed using model estimates from the 'reference' treatment group, 2) the imputed exacerbations are computed using the subject's baseline characteristics (their model covariates), but this estimate is *not* conditioned on the observed data.

First the on-treatment negative binomial analysis is run so that samples of all the model parameters i.e. the estimated "betas" associated with treatment, gender, exacerbation history etc., and the estimated dispersion parameter can be taken (from their joint posterior distribution). From each sample, it is possible to construct a mean for any subjects with "missing" data. This mean together with the estimated dispersion parameter makes it possible to sample from the negative binomial distribution for the number of exacerbations "experienced" by the subject during their unobserved period.

The counts from the unobserved period are added to the counts from the observed period and the full data set will be analysed up to Week 52 for each sample. The results from the analyses of each sample are combined using Rubin's formulae [Rubin, 87] as implemented in PROC MIANALYZE in SAS.

Jump-to-reference might be considered a worst case scenario which is likely to give a conservative estimate of treatment effect because the missing data is assumed to follow the same 'reference pattern' in all subjects regardless of their study treatment.

This J2R sensitivity analysis will be repeated twice, once using the FF/VI treatment group as the reference, and once using the UMEC/VI treatment group as the reference. However note that in both models, data from all treatment groups will be used in the model, but only one comparison will be presented.

Supportive Statistical Analyses – Jump to Reference
Endpoint(s)
• Annual rate of on-treatment + imputed moderate/severe exacerbations (FF/VI as reference). • Annual rate of on-treatment +imputed moderate/severe exacerbations (UMEC/VI as reference)
Model Specification
• Covariates defined in Section 7.2. Analysis described above.
Model Checking & Diagnostics
• Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analysis
Model Results Presentation
• As defined in Section 7.2. • Note, only unadjusted p-values will be displayed. • Although all subjects will contribute to the models, only a comparison of FF/UMEC/VI and FF/VI will be presented for the FF/VI as reference analysis, and only a comparison of FF/UMEC/VI and UMEC/VI will be presented for the UMEC/VI as reference analysis

7.3.2.3. Jump to Reference (J2R) - Using On and Off-treatment Data

All exacerbations (on and off-treatment) will be analysed with a J2R missing data sensitivity analysis as for on-treatment exacerbations. Here however, the unobserved period will be defined for subjects that prematurely withdraw from the study from the date of study conclusion up to the projected Week 52 date (see Section 11.5.1.4). Thus, all exacerbations observed in the study will be included in this analysis, not just on-treatment exacerbations.

8. SECONDARY EFFICACY STATISTICAL ANALYSES

8.1. Overview of Planned Efficacy Analyses for Secondary Endpoints

The secondary efficacy analyses will be based on the ITT population. Since off-treatment data was not collected for Trough FEV1 and SGRQ, all analyses for these endpoints will use on-treatment data only.

Table 4 provides an overview of the planned secondary efficacy analyses, with the detailed list of data displays being presented in Section 11.12.

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
Trough FEV1														
Baseline FEV1				Y			Y							
Trough FEV1	Y[1]			Y			Y	Y[1]	Y[2,13]		Y			Y
Sensitivity Analysis: Trough FEV1, imputing data following FF/UMEC/VI	Y[10]							Y[10]	Y[11]					

	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
discontinuation using jump to reference assumption														
SGRQ Total Score														
Baseline SGRQ Scores				Y			Y							
SGRQ Total Score	Y[1]			Y[9]			Y[9]	Y[1]	Y[2,13]		Y[9]	Y[3]		Y[9]
SGRQ Individual Item Responses							Y							
Sensitivity Analysis: SGRQ Total Score, imputing data following FF/UMEC/VI discontinuation using jump to reference assumption	Y[10]							Y[10]	Y[11]					
COPD Exacerbations														
Time to First On-treatment Moderate/Severe Exacerbation	Y[4]	Y[6]		Y	Y[5]									
Sensitivity Analysis: Time to First Moderate/Severe Exacerbation Including Off-treatment Data	Y[4]	Y[12]			Y[5]									
Sensitivity Analysis: Time to First On-treatment Moderate/Severe Exacerbation or treatment discontinuation	Y[4]	Y[12]			Y[5]									
Time to First On-treatment Moderate/Severe Exacerbation by Eosinophil Subgroup	Y[4]	Y[6]		Y	Y[5]									
Annual Rate of On-treatment Moderate/Severe Exacerbations by Eosinophil Subgroup	Y[7]	Y[8]												

	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
Annual Rate of On-treatment Severe Exacerbations	Y[7]	Y[8]		Y										

NOTES :

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

1. Mixed Models Repeated Measures (MMRM) analysis
2. Least squares (LS) means (95% CI) change from baseline and LS mean (95% CI) treatment differences
3. Box plot and empirical distribution function plot at Week 52
4. Cox proportional hazards analysis
5. Kaplan-Meier plot displaying FF/UMEC/VI, FF/VI and UMEC/VI and repeated displaying FF/VI and UMEC/VI only
6. Plot of hazard ratios (95% CI)
7. Negative binomial regression model
8. Plot of on-treatment adjusted exacerbation rate ratios
9. Summary and listing will include all individual SGRQ domain scores as well as the SGRQ total score
10. Analysis of Covariance (ANCOVA). This analyses will be performed twice; once using FF/VI as the reference group and a second time using UMEC/VI as the reference group
11. LS mean (95% CI) treatment differences at Week 52 for both the primary and all sensitivity analyses for each endpoint separately to be included as a forest plot
12. Hazard ratios (95% CI) for both the primary analyses and all sensitivity analyses to be included as a forest plot
13. Additional plot of LS means (95% CI) change from baseline for UMEC/VI and FF/VI treatment groups only

8.2. Trough FEV1 and SGRQ Total Score

8.2.1. Planned Primary Statistical Analyses for Trough FEV1 and SGRQ Total Score

Secondary Statistical Analyses
Endpoint(s)
• Change from baseline in trough FEV1 • Change from baseline SGRQ total score
Model Specification
• Mixed Models Repeated Measures (MMRM) model. • While missing data are not explicitly imputed in the primary MMRM analyses, there is an underlying assumption that the data are missing at random. All available scheduled post-baseline assessments will be utilized and via modeling of the within-subject correlation structure, the derived treatment differences will be adjusted to take into account missing data. • The MMRM analysis for trough FEV1 will include on-treatment FEV1 measurements at Weeks 4, 16, 28, 40 and 52. The MMRM analysis for SGRQ total score will include on-treatment SGRQ total scores at Weeks 4, 28 and 52. • Although the secondary endpoints are Change from baseline in trough FEV1 at Week 52 for

Secondary Statistical Analyses

FF/UMEC/VI vs. FF/VI and Change from baseline in SGRQ total Score at Week 52 for FF/UMEC/VI vs. FF/VI, results for all treatment comparisons at all time points where data are scheduled to be collected will be included in the analysis and presented in the displays.

- Terms in the model:
  - **Response**: trough FEV1 or SGRQ Total score at each visit.
  - **Categorical**: treatment group, smoking status (screening), geographical region, visit
  - **Continuous**: baseline FEV1 or baseline SGRQ Total score
  - **Interaction:** baseline*visit, treatment group*visit
  - **Repeated**: visit
- The model will be fit with an unstructured variance-covariance matrix.
- 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.
- Baseline is defined in Section 11.4.2
- Two models will be fitted; one with a response variable of change from baseline and one with the response variable as the raw value.

Model Checking & Diagnostics

- Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analysis.

Model Results Presentation

- Least-square (LS) means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors as well as 95% CIs. The estimated treatment difference along with corresponding standard error, 95% CI for each Week will be presented.
- Both adjusted (accounting for the Hochberg multiplicity adjustment, see Section 11.9) and unadjusted p-values will be presented for the pairwise treatment comparison at Week 52 of FF/UMEC/VI versus FF/VI. Unadjusted p-values only will be presented at other visits for the comparison of FF/UMEC/VI versus FF/VI and at all visits for the treatment comparisons of FF/UMEC/VI versus UMEC/VI and UMEC/VI versus FF/VI.
- The LS mean treatment differences (and associated 95% CIs) for all weeks will also be presented graphically for FF/UMEC/VI versus FF/VI and FF/UMEC/VI versus UMEC/VI.
- The LS mean change from baseline values (and 95% CIs) for the three treatment groups across weeks will be presented and repeated displaying the FF/VI and UMEC/VI treatment groups only.

Example SAS Code

```
proc mixed data=dsetin;
    class trtcd visit subjid smk region;
    model endpoint=trtcd baseline smk region visit visit*baseline visit*trtcd / ddfm =kr;
    repeated visit / subject=subjid type=un;
    lsmeans trtcd*visit / cl diff e om=OMdset at (baseline)=(&blm.);
    ods output lsmeans=lsmeans;
    ods output diffs=diffs;
```

Secondary Statistical Analyses
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.]

8.2.2. Planned Sensitivity Statistical Analyses for Trough FEV1 and SGRQ Total Score

8.2.2.1. Jump to Reference - Using On-treatment Data

On-treatment trough FEV1 will be analysed in a sensitivity analysis to examine the robustness of the FEV1 analysis to departures from the implicit assumption that missing data is missing-at-random (MAR).

Subjects with missing on-treatment FEV1 data will have their "missing" data imputed and the Week 52 data (actual or imputed) will be analysed.

The jump-to-reference (J2R) multiple imputation method is based a pattern mixture model fully described by [Carpenter et al, 2013].

First the on-treatment MMRM analysis is run so that samples of all the model parameters i.e. the estimated "betas" associated with treatment, gender, exacerbation history, etc., and the estimated variance and covariance parameters can be taken (from their joint posterior distribution). From each sample it is possible to construct a mean for any subjects with "missing" data. In the J2R method, the mean estimate is constructed using the estimated beta associated with the reference treatment, as well as all the subject's other covariates. This estimated mean together with the sampled estimated variance parameters makes it possible to sample from a normal distribution for the trough FEV1 at a particular missing visit. First however, the unconditional distribution is updated using the appropriate conditional distribution algebra and the subject's own observed data. Then the sample is taken using the conditional normal distribution parameters.

The Week 52 data from each sample (imputed for some subjects, and non-missing for most subjects) is analysed using an ANCOVA model using the same covariates as the original model of FEV1 (with the exception of the visit covariate and its interactions). The results from the analyses of each sample are combined using Rubin's formulae [Rubin, 1987] as implemented in PROC MIANALYZE in SAS.

Jump-to-reference might be considered a worst case scenario which is likely to give a conservative estimate of treatment effect because the missing data is assumed to follow the same 'reference pattern' in all subjects regardless of their study treatment.

This J2R sensitivity analysis will be repeated twice, once using the FF/VI treatment group as the reference, and once using the UMEC/VI treatment group as the reference. However note that in both models, data from all treatment groups will be used in the model, but only one comparison will be presented.

SGRQ will be analysed in exactly the same way.

Sensitivity Statistical Analyses – Jump to Reference
Endpoint(s)
• Change from baseline in trough FEV1 • Change from baseline SGRQ total score
Model Specification, Checking & Diagnostics, Results Presentation and SAS Code
• Analysis of Covariance (ANCOVA) model using data generated from multiple imputation methods and the same covariates as the original model (except visit and its interactions). • Analysis model and results presentation will be the same as described in Section 8.2.1, but imputing for missing data as described above using the Jump to Reference method and only presenting unadjusted p-values.

8.3. Time to First COPD Moderate/Severe Exacerbation

8.3.1. Planned Primary Statistical Analyses for Time to First On-treatment Moderate/Severe Exacerbation

Secondary Statistical Analyses
Endpoint
• Time to first on-treatment moderate/severe exacerbation
Model Specification

• Cox's proportional hazards model
 	
• Terms in the model:
  • **Response**: time to first on-treatment, moderate/severe exacerbation
  • **Categorical**: treatment group, gender, exacerbation history (≤1, ≥2 moderate/severe), smoking status (screening), geographical region
  • **Continuous**: post-bronchodilator % predicted FEV1 (Screening)
 	
• The 'exact' method will be used for handling ties. If the analysis will not run using the 'exact' method, then the 'Efron' method for handling ties will be used instead.
 	
• Kaplan-Meier survivor functions will be obtained for each treatment group using PROC LIFETEST with a TIME statement.

Model Checking & Diagnostics
• Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analysis
Model Results Presentation
• Hazard ratios and the percent reduction in risk for the pairwise treatment comparisons with associated 95% CIs and p-values will be presented. • Both adjusted (accounting for the Hochberg multiplicity adjustment, see Section 11.9) and unadjusted p-values will be presented for the pairwise treatment comparisons of FF/UMEC/VI versus FF/VI and FF/UMEC/VI versus UMEC/VI. Only unadjusted p-values will be presented for the treatment comparison of UMEC/VI versus FF/VI. The probability of having a moderate/severe exacerbation, 95% CI and first quartile and median time to exacerbation for each treatment group will be presented. • The Kaplan-Meier curves will be presented showing the probability of having an event over

time for each treatment group separately plotted on the same figure. This will be repeated displaying UMEC/VI and FF/VI only.
Example SAS Code
proc phreg data=dsetin; *class trtcd smk region exachis gender;* *model timeto1*eventflag(0) = trtcd smk region gender pctpredFEV exachis/ risklimits ties=exact;* *hazardratio trtcd / diff=all;* *run;* *proc lifetest data=destin outsurv=survest;* *time timeto1*eventflag(0);* *strata trtcd;* *run;*

8.3.2. Planned Sensitivity Statistical Analyses for Time to First On-treatment Moderate/Severe Exacerbation

8.3.2.1. Time to First Moderate/Severe Exacerbation Including Off-treatment Data

Secondary Statistical Analyses
Endpoint
• Time to first moderate/severe exacerbation including off-treatment data
Model Specification
• As specified in Section 8.3.1
Model Checking & Diagnostics
• Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analysis.
Model Results Presentation
• As specified in Section 8.3.1 • Note, only unadjusted p-values will be displayed.

8.3.2.2. Time to First On-treatment Moderate/Severe Exacerbation or Premature Treatment Discontinuation

Secondary Statistical Analyses
Endpoint
• Time to first on-treatment moderate/severe exacerbation or premature treatment discontinuation (See Section 11.5.3.1)
Model Specification
• As specified in Section 8.3.1
Model Checking & Diagnostics
• Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analysis.
Model Results Presentation
• As specified in Section 8.3.1 • Note, only unadjusted p-values will be displayed.

8.4. Time to First On-treatment Moderate/severe Exacerbation by Eosinophil Subgroup

Secondary Statistical Analyses

Endpoint

- Time to first on-treatment moderate/severe exacerbation by Eosinophil Subgroup

Model Specification

- Cox's proportional hazards model
- Terms in the model:
  - **Response**: time to first on-treatment, moderate/severe exacerbations
  - **Categorical**: treatment group, gender, exacerbation history (≤1, ≥2 moderate/severe), smoking status (screening), geographical region, EOS subgroup
  - **Continuous**: post-bronchodilator % predicted FEV1 (Screening)
  - **Interaction**: treatment group*EOS subgroup
- The 'exact' method will be used for handling ties. If the analysis will not run using the 'exact' method, then the 'Efron' method for handling ties will be used instead.
- Kaplan-Meier survivor functions will be obtained for each treatment group using PROC LIFETEST with a TIME statement.

Model Checking & Diagnostics

- Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analysis.

Model Results Presentation

- Hazard ratios (percent reduction in risk) for pairwise treatment comparisons, within each level of eosinophil subgroup, with associated 95% CIs and unadjusted p-values will be presented.
- The probability of having a moderate/severe exacerbation, 95% CI and first quartile and median time to exacerbation for each treatment group within each level of eosinophil subgroup will be presented.
- The Kaplan-Meier curves will be presented showing the probability of having an event over time for each treatment group separately plotted on the same figure. This will be repeated for each level of the eosinophil subgroup. This will be repeated displaying the FF/VI and UMEC/VI treatment groups only.

Example SAS Code

```
proc phreg data=dsetin;
      class trtcd smk eosinsubgroup region exachis gender;
      model timeto1*eventflag(0) = trtcd gender exachis smk region eosinsubgroup pctpredFEV
      trtcd*eosinsubgroup / risklimits ties=exact;
      [note: contrast statements will be used for the pairwise comparisons];
run;

proc lifetest data=destin outsurv=survest;
     time timeto1*eventflag(0);
    strata trtcd eosinsubgroup;
run;
```

8.5. Annual Rate of On-treatment Severe Exacerbations

Secondary Statistical Analyses
Endpoint(s)
• Annual rate of on-treatment severe exacerbations
Model Specification, Checking & Diagnostics, Results, Presentation and SAS Code
• This endpoints will be analyzed using the same methodology as the primary analysis of annual rate of moderate/severe exacerbations in Section 7.2 • Note, only unadjusted p-values will be displayed.

8.6. Annual Rate of On-treatment Moderate/severe Exacerbations by Eosinophil Subgroup

Secondary Statistical Analyses
Endpoint(s)
• Annual rate of on-treatment moderate/severe exacerbations by Eosinophil Subgroup
Model Specification

• Generalized linear model assuming a negative binomial distribution
 	
• Terms in the model:
  • **Response**: number of recorded, on-treatment, moderate/severe exacerbations experienced per subject.
  • **Categorical**: treatment group, gender, exacerbation history (≤1, ≥2 moderate/severe), smoking status (screening), geographical region, EOS subgroup
  • **Continuous**: post-bronchodilator % predicted FEV1 (Screening)
  • **Interaction**: treatment*EOS subgroup
  • **Offset**: As defined in Section 11.5.3.1

Model Checking & Diagnostics
• Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analysis
Model Results Presentation
• Treatment group model estimated exacerbation rates and associated 95% CIs, pairwise treatment rate ratios and associated 95% CIs and unadjusted p-values will be presented for each level of subgroup. The pairwise treatment percent reductions in annual exacerbation rate and associated 95% CIs will also be presented in the same table. • The pairwise treatment rate ratios for FF/UMEC/VI versus FF/VI and FF/UMEC/VI versus UMEC/VI and associated 95% CIs will also be presented graphically for each level of subgroup.
Example of SAS Code
proc genmod data=dsetin; *class trtcd gender exachis smk region eosinsubgroup;* *model no_exac = trtcd gender exachis smk pctpredFEV region eosinsubgroup* *trtcd*eosinsubgroup / dist=negbin link=log offset=log_tm wald type3;* *[note: both contrast and estimate statements will be used for the pairwise comparisons]* *lsmeans trtcd*eosinsubgroup / cl diff om;* *run;*

9. OTHER STATISTICAL ANALYSES

9.1. Other Efficacy and Health Outcomes Analyses

9.1.1. Overview of Planned Efficacy and Health Outcomes Analyses for Other Endpoints

The other efficacy and health outcome analyses will be based on the ITT population including on-treatment data only, unless otherwise specified. Summaries and analyses of the BDI/TDI will use the TDI population.

Table 5 provides an overview of the planned analyses for the other efficacy endpoints, with the detailed list of data displays being presented in Section 11.12.

Table 5 Overview of Planned Efficacy and Health Outcome Analyses for Other Endpoints

	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
COPD Exacerbations														
Post-treatment Moderate/Severe Exacerbations				Y			Y							
Annual Rate of All (Mild, Moderate and Severe) On-treatment Exacerbations (repeat for moderate; requiring systemic/oral corticosteroids; requiring antibiotics)	Y[1]			Y										
Annual Rate of On-treatment Severe Exacerbations by Eosinophil Subgroup	Y[1]			Y										
Time to Each On-treatment Moderate/Severe Exacerbation (repeat for severe exacerbations)	Y[2]													
Time to first on-treatment severe exacerbation by eosinophil subgroup	Y[3]													
Time to first on-treatment severe exacerbation (repeat for	Y[3]													

	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
mild/moderate/severe; moderate; requiring systemic/oral corticosteroids; requiring antibiotics)														
All Cause Mortality														
Adjudicated Cause of On-treatment Death (repeat for both on- and off-treatment combined)				Y[12]										
Time to Death from Any Cause (On-treatment, repeat for on and off treatment combined)	Y[3]	Y[3]		Y[3]										
Spirometry														
Baseline Pre-bronchodilator FEV1 by Eosinophil Subgroup				Y										
Trough FEV1 by Eosinophil Subgroup	Y[5]			Y				Y[5]			Y			
Post-bronchodilator FEV1	Y[5]			Y			Y	Y[5]	Y[6, 13]		Y			
FEV1 Reversibility	Y[5]			Y				Y[5]			Y			
Percentage of subjects with an increase from baseline in trough FEV1 ≥100mL	Y[10]			Y[10]			Y							
Percentage of subjects with an increase from baseline in trough FEV1 ≥100mL by Eosinophil Subgroup	Y[10]			Y[10]										
Baseline FVC				Y			Y							
Trough FVC	Y[5]			Y				Y[5]	Y[6, 13]		Y			
Post-Bronchodilator FVC	Y[5]			Y			Y	Y[5]	Y[6, 13]		Y			
SGRQ														
Baseline SGRQ Total Score by Eosinophil Subgroup				Y										
SGRQ Total Score by Eosinophil Subgroup	Y[5]			Y				Y[5]			Y			
SGRQ Total Score by				Y[8]	Y[9]									

	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
Subject Global Rating of Change in COPD Severity														
Proportion of Responders according to SGRQ Total Score	Y[10]			Y[10]			Y							
Proportion of Moderate/Major Responders according to SGRQ Total Score	Y[10]			Y[10]										
Proportion of Major Responders according to SGRQ Total Score	Y[10]			Y[10]										
Proportion of Responders according to SGRQ Total Score by Eosinophil Subgroup	Y[10]			Y[10]										
COPD Assessment Test (CAT)														
Baseline CAT Score				Y[12]										
CAT Score	Y[5]			Y				Y[5]	Y[6, 13]		Y			
CAT Score by Eosinophil Subgroup	Y[5]			Y				Y[5]			Y			
Proportion of Responders according to CAT Score	Y[10]			Y[10]										
Proportion of Responders according to CAT Score by Eosinophil Subgroup	Y[10]			Y[10]										
BDI/TDI (TDI Population)														
BDI				Y[12]										
TDI Focal Score	Y[5]	Y[6, 13]		Y										
TDI Focal Score by Eosinophil Subgroup	Y[5]			Y										
TDI Category of Improvement and Deterioration				Y										
Proportion of Responders according to TDI Focal Score	Y[10]			Y[10]										
Proportion of Moderate/Major Responders according to TDI Focal Score	Y[10]			Y[10]										

	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
Proportion of Major Responders according to TDI Focal Score	Y[10]			Y[10]										
Proportion of Responders according to TDI Focal Score by Eosinophil Subgroup	Y[10]			Y[10]										
Daily Diary Assessments														
Mean Number of Occasions of Rescue Use per Day, Four Week Intervals	Y[5]			Y				Y[5]	Y[6, 13]		Y			
Percentage of Rescue-Free Days, Four Week Intervals	Y[5]			Y				Y[5]	Y[6, 13]		Y			
Mean Number of Nighttime Awakenings per night, Four Week Intervals	Y[5]			Y				Y[5]	Y[6, 13]		Y			
Percentage of Days Symptoms Stopped Usual Activities, Four Week Intervals	Y[5]			Y				Y[5]	Y[6, 13]		Y			
Subject Global Ratings														
Subject Global Rating of Activity Limitation				Y										
Subject Global Impression of Change in Activity Limitation	Y[11]			Y										
Subject Global Rating of COPD Severity				Y										
Subject Global Rating of Change in COPD Severity	Y[11]			Y										
EQ-5D-5L														
Utility Index				Y										
VAS Scores				Y										
Healthcare Resource Use														
Healthcare Resource Utilization (all-cause and repeated by contact type)				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. Negative binomial regression model
2. Andersen-Gill model for recurrent events
3. Cox proportional hazards analysis of time to event and Kaplan-Meier plot
4. Domain and total scores
5. MMRM analysis
6. Least squares (LS) means (95% CI) change from baseline and LS mean (95% CI) treatment differences. Note: TDI will present LS means for the analysis of the absolute value and not the change from baseline.
7. Box plot and empirical distribution function plot
8. For combined treatment groups and by treatment group at Week 52
9. Box plot for combined treatment groups and by treatment group at Week 52
10. Generalized linear mixed model with responder status
11. Logistic regression analysis
12. Repeat for by eosinophil subgroup
13. Additional plot of LS means (95% CI) change from baseline for UMEC/VI and FF/VI treatment groups only

9.1.1.1. All Cause Mortality

Summaries of on-treatment and on/off-treatment adjudicated cause of death will be provided. The definitions of on-treatment and off-treatment for all cause mortality are defined in Section 11.3.2. The censoring rules for time to all cause mortality for on-treatment and on/off-treatment death are defined in Section 11.5.3.5.

9.1.1.2. St. George's Respiratory Questionnaire Responder Analysis

Subjects will be classified as responders or non-responders according to the SGRQ total score as described in Section 11.5.3.3.

Week 52 SGRQ total score and change from baseline total score will be summarized by Week 52 subject global rating of change in COPD severity for the combined treatment groups. Results of this summary will be used to define cut-offs for moderate and major responders as described in Section 11.5.3.3. A similar table will also be produced by treatment group.

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

The BDI and TDI focal scores [Mahler, 2004] will be calculated as described in Section 11.5.3.5.

Subjects will be classified as responders or non-responders according to the TDI focal score as defined in Section 11.5.3.5. Response will be further classified as moderate or major as defined in Section 11.5.3.5.

9.1.1.4. COPD Assessment Test (CAT)

The CAT score is computed as detailed in Section 11.5.3.4. Subjects will be classified as responders or non-responders according to the CAT score as described in Section 11.5.3.4.

9.1.1.5. Subject Global Ratings

The Week 52 subject global rating of change in COPD severity will be used to define cut-offs for moderate and major responders according to the SGRQ total score as defined in Section 11.5.3.3.

9.1.1.6. Daily Diary Assessments

Rescue salbutamol use recorded on the daily eDiary will be summarized as the mean number of occasions of rescue use per day and the percentage of rescue-free days in four-week interval periods as described in Section 11.5.3.7.

Symptoms stopping usual activities (yes/no) recorded on the daily eDiary will be summarized as the percentage of days symptoms did stop usual activities by four-week interval periods as described in Section 11.5.3.7.

Night-time awakenings recorded on the daily eDiary will be summarized as the mean number of night-time awakenings per night by four-week interval periods as described in Section 11.5.3.7.

All diary analyses performed will be performed by four-weekly periods; the table will display estimates for each 4-weekly period.

Symptoms concerning sputum purulence (color), sputum volume, wheezing, sore throat, cough, colds (nasal discharge and/or nasal congestion), shortness of breath, fever without other cause were used solely for the purpose of triggering contact with site personnel for exacerbation assessment and will not be reported in any statistical displays.

9.1.1.7. EuroQol Questionnaire (EQ-5D-5L)

The EQ-5D-5L will be completed on Day 1, Week 28 and Week 52. Two scores will be summarized; the EQ-5D-5L utility score and the EQ-5D-5L visual analogue scale (VAS) score.

For the EQ-5D-5L utility score, EQ-5D-5L health states will be converted to a single summary utility index by applying a formula that essentially attaches weights to each of the levels in each dimension. The formula is based on the valuation of EQ-5D-5L health states from general population samples in the country. The weights to be applied in the formula are not yet available for all countries participating in the study. Therefore, utility scores will be calculated using England weighting as published at the EuroQol website [EuroQol website].

Missing individual response for any dimension will not be imputed. Consequently, the summary index will be missing since it is based only on a complete set of responses for all 5 dimensions.

Individual country data may be analyzed post hoc using appropriate country based tariffs.

9.1.1.8. Unscheduled Healthcare Resource Utilization

Summaries of all-cause unscheduled healthcare resource utilization will be provided for the on-treatment period for the ITT population. This will be repeated by contact type.

9.1.2. Planned Efficacy Statistical Analyses of Other Endpoints

9.1.2.1. Time to First On-treatment Exacerbation

Secondary Statistical Analyses
Endpoint
• Time to first on-treatment severe exacerbation • Time to first on-treatment mild/moderate/severe exacerbation • Time to first on-treatment moderate exacerbation • Time to first on-treatment exacerbation requiring systemic/oral corticosteroids • Time to first on-treatment exacerbations requiring antibiotics
Model Specification

• Cox's proportional hazards model
• Terms in the model:
  • **Response**: time to first on-treatment exacerbation (type of exacerbation dependent on endpoint)
  • **Categorical**: treatment group, gender, exacerbation history (≤1, ≥2 moderate/severe), smoking status (screening), geographical region
  • **Continuous**: post-bronchodilator % predicted FEV1 (Screening)
• The 'exact' method will be used for handling ties. If the analysis will not run using the 'exact' method, then the 'Efron' method for handling ties will be used instead.
• Kaplan-Meier survivor functions will be obtained for each treatment group using PROC LIFETEST with a TIME statement.

Model Checking & Diagnostics
• Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analysis.
Model Results Presentation
• Results will be presented as described in Section 8.3.1 • Note, only unadjusted p-values will be displayed.

9.1.2.2. Time to First On-treatment Severe Exacerbation by Eosinophil Subgroup

Secondary Statistical Analyses
Endpoint
• Time to first on-treatment severe exacerbation by eosinophil subgroup
Model Specification, Model Checking & Diagnostics, Model Results Presentation
• Defined in Section 8.4

9.1.2.3. Annual Rate of On-treatment Exacerbations

Other Efficacy Statistical Analyses
Endpoint(s)
• Annual rate of all on-treatment exacerbations (mild, moderate, severe) • Annual rate of on-treatment moderate exacerbations • Annual rate of on-treatment exacerbations requiring systemic/oral corticosteroids • Annual rate of on-treatment exacerbations requiring antibiotics • Annual rate of on-treatment severe exacerbations by eosinophil subgroup
Model Specification, Checking & Diagnostics, Results Presentation and SAS Code
• These endpoints will be analyzed and presented as described in Section 7.2 and Section 8.6. • Note, only unadjusted p-values will be displayed.

9.1.2.4. Time to Onset of Each Exacerbation

Other Efficacy Statistical Analyses
Endpoint(s)
• Time to onset of each on-treatment moderate/severe exacerbation • Time to onset of each on-treatment severe exacerbation
Model Specification

• Andersen-Gill regression model for recurrent events
• Terms in the model:
  • **Response**: time to each on-treatment exacerbation (type of exacerbation dependent on endpoint)
  • **Categorical**: treatment group, gender, exacerbation history (≤1, ≥2 moderate/severe), smoking status (screening), geographical region
  • **Continuous**: post-bronchodilator % predicted FEV1 (Screening)
• A robust sandwich covariance matrix structure for the within subject correlation [Therneau, 2000] will be used to allow for the lack of independence among multiple events per subject over time (to achieve this, the COVS(AGGREGATE) option will be used in the PHREG statement).
• The 'exact' method will be used for handling ties. If the analysis will not run using the 'exact' method, then the 'Efron' method for handling ties will be used instead.

Model Checking & Diagnostics
• Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analysis.
Model Results Presentation
• Hazard ratios and the percent reduction in risk for the pairwise treatment comparisons with associated 95% CIs and unadjusted p-values will be presented.
Example SAS Code
proc phreg data=dsetin covsandwich(aggregate); *id subjid;* *class trtcd smk region exachis gender;* *model (start stop)*eventflag(0) = trtcd smk gender exachis region pctpredFEV / risklimits ties=exact;* *hazardratio trtcd / diff=all;* *run;*

9.1.2.5. Trough FEV1, SGRQ Total Score, CAT score and TDI by Eosinophil Subgroup

Other Efficacy Statistical Analyses
Endpoint(s)
• Change from baseline in trough FEV1 by Eosinophil Subgroup • Change from baseline in SGRQ total score by Eosinophil Subgroup • Change from baseline in CAT score by Eosinophil Subgroup • TDI focal score by Eosinophil Subgroup
Model Specification, Checking & Diagnostics, Results Presentation and SAS Code
• These endpoints will be analyzed using the same methodology as trough FEV1 in Section 8.2.1. Eosinophil subgroup will be added to the model as a categorical variable as well as the following interactions: treatment group*Eosinophil subgroup, visit*Eosinophil subgroup, treatment group*visit*Eosinophil subgroup • Since TDI is a transitional index there will be no change from baseline analysis for TDI. • Baseline is defined in Section 11.4.2. • LS means and LS mean change from baseline values for each treatment group within each level of Eosinophil subgroup will be presented with their associated standard errors as well as 95% CIs. • The estimated treatment difference for FF/UMEC/VI versus FF/VI and FF/UMEC/VI versus UMEC/VI along with corresponding standard error, 95% CI and p-value for each Week within each level of Eosinophil subgroup will be presented. • Note, only unadjusted p-values will be displayed. • For this subgroup analyses, 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, with a separate OMdset created for each level of the subgroup.

9.1.2.6. Post-bronchodilator FEV1 and FVC, Trough FVC, CAT, TDI

Other Efficacy Statistical Analyses
Endpoint(s)
• Change from baseline in post-bronchodilator FEV1 • Change from baseline in post-bronchodilator FVC • Change from baseline in trough FVC • Change from baseline in FEV1 reversibility • Change from baseline in CAT Score • TDI
Model Specification, Checking & Diagnostics, Results Presentation and SAS Code
• These endpoints will be analyzed using the same methodology as trough FEV1 in Section 8.2.1 • Since TDI is a transitional index there will be no change from baseline analysis for TDI. • Baseline is defined in Section 11.4.2.

Other Efficacy Statistical Analyses
• Note, only unadjusted p-values will be displayed.

9.1.2.7. Proportion of Responders According to FEV1, SGRQ, CAT and TDI

Other Efficacy Statistical Analyses
Endpoint(s)
• Percentage of subjects with an increase from baseline in trough FEV1 ≥ 100mL • Proportion of responders according to SGRQ total score • Proportion of moderate/major responders according to SGRQ total score • Proportion of major responders according to SGRQ total score • Proportion of responders according to CAT score • Proportion of responders according to TDI focal score • Proportion of moderate/major responders according to TDI • Proportion of major responders according to TDI
Model Specification
• Generalized linear mixed model • Terms in the model: Dependent : response (yes/no) Categorical : treatment group, smoking status (screening), geographical region, visit, subject Continuous : baseline (FEV1, SGRQ total , CAT score or BDI) Interaction : baseline*visit, treatment group*visit • The model will be fit with an unstructured variance-covariance matrix with one single model to include all visits where the assessment in question is scheduled to be performed. • Computation of confidence intervals for the odds ratios is based on the individual Wald tests.
Model Checking & Diagnostics
• Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analysis.
Model Results Presentation
• Number and percentage of responders and non-responders for each treatment at each week • Odds ratio for pairwise comparisons with associated 95 % CIs and unadjusted p-values
Example SAS Code
proc glimmix data=dsetin; *class trtcd smk region visit subjid;* *model respond(event="1")=trtcd baseline smk region visit visit*baseline visit*treatment / dist=binary link=logit ddfm=kr solution;* *lsmeans trtcd*visit / cl diff or om;* *random visit / subject=subjid residual type=un;* *ods outputs diffs=differs;* *run;*

9.1.2.8. Proportion of Responders According to FEV1, SGRQ, CAT and TDI by Eosinophil Subgroup

Other Efficacy Statistical Analyses
Endpoint(s)
• Percentage of subjects with an increase from baseline in trough FEV1 ≥ 100mL by Eosinophil Subgroup • Proportion of responders according to SGRQ total score by Eosinophil Subgroup • Proportion of responders according to CAT score by Eosinophil Subgroup • Proportion of responders according to TDI focal score by Eosinophil Subgroup
Model Specification, Checking & Diagnostics, Results Presentation and SAS Code
• These endpoints will be analyzed using the same methodology as in Section 9.1.2.7. Eosinophil subgroup will be added to the model as a categorical variable as well as the following interactions: treatment group*Eosinophil subgroup, visit*Eosinophil subgroup, treatment group*visit*Eosinophil subgroup • Baseline is defined in Section 11.4.2. • Number and percentage of responders and non-responders for each treatment at each week within each level of Eosinophil subgroup will be presented • Odds ratio for pairwise comparisons at each visit within each level of eosinophil subgroup with associated 95 % CIs will be presented • Note, only unadjusted p-values will be displayed.

9.1.2.9. Time to Death from Any Cause

Other Efficacy Statistical Analyses
Endpoint(s)
• Time to death from any cause (on-treatment) • Time to death from any cause (on- and off-treatment)
Model Specification, Checking & Diagnostics, Results Presentation and SAS Code

• Cox's proportional hazards model
• Terms in the model:
  • **Response**: time to death
  • **Categorical**: treatment group, gender
  • **Continuous**: age
• The 'exact' method will be used for handling ties. If the analysis will not run using the 'exact' method, then the 'Efron' method for handling ties will be used instead.
• Kaplan-Meier survivor functions will be obtained for each treatment group using PROC LIFETEST with a TIME statement.

Model Checking & Diagnostics and Results Presentation
• The model checking and results presentation is detailed in Section 8.3.1 • Note, only unadjusted p-values will be displayed.

9.1.2.10. Rescue Use, Symptoms and Nighttime Awakenings

Other Efficacy Statistical Analyses
Endpoint(s)
• Mean number of occasions of rescue use per day by four weekly intervals • Percentage of rescue-free days by four weekly intervals • Percentage of days symptoms stopped usual activities by four weekly intervals • Mean number of nighttime awakenings per night by four weekly intervals
Model Specification, Checking & Diagnostics, Results Presentation and SAS Code
• These endpoints will be analyzed using the same methodology and presentation as trough FEV1 in Section 8.2.1. • Visit will be replaced with all available four-weekly periods (Weeks 1-4, 5-8 and up to Weeks 49-52) and LS Means for each four weekly interval will be presented. • Baseline is defined in Section 11.4.2. • Note, only unadjusted p-values will be displayed.

9.1.2.11. Subject Global Ratings of Change

Other Efficacy Statistical Analyses
Endpoint(s)
• Subject global rating of change in activity limitation • Subject global rating of change in COPD severity
Model Specification
• Logistic regression model • Terms in the model: Dependent : change response (7-point scale) Categorical : treatment group, smoking status (screening), geographical region • The model will be fit at each visit (Weeks 4, 16, 28, 40 and 52). • Computation of confidence intervals for the odds ratios is based on the individual Wald tests
Model Checking & Diagnostics
• Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analysis.
Model Results Presentation
• Number and percentage of subjects reporting each category of change at each visit • Odds ratio, 95% CI and unadjusted p-values for the pairwise treatment comparisons
Example SAS Code
proc logistic data=dsetin; *class trtcd smk region / param=glm;* *model changevar = trtcd smk region / l=logit;* *[note: both contrast and estimate statements will be used for the pairwise comparisons]* *run;*

9.2. Safety Analyses

9.2.1. Overview of Planned Analyses

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

Section 9.2.2 to Section 9.2.12 provide the overviews of the planned safety analyses, with the detailed list of data displays being presented in Section 11.12.

9.2.2. Overview of Planned Exposure Analyses

Table 6 Overview of Planned Exposure Analyses

	Data Displays Generated		
	Table	Figure	Listing
Exposure			
Exposure Data	Y[1]	Y	Y
Post-treatment Duration on Study	Y[1]		Y
On and Post-treatment Duration on Study	Y[1]		Y

NOTES :

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1. Repeat by eosinophil subgroup

9.2.3. Overview of Planned Adverse Event Analyses

Table 7 Overview of Planned Adverse Event Analyses

	Data Displays Generated		
	Table	Figure	Listing
Adverse Events (AEs)			
Overview of On-treatment AEs	Y		
All AEs (ASE)			Y
On-treatment AEs	Y[1]		
On-treatment Drug-Related AEs	Y		
On-treatment AEs Leading to Permanent Discontinuation of Study Treatment or Withdrawal from the Study	Y		Y[5]
Ten Most Frequent On-treatment AEs in Each Treatment Group	Y		
On-treatment Common Non-Serious AEs (3% or More of Subjects in Any Treatment Group)	Y		
On-treatment AE Categories of Interest in the Elderly by Age	Y		
Relationship of AE System Organ Class, Preferred Term and Verbatim Text (ASE)	Y		
Subject Numbers for Individual AEs (ASE)			Y
Serious Adverse Events (SAEs)			
Pre-treatment SAEs	Y[2]		Y[5]
Pre-treatment Fatal SAEs (ASE)	Y		
Pre-treatment SAEs Leading to Withdrawal from Study (ASE)	Y		

	Data Displays Generated		
	Table	Figure	Listing
Subjects and Number of Occurrences of on-treatment serious, drug-related serious, fatal and drug-related SAEs	Y		
On-treatment SAE	Y[3]		Y[5]
On-treatment Drug-Related SAEs	Y		
On-treatment Drug-Related Fatal SAEs	Y		
Post-treatment SAEs	Y		Y[5]
Post-treatment Fatal SAEs	Y		
Reasons for Considering as a Serious AE			Y
Adjudicated Serious Adverse Reports			
Adjudicated On-treatment Serious Adverse Reports	Y[3]		
Adjudicated Post-treatment Serious Adverse Reports	Y[3]		
AEs of Special Interest (AESI)			
On-treatment AESI	Y[6]		
Analysis of Time to First On-treatment Event in the Pneumonia AESI Group	Y[4,6]	Y[4,7]	
Pneumonia Risk Factors at Screening for those Subjects with an on-treatment event in the pneumonia AESI group	Y[6]		
Analysis of Time to First On-treatment Event in the CV AESI Group	Y[4]	Y[4,7]	
Summary of Incidence of On-treatment Pneumonia AESI and Adjudicated Pneumonia	Y		
SAEs of Special Interest (SAESI)			
On-treatment Serious AESI	Y[3]		
Analysis of Time to First On-treatment event in the Pneumonia AESI group resulting in hospitalization, prolonged hospitalization or death	Y[4]	Y[4,7]	
Analysis of Time to First On-treatment event in the CV AESI group resulting in hospitalization, prolonged hospitalization or death	Y[4]	Y[4,7]	

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- Individual = Represents FL related to any displays of individual subject observed raw data.

1. Repeat by country
2. Repeat for ASE population
3. Repeat for fatal and non-fatal separately
4. Cox proportional hazards analysis and Kaplan-Meier plot for time to first event
5. Combined listing for all reported AEs (any treatment phase). SAE listing will be split by fatal and non-fatal SAEs and based on the ASE population
6. Repeat by eosinophil subgroup
7. Additional Kaplan-Meier plot for UMEC/VI and FF/VI treatment groups only

9.2.3.1. Adverse Events of Special Interest

Adverse events 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 Activities (MedDRA) Queries (SMQs) and other groupings for AESI is provided in Section 11.5.4.2.

A summary of AE categories of interest in the elderly by age and overall for each treatment group will be provided for AESI. The list of AE categories of interest in the elderly is provided in Section 11.5.4.2.

A summary of the number of events in the pneumonia AESI group and the number of these that had investigator-reported pneumonia (on the pneumonia eCRF form, and split by those supported/not supported by x-ray/CT scan) and/or that had an associated adjudicated report of pneumonia will be provided. This will be repeated for serious events in the pneumonia AESI group within the same table. The number of investigator-reported pneumonia events not reported as pneumonia AESI will also be provided and the number of adjudicated serious adverse reports of pneumonia not associated with a pneumonia AESI. Association between events in the pneumonia AESI group and adjudicated reports of pneumonia is defined in Section 11.5.4.2.

9.2.3.2. Pneumonia Risk Factors

Baseline characteristics to identify potential pneumonia risk factors at screening, as defined in Section 11.5.2.5, will be summarised for those subjects who have an on-treatment event in the pneumonia AESI group.

9.2.3.3. 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.

9.2.3.4. Oropharyngeal Examination

Oropharyngeal examination was conducted as part of the physical examination and included in source documentation. Any adverse finding will be recorded as an AE or SAE and included in summaries and listings of AEs/SAEs.

9.2.4. Overview of Major Adverse Cardiac Events (MACE)

Table 8 Overview of Planned MACE Analyses

	Data Displays Generated		
	Table	Figure	Listing
Major Adverse Cardiac Events (MACE)			
On-treatment MACE (Narrow Definition)	Y		
On-treatment MACE (Broad Definition)	Y		

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- Individual = Represents FL related to any displays of individual subject observed raw data.

9.2.4.1. Major Adverse Cardiac Events

Major adverse cardiac event (MACE) endpoints will be based on both eCRF and adjudicated data. The definition is shown in Section 11.5.4.9.

9.2.5. Overview of Pneumonia Details (from the eCRF Pneumonia Form)

Table 9 Overview of Planned Pneumonia Details (from the eCRF pneumonia form) Analyses

	Data Displays Generated		
	Table	Figure	Listing
Pneumonia (eCRF Pneumonia Form)			
On-treatment Pneumonia Incidence	Y[1]		
On-treatment Details of Pneumonia	Y[1]		

NOTES :

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- 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. Repeat tables for events resulting in hospitalization, prolonged hospitalization or death

9.2.6. Overview of the Composite Endpoints

Table 10 Overview of Planned Composite Endpoint Analyses

	Data Displays Generated		
	Table	Figure	Listing
Composite endpoints			
Analysis of Time to First event in the Pneumonia AESI group or moderate/severe exacerbation Composite	Y	Y[1]	
Analysis of time to first severe exacerbation or event in the pneumonia AESI group resulting in hospitalization, prolonged hospitalization or death	Y	Y[1]	
Analysis of time to first severe exacerbation or event in the CV AESI group resulting in hospitalization, prolonged hospitalization or death or event in the pneumonia AESI group resulting in hospitalization, prolonged hospitalization or death	Y	Y[1]	
Percentage of subjects with an event in the pneumonia AESI group and percentage of subjects with a moderate/severe exacerbation.		Y[1]	

NOTES :

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- Individual = Represents FL related to any displays of individual subject observed raw data.

1. Kaplan-Meier plot displaying FF/UMEC/VI, FF/VI and UMEC/VI and repeated displaying FF/VI and UMEC/VI only

9.2.7. Overview of Bone Fractures

Table 11 Overview of Bone Fracture Analyses

	Data Displays Generated		
	Table	Figure	Listing
Bone Fractures			
On-treatment Bone Fractures	Y		

NOTES :

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- 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

9.2.8. Overview of Chest Imaging

Table 12 Overview of Planned Chest Imaging Analyses

	Data Displays Generated		
	Table	Figure	Listing
Radiography (Chest Imaging)			
On-treatment Chest Imaging	Y		

NOTES :

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- 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

9.2.9. Overview of Liver Events

Table 13 Overview of Planned Liver Events Analyses

	Data Displays Generated		
	Table	Figure	Listing
Liver Events			
Liver Monitoring/Stopping Event Reporting	Y		
Hepatobiliary Laboratory Abnormalities	Y		
Medical Conditions for Subjects with Liver Stopping Events			Y
Liver Event Substance Use			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

9.2.10. Overview of Laboratory Parameters

Table 14 Overview of Planned Laboratory Parameters Analyses

	Absolute				Change from Baseline	
	Summary		Individual		Summary	
	T	F	F	L	T	F
Laboratory Parameters						
Liver Function Tests		Y[1]				
Chemistry Values for Subjects with at Least One Value Outside the Normal Range				Y		
Chemistry Data	Y	Y[2]			Y	Y[3]
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 Normal Range				Y		
Hematology Data	Y	Y[2]			Y	Y[3]
Hematology Data Outside the Normal Range	Y					
Hematology Changes from Baseline Relative to the Normal Range	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. Trellis display of maximum post-baseline liver function test values (to include alanine aminotransferase, aspartate aminotransferase, alkaline phosphotase and bilirubin) versus baseline liver function test values divided by Upper Limit of Normal (ULN)
2. Separate scatter plots for maximum and minimum post-baseline versus baseline divided by ULN for maximum and Lower Limit of Normal (LLN) for minimum
3. Separate box plots of change from baseline in maximum and minimum post-baseline values

9.2.11. Overview of Vital Signs

Table 15 Overview of Planned Vital Signs Analyses

	Absolute				Change from Baseline	
	Summary		Individual		Summary	
	T	F	F	L	T	F
Vital Signs						
Vital Sign Data (Pulse Rate, Systolic Blood Pressure (BP), Diastolic BP)	Y				Y	
Statistical Analysis of Pulse Rate (bpm)	Y[1]				Y[1]	
Statistical Analysis of Systolic BP (mmHg)	Y[1]				Y[1]	
Statistical Analysis of Diastolic BP (mmHg)	Y[1]				Y[1]	

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. MMRM analysis

9.2.11.1. Vital Signs

Vital signs collected at study treatment discontinuation will be included in 'worst case post-baseline' summaries but will not be summarized separately. See Section 11.5.4.4 for the definition of 'worst case post-baseline'. See Section 9.2.13.1 for details on the statistical analysis of vital signs data.

9.2.12. Overview of ECGs

	Absolute				Change from Baseline	
	Summary		Individual		Summary	
	T	F	F	L	T	F
12-Lead ECGs						
ECG Values (PR interval, QTcB, QTcF, and mean heart rate)	Y[1]				Y[1]	
ECG Values (PR interval, QTcB, QTcF, and mean heart rate) for Subjects with Any Abnormal Finding				Y		
ECG Findings	Y[1]					
ECG Findings Shifts from Baseline, repeated for shift between pre and post treatment at Week 4	Y[1]					
ECG Abnormalities	Y[1,6]			Y		
ECG Abnormalities (>3% in Any Treatment Group)	Y					
QTcF Categories	Y[1]				Y[1]	
Maximum Post-Baseline QTcF		Y[1,3]				Y[1,3]
Statistical Analysis of Pre-dose QTcF at Week 4	Y[5]				Y[5]	
Statistical Analysis of Post-dose QTcF	Y[2]				Y[2,4]	
Change from pre-dose to post-dose ECG Heart Rate at Week 4 (Pre-dose ECG population)	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. Repeat for pre-dose ECG population
2. MMRM analysis
3. Empirical distribution function plot; maximum defined as the maximum value of individual measurements (including unscheduled measurements)

4. One combined table for endpoint and change from baseline endpoint
5. ANCOVA analysis
6. Summary will include event rates

9.2.12.1. ECGs

12-Lead ECGs are collected at Screening (Visit 1) and approximately 15-45 minutes after dosing on treatment at Week 4, Week 28 and Week 52, or at the Study Treatment Discontinuation Visit. In addition, at Week 4 (from sites included in the ECG substudy) one additional ECG will be collected pre-dose. This pre-dose ECG will not be included on the ITT displays of scheduled post-dose ECG assessments but will be included in the determination of the maximum/worst case post baseline summaries for all ECG summaries, see Section 11.5.4.4. ECG displays will be repeated for the ECG population summarizing all ECG data as detailed in Section 9.2.12.

All ECG data present in the database will be considered valid and will be reported. ECGs collected at study treatment discontinuation will be included in 'worst case post-baseline' summaries but will not be summarized separately. See Section 11.5.4.4 for the definition of 'worst case post-baseline'. See Section 9.2.13.1 for details on the statistical analysis of ECG data.

9.2.13. Planned Statistical Analyses of Safety Endpoints

9.2.13.1. Vital Signs and ECGs

Statistical Analysis of Safety Endpoints – MMRM Analysis
Endpoints
• Pulse rate • Systolic BP • Diastolic BP • QTcF (Post-dose)
Model Specification, Checking, Results Presentation and SAS code

• These endpoints will be analyzed using similar methodology and presentation as trough FEV1 in Section 8.2.1.
 	
• Terms in the model:
  • **Response**: Value (dependent on endpoint) at each visit.
  • **Categorical**: treatment group, smoking status (screening), geographical region, visit
  • **Continuous**: baseline
  • **Interaction:** baseline*visit, treatment group*visit
  • **Repeated**: visit
 	
• Baseline is defined in Section 11.4.2
 	
• Two models will be fitted; one with a response variable of change from baseline and one with the response variable as the raw value.

Statistical Analysis of Safety Endpoints – ANCOVA Analysis
Endpoints
• QTcF (Pre-dose) at Week 4 (Pre-dose ECG population only)
Model Specification

• ANCOVA model.
 	
• Terms in the model:
  • **Response**: Pre-dose QTc(F) at Week 4.
  • **Categorical**: treatment group, smoking status (screening), geographical region
  • **Continuous**: baseline QTc(F)
 	
• Baseline is defined in Section 11.4.2
• Two models will be fitted; one with a response variable of change from baseline and one with the response variable as the raw value.

Model Checking & Diagnostics
• Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analysis
Model Results Presentation
• Least-square (LS) means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors as well as 95% CIs. The estimated treatment difference along with corresponding standard error, 95% CI and unadjusted p-values will be presented.
Example SAS Code
proc mixed data=dsetin; *class trtcd visit subjid smk region;* *model endpoint=trtcd baseline smk region / ddfm =kr;* *lsmeans trtcd / cl diff e om;* *ods output lsmeans=lsmeans;* *ods output diffs=diffs;* *run;*

9.2.13.2. Time to First Event in the Pneumonia AESI Group, Cardiovascular AESI Group

Safety Statistical Analyses Time to First Pneumonia
Endpoint
• Time to first on-treatment event in the Pneumonia AESI group • Time to first on-treatment event in the Pneumonia AESI group resulting in hospitalization, prolonged hospitalization or death. • Time to first on-treatment event in the Cardiovascular AESI group • Time to first on-treatment event in the Cardiovascular AESI group resulting in hospitalization, prolonged hospitalization or death.

Model Specification

- Cox's proportional hazards model
- Terms in the model:
  - **Response**: time to first event in the Pneumonia/Cardiovascular AESI group (definition dependent on endpoint)
  - **Categorical**: treatment group, geographical region
- The 'exact' method will be used for handling ties. If the analysis will not run using the 'exact' method, then the 'Efron' method for handling ties will be used instead.
- Kaplan-Meier survivor functions will be obtained for each treatment group using PROC LIFETEST with a TIME statement.

Model Checking & Diagnostics

- Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analysis.

Model Results Presentation

- Hazard ratios (and percent reduction in risk for pairwise treatment comparisons with associated 95% CIs and unadjusted p-values will be presented.
- The probability of having an event, 95% CI and first quartile and median time to event for each treatment group will be presented.
- The Kaplan-Meier curves will be presented showing the probability of having an event over time for each treatment group separately plotted on the same figure. This will be repeated displaying FF/VI and UMEC/VI treatment groups only.

Example SAS Code

```
proc phreg data=dsetin;
      class trtcd region;
      model timeto1*eventflag(0) = trtcd region / risklimits ties=exact;
      hazardratio trtcd / diff=all;
run;

proc lifetest data=destin outsurv=survest;
     time timeto1*eventflag(0);
    strata trtcd;
run;
```

9.2.13.3. Time to First Event in the Pneumonia AESI Group by Eosinophil Subgroup

Safety Statistical Analyses Time to First Pneumonia by Eosinophil Subgroup
Endpoint
• Time to first on-treatment event in the Pneumonia AESI group by eosinophil subgroup
Model Specification, Checking & Diagnostics, Results Presentation and SAS Code
• This endpoint will be analyzed using the same methodology as in Section 9.2.13.2 with Eosinophil subgroup added to the model as a categorical variable as well as the interaction: treatment group*Eosinophil subgroup • Hazard ratios (and percent reduction in risk for pairwise treatment comparisons within each level of eosinophil subgroup with associated 95% CIs and unadjusted p-values will be presented. • The probability of having an event, 95% CI and first quartile and median time to pneumonia for each treatment group within each level of eosinophil subgroup will be presented. • The Kaplan-Meier curves will be presented showing the probability of having an event over time for each treatment group separately plotted on the same figure. This will be repeated for each level of the eosinophil subgroup. These will be repeated displaying FF/VI and UMEC/VI treatment groups only.

9.2.13.4. Time to First Event in the Pneumonia AESI Group or COPD Exacerbation

Safety Statistical Analyses Time to First Pneumonia
Endpoint
• Time to first on-treatment event in the Pneumonia AESI group or moderate/severe exacerbation composite • Time to first on-treatment event in the Pneumonia AESI group resulting in hospitalization, prolonged hospitalization or death or severe exacerbation composite
Model Specification

• Cox's proportional hazards model
• Terms in the model:
  • **Response**: time to first event in the Pneumonia AESI group or exacerbation (definition dependent on endpoint)
  • **Categorical**: treatment group, gender, exacerbation history (≤1, ≥2 moderate/severe), smoking status (screening), geographical region
  • **Continuous**: post-bronchodilator % predicted FEV1 (Screening)
• The 'exact' method will be used for handling ties. If the analysis will not run using the 'exact' method, then the 'Efron' method for handling ties will be used instead.
• Kaplan-Meier survivor functions will be obtained for each treatment group using PROC LIFETEST with a TIME statement.

Model Checking & Diagnostics
• Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analyses.

Model Results Presentation
• Hazard ratios (and percent reductions in risk for pairwise treatment comparisons with associated 95% CIs and unadjusted p-values will be presented. • The probability of having an event, 95% CI and first quartile and median time to pneumonia for each treatment group will be presented. Risk reductions will also be presented. • The Kaplan-Meier curves will be presented showing the probability of having an event over time for each treatment group separately plotted on the same figure. This will be repeated displaying FF/VI and UMEC/VI treatment groups only.
Example SAS Code
proc phreg data=dsetin; *class trtcd smk region gender exachis;* *model timeto1*eventflag(0) = trtcd smk region gender exachis pctpred/ risklimits ties=exact;* *hazardratio trtcd / diff=all;* *run;* *proc lifetest data=destin outsurv=survest;* *time timeto1*eventflag(0);* *strata trtcd;* *run;*

9.2.13.5. Time to First Exacerbation, Event in the CV AESI Group and Event in the Pneumonia AESI Group Composite Endpoints

Other Efficacy Statistical Analyses
Endpoint(s)
• Time to first severe COPD exacerbation, event in the CV AESI group that resulted in hospitalization, prolonged hospitalization or death and event in the pneumonia AESI group that resulted in hospitalization, prolonged hospitalization or death composite
Model Specification and Presentation
• These endpoints will be analysed and presented as described in Section 9.2.13.4 • Note, only unadjusted p-values will be displayed.

9.3. Pharmacokinetic Analyses

Population PK analysis will be the subject of a separate RAP.

9.4. Pharmacogenetics Analyses

Pharmacogenetics analyses will be the subjects of a separate RAP

9.5. Biomarker Analyses

The analyses of fibrinogen will be the subject of a separate RAP

10. REFERENCES

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11. APPENDICES

11.1. Appendix 1: Time & Events

Time and Events Table

Protocol Activity	Pre-Screen	Screen	Treatment							Follow Up
	Visit 0	Visit 1 Screen/ run-in	Visit 2 Random-ization	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	IP Discontinu-ation Visit	Safety Follow-up Contact
Study Day		Week -2	Week 0	Week 4	Week 16	Week 28	Week 40	Week 52		1 week Fw-up
Window		-3/+8d		-4/+2d	-8/+6d	-8/+6d	-8/+6d	-8/+6d		-1/+4d
Procedures										
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	X	X
Inclusion/Exclusion Criteria		X	X							
Smoking History		X								
Smoking status		X				X		X	X	
Smoking Cessation Counselling		X						X	X	
Register Visit in RAMOS	X	X	X	X	X	X	X	X	X	X
Efficacy assessments										
Spirometry		X	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	
Reversibility Testing [e]		X								
Diary/device training and registration		X	X							
Diary Review			X	X	X	X	X	X	X	

Protocol Activity	Pre-Screen	Screen	Treatment							Follow Up
	Visit 0	Visit 1 Screen/ run-in	Visit 2 Random-ization	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	IP Discontinu-ation Visit	Safety Follow-up Contact
Study Day		Week -2	Week 0	Week 4	Week 16	Week 28	Week 40	Week 52		1 week Fw-up
Window		-3/+8d		-4/+2d	-8/+6d	-8/+6d	-8/+6d	-8/+6d		-1/+4d
Procedures										
Exacerbation Assessment		X	X	X	X	X	X	X	X	X
SGRQ-C [f]			X	X		X		X	X	
BDI[f]			X							
TDI[f]				X		X		X	X	
CAT[f]		X	X	X		X		X	X	
EQ-5D-5L[f]			X			X		X	X	
Subject Global Rating of Activity Limitation[f]			X	X	X	X	X	X	X	
Subject Global Impression of Change in Activity Limitation[f]				X	X	X	X	X	X	
Subject Global rating of severity of COPD[f]			X							
Subject Global rating of Change in COPD[f]				X	X	X	X	X	X	
Healthcare Resource Utilisation				X	X	X	X	X	X	
eDiary close out[g]			X					X	X	
Safety Assessments										
Physical examination[h]		X				X		X	X	
Adverse Events Assessment		X	X	X	X	X	X	X	X	X
Vital signs[i]		X		X		X		X	X	
ECG		X		X[j]		X		X	X	
Chest X-ray[k]		X								
Oropharyngeal examination		X	X	X	X	X	X	X	X	
Pulse oximetry[l]			X							
Laboratory Assessments										
Blood draw for PK					X[m]	X[n]				
Blood Draw for Genetics research[o]			X							

Protocol Activity	Pre-Screen	Screen	Treatment							Follow Up
	Visit 0	Visit 1 Screen/ run-in	Visit 2 Random-ization	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	IP Discontinu-ation Visit	Safety Follow-up Contact
Study Day		**Week -2**	**Week 0**	**Week 4**	**Week 16**	**Week 28**	**Week 40**	**Week 52**		**1 week Fw-up**
Window		**-3/+8d**		**-4/+2d**	**-8/+6d**	**-8/+6d**	**-8/+6d**	**-8/+6d**		**-1/+4d**
Procedures										
Hematology			X							
Hematology/biochemistry[p]		X			X	X		X	X	
Urine Pregnancy Test[q]		X		X	X	X	X	X	X	
Hepatitis B and C tests		X								
Exploratory Lab Assessment										
Blood draw for fibrinogen					X					
Study Treatment										
Dispense IP			X	X	X	X	X			
Administer IP in clinic[r]			X	X	X	X	X	X	X	
Assess IP compliance				X	X	X	X	X	X	
Collect IP				X	X	X	X	X	X	
Dispense albuterol/salbutamol		X	X	X	X	X	X			
Collect albuterol/salbutamol			X	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. At Visits 2-7 (and the IP discontinuation visit) both pre and post-bronchodilator spirometry will be conducted. Pre-bronchodilator spirometry will be performed prior to taking morning dose of IP, between 6am and 11am and after withholding rescue albuterol/salbutamol for ≥4 hours. Post-bronchodilator spirometry will be conducted (prior to taking morning dose of IP) approximately 10-30 minutes after administering 4 puffs of albuterol/salbutamol.
e. Subjects are required to withhold their usual morning doses of their COPD meds including rescue albuterol/salbutamol for the protocol designated period prior to reversibility testing.
f. Patient reported assessments should be conducted in the following order and before other study assessments: SGRQ-C, BDI/TDI, EQ-5D-5L, CAT, Subject Global Rating of Activity Limitation, Subject Global Impression of Change in Activity Limitation, Subject Global Rating of severity of COPD and Change in COPD. BDI/TDI will be conducted in a subset of subjects at selected sites.
g. Close out eDiary for any subject who fails to randomize, discontinues IP, or completes visit 7.
h. Physical examination may include height, weight, blood pressure, temperature, heart rate.
i. Vital signs must be performed prior to spirometry and prior to taking morning dose of IP.
j. ECG to be obtained 15 minutes to 45 minutes post-dose at treatment Visits 3, 5 and 7 and IP Discontinuation Visit (if applicable). In addition, at V3 (in a subset of subjects at selected sites) one additional ECG will be collected pre-dose.
k. Chest X-ray 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
l. Pulse oximetry must be performed at V2 and anytime there is a suspected pneumonia or a moderate/severe exacerbation.
m. In a subset of 300 subjects at selected sites, PK samples to be obtained at two timepoints at Visit 4: pre-dose and in the window 5 to15 minutes post-dose.
n. In a subset of 300 subjects at selected sites, PK samples to be obtained at two timepoints at Visit 5: 5 to 15 minutes post–dose and 45 to 90 minutes post-dose.
o. Genetic consent must be obtained prior to obtaining a blood sample.
p. Hematology and chemistry panels will include liver chemistry, and potassium and glucose levels.
q. All female subjects of child bearing potential will have a urine pregnancy test at each visit except Visits 2 and follow-up.
r. Subjects must withhold their morning dose of IP at each clinic visit and not take their IP dose until instructed to do so by study staff.

NOTE:

1. Subjects who have permanently discontinued IP (and have not withdrawn consent) will complete the discontinuation IP visit and the safety follow-up contact and then will continue in the study to complete all remaining per protocol scheduled visits by phone contact to collect Exacerbations, SAEs and Concomitant Medications.

2. * In China only, Serious AEs will be recorded from the time the consent form is signed until the 7-day safety follow-up visit/telephone contact has been completed, or until Visit 7(telephone contact) for subjects who have discontinued IP but continue in the study

11.2. Appendix 2: Assessment Windows

11.2.1. General

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 Study Treatment Discontinuation 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. In order to collect all questionnaires that are scheduled to be performed at the Study Treatment Discontinuation Visit, diary data is reported on the Logpad as a Study Treatment Discontinuation Visit. If the date of the Study Treatment Discontinuation diary assessment is the same as the date of a scheduled visit date from the eCRF and there is no diary data present at the scheduled visit in question, the Study Treatment Discontinuation diary data will be listed, summarized and analyzed as part of the scheduled visit (if the diary data was scheduled to be performed at the visit in question).

11.3. Appendix 3: 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 will consider all scheduled and unscheduled measurements that have been assigned a treatment phase of 'On-treatment'.

11.3.1. 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. COPD medication combinations taken at study treatment discontinuation will include all COPD medications that were taken between study treatment discontinuation date and study treatment discontinuation date + 14 days inclusive.

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

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

Treatment Phase	Definition
	equal to the study treatment stop date) defined as follows. (conmed start date <= study treatment stop date or conmed start date is missing) and (conmed stop date >= study treatment start date or (conmed stop date is completely missing and study treatment start date is non-missing))
Post-treatment	If study treatment stop date > study treatment start date then this includes medications taken between the date of study treatment stop date and the date of study conclusion (inclusive) defined as follows: (conmed start date <= study conclusion date or conmed start date is missing) and (conmed stop date >= study treatment stop date or (conmed stop date is completely missing and study treatment stop date is non-missing)) If study treatment stop date = study treatment start date then this includes medications taken between the date of study treatment stop date + 1 and the date of study conclusion (inclusive) defined as follows. (conmed start date <= study conclusion date or conmed start date is missing) and (conmed stop date > study treatment stop date or (conmed stop date is completely missing and study treatment stop date is non-missing))
Post-study	Medications that start after the date of study conclusion. Defined as: conmed start date > study conclusion date Note: this post-study data will not be included in any summaries or analyses (but will be listed)

NOTES:

- A concomitant medication will be classed in every period of the study in which it was taken (e.g., prior to screening, run-in, on- treatment, post-treatment, post-study).
- See Section 11.6.1 for handling of partial dates.
- If the study treatment stop date is missing, it will be imputed as described in Section 11.5.1.2.

11.3.2. All Cause Mortality

For the summaries and analyses of the efficacy endpoint of all cause mortality, treatment phases will be defined as described in the table below after any imputation of partial death dates as described in Section 11.6.1:

Pre-treatment	Death Date < Treatment Start Date (i.e. subject did not start study treatment)
On-treatment	Treatment Start Date ≤ Death Date ≤ Treatment Stop Date + 7
Off-treatment	Subjects that prematurely discontinued study treatment that attended the Week 52 visit: Treatment Stop Date + 7 < Death Date ≤ date of Week 52 + 7 Subjects that prematurely discontinued study treatment that withdrew from the study prior to Week 52: Treatment Stop Date + 7 < Death Date ≤ projected Week 52 date + 7
Post-study	Subjects that completed study treatment: Death Date > Treatment Stop Date + 7 Subjects that prematurely discontinued study treatment that attended the Week 52 visit: Death Date > date of Week 52 + 7 Subjects that prematurely discontinued study treatment that withdrew from the study prior to Week 52: Death Date > projected Week 52 date + 7
Note: Study treatment completion is defined in Section 11.5.1.3. The projected Week 52 date is defined in Section 11.5.1.4.	

11.3.3. Other Data

11.3.3.1. Post-treatment and Post-study Phases

For all events and assessments the post-treatment and post-study phases will be defined as follows:

Post/Off-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 or the maximum of (the subjects last phone contact or their last clinic visit or the date the subject was lost to follow-up) for those subjects who discontinued study treatment prematurely.
Post-study	Event Onset Date or Assessment Date > study conclusion date. Note: this post-study data will not be included in any summaries or analyses (but will be listed)

11.3.3.2. Pre-treatment and On-treatment where Time is Recorded

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, the pre-treatment and on-treatment phases will be defined as follows:

Pre-treatment	Event Onset Date/Time or Assessment Date/Time ≤ Treatment Start Date/Time
On-treatment	Treatment Start Date/Time < (Event Onset or Assessment Date/Time) ≤ Treatment Stop Date + 1 or any assessment with a missing or partial date unless there is evidence it was not on-treatment

11.3.3.3. Pre-treatment and On-treatment where Time is Not Recorded

The pre-treatment and on-treatment phases will be defined as described in the table below for the following events and assessments:

- Event-based data with an onset date reported
- Unscheduled assessments that have a date reported
- Assessments for which no planned relative time is recorded in the database, the scheduled Day 1 assessment is to be performed post-dose and have a date reported

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 or any assessment with a missing or partial date unless there is evidence it was not on-treatment

The pre-treatment and on-treatment phases will be defined as described in the table below for the following events and assessments:

- Assessments for which no planned relative time is recorded in the database, the scheduled Day 1 assessment is to be performed pre-dose and have a date reported

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 or any assessment with a missing or partial date unless there is evidence it was not on-treatment

11.4. Appendix 4: Data Display Standards and Handling Conventions

11.4.1. Study Treatment and Subgroup Display Descriptors

11.4.1.1. Study Treatment

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order
1	FF/UMEC/VI 100/62.5/25	FF/UMEC/VI 100/62.5/25	1
2	FF/VI 100/25	FF/VI 100/25	2
3	UMEC/VI 62.5/25	UMEC/VI 62.5/25	3

11.4.1.2. Treatment Comparisons

For all analyses outputs the treatment comparisons that will be displayed are as follows:

- FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25
- FF/UMEC/VI 100/62.5/25 vs. UMEC/VI 62.5/25
- UMEC/VI 62.5/25 vs FF/ VI 100/25. Note this comparison will not be displayed on any sensitivity analyses that involve imputation.

11.4.1.3. Eosinophils Subgroup and Display Descriptors

Baseline eosinophil subgroup will be derived using the most recent individual eosinophil value prior to the first dose of study treatment and categorized into the following groups:

- < 0.15 10^9/L
- >= 0.15 10^9/L

	Eosinophils Subgroup	
Code	Table Decode	Order
1	< 0.15 10^9/L	1
2	>= 0.15 10^9/L	2

11.4.2. Baseline Definitions & Derivations

Parameter	Study Assessments Collected Prior to Dosing		Baseline Definition
	Screening	Day 1 Pre-Dose	
Efficacy and Health Outcomes			
Trough FEV1, Trough FVC	X	X	Day 1 pre-dose and pre-bronchodilator nominal time-point
Post-bronchodilator FEV1, Post-bronchodilator FVC	X	X	Day 1 pre-dose and post-bronchodilator nominal time-point
FEV1 reversibility (mL)	X	X	Day 1 FEV1 reversibility (mL)
SGRQ total and domain scores		X	Day 1
CAT score	X	X	Day 1
EQ-5D-5L		X	Day 1
BDI (TDI Baseline)		X	Day 1
Subject global ratings		X	Day 1
Mean number of occasions of rescue use, mean number of nighttime awakenings per night	X	X	Average of measurements from Day -13 to Day 1 inclusive (at least 7 days must be non-missing)
Percentage of rescue-free days, percentage of days symptoms stopped usual activities	X	X	Percentage is calculated as total number of rescue-free days (or total number of days symptoms stopped usual activities) divided by total number of days with non-missing value (from Day -13 to Day 1 inclusive (at least 7 days must be non-missing)) x100
Safety			
Blood pressure	X		Values from most recent assessment prior to first dose of study treatment which records both systolic and diastolic BP (generally Screening but could be a test repeat).
Pulse rate	X		Most recent individual value prior to first dose of study treatment

Parameter	Study Assessments Collected Prior to Dosing		Baseline Definition
	Screening	Day 1 Pre-Dose	
Laboratory tests: Excluding hematology	X		Most recent individual value prior to first dose of study treatment
Laboratory tests: Hematology (including blood eosinophils)	X	X	Most recent individual value prior to first dose of study treatment
ECG endpoints	X		Values from most recent ECG conducted prior to first dose of study treatment

NOTES :

- Only records that have been assigned a treatment phase of 'pre-treatment' as defined in Section 11.3.3 will be considered as baseline assessments.
- 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.

11.4.3. 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/ctt116855/final_01
QC Spreadsheet	: /arenv/arwork/gsk2834425/ctt116855/final_01/documents
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM Implementation Guide Version 3.1.3 & ADaM Implementation Guide Version 1.0). • 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	
• Rich Text Format (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:

Reporting Standards
○ 4.03 to 4.23: General Principles ○ 5.01 to 5.08: Principles Related to Data Listings ○ 6.01 to 6.11: Principles Related to Summary Tables ○ 7.01 to 7.13: Principles Related to Graphics
Formats
• All data (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. • Summaries of continuous data will include number of subjects, mean, standard deviation, median, first quartile, third quartile, minimum and maximum, • 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 in the eCRF.
Planned and Actual Time
• Reporting for tables, figures and statistical analyses: ○ Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. Actual time will be used for calculation of times to events and Kaplan-Meier plots. • Reporting for listings: ○ Planned and actual time relative to study treatment dosing will be shown in listings (refer to IDSL Statistical Principle 5.05.1).
Unscheduled Visits
• Unscheduled visits will not be included in summary tables except as part of a maximum/minimum/worst case post-baseline assessment or if they are assigned as the baseline assessment as detailed in Section 11.4.2. • All unscheduled visits/unplanned readings will be included in listings.
Cardiovascular Event Reports
• Laboratory results, ECG results/findings and vital signs measurements collected as part of cardiovascular event reports will not be included in any tables, listings or any minimum/maximum post-baseline assessments.
Descriptive Summary Statistics

Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %

p-value
• Both adjusted and unadjusted p-values will be displayed on the primary analyses outputs for

Reporting Standards
the endpoints within the hierarchy (detailed in Section 11.9) and will be labeled 'Adjusted p-value' and 'Unadjusted p-value' • All other p-values will be unadjusted and labeled purely as 'p-value'.
Time to event results
• For all time to event analyses, the first quartile and median time to event will be presented. If less than 25% of subjects experienced the event within a treatment group then the first quartile will be displayed as NA (not applicable) for that treatment. If less than 50% of subjects experienced the event within a treatment group then the median will be displayed as NA (not applicable) for that treatment.
Graphical Displays
• Refer to IDSL Statistical Principals 7.01 to 7.13.

11.5. Appendix 5: Derived and Transformed Data

11.5.1. General

11.5.1.1. Study Day

Study Day
• Calculated as the number of days from treatment start date: o Reference date = missing → Study Day = missing o Reference date < treatment start date → Study Day = reference date – treatment start date o Reference date ≥ treatment start date → Study Day = reference date – treatment start date + 1

11.5.1.2. Treatment Stop Date

Study Treatment Stop Date
• If the treatment stop date is missing, it will be imputed as follows: o If any of Study Treatment Discontinuation Visit date, Visit 7 (Week 52) date, date of death are non-missing then the study treatment stop date will be imputed as the minimum of (Study Treatment Discontinuation Visit date, Visit 7 (Week 52) date, date of death, date that all study treatment containers were returned). o For all other subjects, the last recorded exposure start or stop date will be used.

11.5.1.3. Study and Treatment Completion

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 7. • A subject is considered to have completed the study if they either attended Visit 7 or had a phone contact at Visit 7.

11.5.1.4. Projected Week 52 Date

For those subjects who have withdrawn from the study prior to Week 52, a projected Week 52 date will be derived as follows:

Projected Week 52 Date=Date of randomisation + 52 weeks

11.5.1.5. At Risk Period for Calculation of Raw Event Rate

11.5.1.5.1. All Cause Mortality

For calculations of raw event rate the ‘at risk period’ in years (used for the denominator) will be defined as follows:

- On-treatment at risk period:
    - For subjects that completed the study up to Week 52 the on-treatment at risk period will derived as:
      (minimum (date of end of study treatment + 7, date of death, date of study conclusion) – date of start of treatment + 1)/365.25
    - For subjects that prematurely withdrew from the study prior to Week 52 and that have a survival status reported the on-treatment at risk period will derived as:
      (minimum (date of end of study treatment + 7, date of death, date last known alive) – date of start of treatment + 1)/365.25
    - For subjects that prematurely withdrew from the study prior to Week 52 and that do not have a survival status reported the on-treatment at risk period will derived as:
      (minimum (date of end of study treatment + 7, date of death, date of study conclusion) – date of start of treatment + 1)/365.25
- On and off-treatment at risk period:
    - For subjects that did not prematurely discontinue study treatment the on and off-treatment at risk period will derived as:
      (minimum (date of end of study treatment + 7, date of death, date of study conclusion) – date of start of treatment + 1)/365.25
    - For subjects that prematurely discontinued the study treatment period and completed the study up to Week 52 the on and off-treatment at risk period will derived as:
      (Date of study conclusion – date of start of treatment + 1)/365.25
    - For subjects that prematurely discontinued the study treatment period and prematurely withdrew from the study prior to Week 52 the on and off-treatment at risk period will derived as
      (minimum(Date last known alive, Date of Death, Projected date of Week 52 (as defined in Section 11.5.1.4) + 7) – date of start of treatment + 1)/365.25
    - For subjects that prematurely withdrew from the study prior to Week 52 and that do not have a survival status reported the on and off-treatment at risk period will derived as:
      (Date of study conclusion – date of start of treatment + 1)/365.25

11.5.1.5.2. Other Data

For calculations of raw event rate the ‘at risk period’ in years (used for the denominator) will be defined as follows:

- On-treatment at risk period:
    - (minimum (date of end of study treatment+1, date of death, date of study conclusion) – date of start of treatment + 1)/365.25
- Post-treatment at risk period:
    - if date of study conclusion > date of end of treatment as follows: (date of study conclusion – date of end of treatment - 1)/365.25
    - Else post-treatment at risk period will be set to 0

11.5.2. Study Population

11.5.2.1. Demographics

Demographics
Age
• Age will be calculated based on the Pre-Screening Visit date (or Screening, if pre-screening not performed). • Only year of birth is collected on the eCRF, therefore day and month of birth are imputed as '30JUN' in order to derive age. • Birth date will be presented in listings as 'YYYY'.
Age Category
• Age categories are based on age as derived above and are defined as: o ≤ 64 years o 65 - 74 years o 75 – 84 years o ≥ 85 years

11.5.2.2. Subject Disposition

Subject Disposition
• For Kaplan-Meier plots of study withdrawal over time and discontinuation from study treatment over time, censoring will be performed as follows: o For study withdrawal, subjects are represented from their Day 1 date to the date of early withdrawal from the study (or date of death). Subjects that completed the study are censored at the earliest of the date of completion and Day 365. o For discontinuation from study treatment, subjects are represented from their Day 1 date to the date of discontinuation from study treatment (or date of death). Subjects that complete study treatment per protocol are censored at the earliest of their study treatment stop date and Day 365.

11.5.2.3. Treatment Compliance

Treatment Compliance
• 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. • Number of doses of study treatment taken by each subject from each inhaler = dose counter start- dose counter stop. ○ Compliance=sum of (dose counter start–dose counter stop) from each inhaler x 100 / (treatment stop date – treatment start date +1) • Compliance 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 compliance will still be calculated using data from all containers received and overall treatment start and stop dates.

11.5.2.4. Cardiovascular Risk Factors

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

11.5.2.5. Pneumonia Risk Factors

Pneumonia Risk Factors at Screening
• The following categories will be summarized to identify pneumonia risk factors: • Age (<65, ≥65) • Gender • BMI (will be defined twice; <21 kg/m^2, ≥21 kg/m^2; <25 kg/m^2, ≥25 kg/m^2)

Pneumonia Risk Factors at Screening
• Smoking status at screening • Pneumonia history • GOLD Grade

11.5.2.6. Concomitant Medications

Concomitant Medications
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
  • 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 and at IP discontinuation will be grouped into the following categories based on the RMC classification:
  • ICS
  • LABA
  • LAMA
  • Xanthine
  • PDE4 Inhibitors
  • Any combination of the above
  • No selected RMC medication combination
 	
• COPD medication combinations taken at study treatment discontinuation for subjects that provided post-treatment information will include all subjects that prematurely discontinued study treatment.

11.5.2.7. Smoking Status

Smoking Status
• Smoking Status at Screening is determined directly from the eCRF. • A subject's smoking status from Visit 2 (Day 1) onwards will be derived from the smoking status at the visit in question and any changes in smoking status from the time of the previous assessment (e.g., date of any changes in status were made). • Only smoking status responses recorded at scheduled visits will be included in the summary tables.

11.5.2.8. COPD Exacerbation History

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 and a separate category of ≥2. • 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. Exacerbation severity is defined in Section 11.5.3.1. • 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).

11.5.2.9. Screening Lung Function and GOLD Grade

Screening Lung Function
Pre-bronchodilator FEV1/FVC, FEV1 Percent Predicted and Reversibility

• Pre-bronchodilator FEV1/FVC ratio and pre-bronchodilator FEV1 as a percentage of predicted normal at Screening are not collected in the eCRF and will be calculated as:
  ○ Pre-bronchodilator FEV1/FVC = Pre-bronchodilator FEV1/Pre-bronchodilator FVC
  ○ Pre-bronchodilator Percent Predicted = (Pre-bronchodilator FEV1/Predicted FEV1) * 100
• The reversibility to salbutamol status of a subject is calculated at Screening and is based on the

Screening Lung Function
Pre-bronchodilator FEV1/FVC, FEV1 Percent Predicted and Reversibility
difference (absolute change and % change) between a subject's pre-salbutamol assessment of FEV1 and their post-salbutamol assessment of 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%

11.5.3. Efficacy and Health Outcomes

11.5.3.1. Exacerbations

COPD Exacerbations
General
• Each COPD exacerbation will be categorized based on severity as follows: ○ Mild: no treatment with systemic/oral corticosteroids and/or antibiotics and no hospitalization and that did not result in death ○ Moderate: required treatment with systemic/oral corticosteroids and/or antibiotics (not involving hospitalization or resulting in death) ○ Severe: required hospitalization or resulted in death • The duration of an exacerbation will be calculated as exacerbation resolution date or date of death - exacerbation onset date + 1. • 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). • The raw event rate per thousand subject-years for exacerbations will be calculated as the number of events x 1000 divided by the at risk period during the time-period of interest as defined in Section 11.5.1.5.2 • For the boxplot of on-treatment moderate/severe annual raw COPD exacerbation rates the individual subject rate will be derived as number of events experienced by the subject x 1000 divided by the individual subject's on-treatment at risk period as defined in Section 11.5.1.5.2.

COPD Exacerbations

Offset variable for rate of exacerbations

For analyses of rate of moderate/severe COPD exacerbations, the offset variable will be defined as follows:

- Including on-treatment data only
    - logarithm of (on-treatment at risk period, as defined in Section 11.5.1.5.2)
- Including both on and off-treatment data
    - logarithm of ([total time in study per subject (defined in Section 11.5.4.1)]/365.25).
- Jump to reference (using on-treatment data)
    - For subjects that complete study treatment:
      logarithm of (on-treatment at risk period, as defined in Section 11.5.1.5.2)
    - For subjects that prematurely discontinue study treatment but complete the study up to Week 52:
      logarithm of ([Actual date of Week 52 – date of start of treatment + 1]/365.25)
    - For subjects that prematurely discontinue from study treatment and withdraw from the study prior to Week 52:
      logarithm of ([Projected Week 52 date (as defined in Section 11.5.1.4) – date of start of treatment + 1]/365.25)
- Jump to reference (using on and off-treatment data)
    - For subjects that complete study treatment:
      logarithm of ([total time in study per subject (defined in Section 11.5.4.1)]/365.25)
    - For subjects that prematurely discontinue study treatment but complete the study up to Week 52:
      logarithm of ([Actual date of Week 52 – date of start of treatment + 1]/365.25)
    - For subjects that prematurely discontinue from study treatment and withdraw from the study prior to Week 52:
      logarithm of ([Projected Week 52 date (as defined in Section 11.5.1.4) – date of start of treatment + 1]/365.25)

Time to First On-treatment Exacerbation

- The time to 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 Day 1 date to the start date of their first exacerbation or date of censoring. Subjects that have not experienced an on-treatment exacerbation are censored at the earliest of the date of their treatment stop date +1 day or the date of death.

COPD Exacerbations
Time to First Exacerbation Including Off-treatment data
• The time to first exacerbation including off-treatment data will be calculated as exacerbation onset date of first exacerbation – date of start of treatment + 1. • Only exacerbations reported during the on-treatment and post-treatment study phases will be considered (see Section 11.3.3 for details of assigning study phase) • Subjects will be represented from their Day 1 date to the start date of their first exacerbation or date of censoring. Subjects that have not experienced an on or off-treatment exacerbation are censored at the earliest of (date of study conclusion or the date of death).
Time to First On-treatment Moderate/severe Exacerbation or Premature Study Treatment Discontinuation
• The time to first on-treatment moderate/severe exacerbation will be calculated as exacerbation onset date of first on-treatment moderate/severe exacerbation – date of start of treatment + 1. • The time to study treatment discontinuation will be calculated as the date of premature study treatment discontinuation – date of start of treatment + 1. • The time to first on-treatment moderate/severe exacerbation or study treatment discontinuation is defined as the earliest of the time to first on-treatment moderate/severe exacerbation or time to premature study treatment discontinuation. • Subjects will be represented from their Day 1 date to the earliest of the event or censoring. 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.
Time to Each On-treatment Exacerbation
• Subjects will be defined as at risk while on treatment from the start of treatment until their first exacerbation, and then from the day after each exacerbation had resolved. • Subjects will be represented from their study treatment start date to the earliest of the date of their treatment stop date +1 day or the date of death.
Association to Chest X-Ray
• A chest X-ray is considered associated with an exacerbation if it is performed within the duration of the exacerbation or performed between -7 days to +10 days (inclusive) of the onset date of the exacerbation.

11.5.3.2. Lung Function

Spirometry
Trough FEV1 and FVC
• The trough value for FEV1 and FVC at Weeks 4, 16, 28, 40 and 52 visit is the pre-dose (prior to taking the morning dose of study treatment) and pre-bronchodilator assessment at that visit.

Spirometry
Post-Bronchodilator FEV1 and FVC
• The post-bronchodilator value for FEV1 and FVC at Weeks 4, 16, 28, 40 and 52 is the pre-dose (prior to taking the morning dose of study treatment), post-bronchodilator assessment (approximately 10 to 30 minutes after administering four puffs of salbutamol).
FEV1 Reversibility (mL)
• The reversibility to salbutamol is calculated at each visit where FEV1 is collected as follows: FEV1 reversibility (mL) = post-salbutamol FEV1 (mL) - pre-salbutamol FEV1 (mL)

11.5.3.3. SGRQ

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). • Details for how to score the SGRQ-C, including handling of missing data or multiple responses to questions, are outlined in the SGRQ-C manual (Jones, 2016). • SGRQ-C domain and total scores 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 baseline, 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 considered a responder according to SGRQ total score if their on-treatment SGRQ total score has decreased at least 4 units from the 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. • Moderate and major response will be defined using cut-offs determined as follows: o Cut-off for defining moderate responder will use the integer value of the mean change from baseline in SGRQ total score at Week 52 for all subjects (combined treatment groups) who rated 'better' in the subject global rating of change in COPD severity at Week 52. o Cut-off for defining major responder will use the integer value of the mean change from baseline in SGRQ total score at Week 52 for all subjects (combined treatment groups) who rated 'much better' in the subject global rating of change in COPD severity at Week 52. • A subject will be considered a major responder if their on-treatment change from baseline in SGRQ total score is ≤ the cut-off value for major responder. • A subject will be considered a moderate or major responder if their on-treatment change from

St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C)
baseline in SGRQ total score is ≤ the cut-off value for moderate responder. • Missing data will be handled as detailed in Section 11.6.

11.5.3.4. CAT

COPD Assessment Test (CAT)
CAT Score
• The CAT consists of eight items each formatted as a six-point differential scale: 0 (no impact) to 5 (high impact). A CAT score will be calculated by summing the non-missing scores on the eight items 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. • If the language of the CAT conducted at a post-baseline visit is different to the language used at Day 1 baseline, the CAT score for that visit and all subsequent visits will be set to missing. • If there is more than one response to a question at a visit or duplicate questionnaires, the CAT score for that visit will be set to missing.
Responder Status according to CAT Score
• A subject will be considered a responder according to CAT score if their on-treatment CAT score has decreased at least 2 units from the baseline CAT total score. • A subject will be considered a non-responder if their on-treatment CAT score has decreased by less than 2 units, has not changed, or has increased compared to baseline. • Missing data will be handled as detailed in Section 11.6.
CAT Score Categories
The CAT score categories will be defined as: • A score < 10 • A score ≥ 10

11.5.3.5. All Cause Mortality

Rate of all cause mortality
The raw event rate per thousand subject-years for adjudicated deaths will be calculated as the number of events x 1000 divided by the at risk period during the time-period of interest as defined in Section 11.5.1.5.1.
Time to On-treatment All Cause Mortality
• The time to on-treatment all cause mortality will be calculated as death date – date of start of treatment + 1. • Subjects will be represented from their Day 1 date to the date of death (on-treatment) or date of censoring. Subjects that have not experienced an on-treatment death are censored as follows:

- Subjects that have completed the study are censored at the earliest of (date of study conclusion and date of study treatment stop + 7 days).
- Subjects that have an off-treatment or post-study death reported are censored at the date of their study treatment stop + 7 days
- Subjects that prematurely withdraw from the study and have a survival status present are censored at the earliest of (date last known alive and date of study treatment stop + 7 days)
- Subjects that prematurely withdraw from the study and do not have a survival status reported at 52 weeks post-randomisation are censored at the earliest of (date of study conclusion and date of study treatment stop + 7 days)

Time to On and Off-treatment All Cause Mortality

- The time to on and off-treatment all cause mortality will be calculated as death date – date of start of treatment + 1.
- Subjects will be represented from their Day 1 date to the date of death (on and off-treatment, as defined in Section 11.3.2) or date of censoring. Subjects that have not experienced an on or off-treatment death are censored as follows:
  - Subjects that have completed study treatment are censored at the earliest of (date of study conclusion and date of study treatment stop + 7 days).
  - Subjects that prematurely discontinued study treatment that attended the Week 52 visit are censored at the earliest of (date of study conclusion and date of Week 52 + 7 days).
  - Subjects that prematurely discontinued study treatment that withdrew from the study prior to Week 52 and have a survival status present are censored at the earliest of (date last known alive and projected Week 52 date + 7).
  - Subjects that prematurely discontinued study treatment that withdrew from the study prior to Week 52 and do not have a survival status present or that have a post-study death reported are censored at the earliest of (date of study conclusion and projected Week 52 date + 7).

11.5.3.6. BDI/TDI

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, and Magnitude of Effort). Each of these scales has five possible scores ranging from 0 to 4 (with lower scores indicating more impairment), with the range of the BDI focal score 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 (Day 1).
- The 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, and Magnitude of Effort). Each of these scales has a possible score ranging from -6 (major deterioration) to +6 (major improvement). TDI focal score is calculated as the sum of the three individual scores and then

BDI/TDI
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 TDI focal score will be set to missing. • If the language of the TDI conducted at a visit is different to the language for the BDI, all TDI scores at that visit and subsequent visits will be set to missing. • If there is more than one response to a question at a visit or duplicate questionnaires, the BDI or TDI score for that visit will be set to missing.
Categorization of TDI Focal Score
• Full categorization of TDI focal score for categorical summary is as follows: 'major improvement ' defined as a score of ≥7 to ≤9 'moderate improvement' defined as a score of ≥4 to <7 'minor improvement' defined as a score of ≥1 to <4 'no change' defined as a score of > -1 to < 1 'minor deterioration' defined as a score of > -4 to ≤ -1, 'moderate deterioration' defined as a score of >-7 to ≤-4 'major deterioration' defined as a score of ≥-9 to ≤-7
Responder Status according to TDI Focal Score
• A subject will be considered a responder if the on-treatment TDI focal score was at least 1 unit. • A subject will be considered a non-responder if their on-treatment TDI focal score was less than 1 unit. • Missing data will be handled as detailed in Section 11.6. • For subjects who are responders at a particular visit, response will be further classified as moderate if the TDI focal score is ≥4 and <7 and as major if the TDI focal score is ≥7.

11.5.3.7. eDiary

Calculation of Daily eDiary Endpoints
General
• Subjects were instructed to complete the daily eDiary in the morning prior to taking any study treatment. • Number of occasions of rescue salbutamol use and number of nighttime awakenings were collected in the daily eDiary. • The Yes/No question of "Did your respiratory symptoms stop you performing your usual activities in the last 24 hours?" were also collected in the eDiary. • The table below shows which daily eDiary records are used to calculate the daily eDiary endpoints for each analysis time period. Any diary data collected in the post-treatment phase of the study will not be slotted. See Section 11.3.3 for details on the assignment of treatment phases.

Calculation of Daily eDiary Endpoints

Daily Record		Analysis Time Period
Beginning Timepoint (day)	Ending Timepoint (day)	
-13	1	Week -1 (Baseline)
2	29	Weeks 1 – 4
30	57	Weeks 5 – 8
58	85	Weeks 9 – 12
86	113	Weeks 13 – 16
114	141	Weeks 17 – 20
142	169	Weeks 21 – 24
170	197	Weeks 25 – 28
198	225	Weeks 29 – 32
226	253	Weeks 33 – 36
254	281	Weeks 37 – 40
282	309	Weeks 41 – 44
310	337	Weeks 45 – 48
338	365	Weeks 49 – 52

Note: There is no Day 0. Any records with actual day>365 will not be assigned to a time period.

Note: Daily eDiary records that were not assigned to a time period will not be used in calculation of daily eDiary endpoints.

- For a subject to be counted in any time period (except for baseline where at least 7 days non-missing entries are required) for a given endpoint they must have at least one diary entry recorded for that endpoint during that time period.
- Any daily eDiary data that were collected post-study treatment discontinuation will be excluded from analysis, including four weekly period data summaries.
- If a subject has more than one daily eDiary record for any given day, the worst case response on that day for each endpoint will be used in the summaries and analyses. i.e. the maximum number of occasions of rescue use reported will be counted for the day in question and used to determine if it was a recue-free day; the maximum number of nighttime awakenings will be counted for the day in question; symptoms stopped usual activities = 'Yes' will be used as the worst case over symptoms stopped usual activities = 'No'.

eDiary Endpoints

- The mean number of occasions of rescue use per day, percentage of rescue-free days, mean number of nighttime awakenings per night and percentage of days symptoms stopped usual activities will be calculated for each subject during the four weekly periods defined above.

11.5.3.8. EQ-5D-5L

EQ-5D-5L

- If the language of the EQ-5D-5L conducted at a post-baseline visit is different to the language used at baseline, the EQ-5D-5L scores for that visit and all subsequent visits will be set to

missing.
- If there is more than one response to a question at a visit or duplicate questionnaires, the EQ-5D-5L health state and utility score for that visit will be set to missing.

11.5.3.9. Healthcare Resource Utilization

Healthcare Resource Utilization
• The total number of visits for each type of healthcare contact (home visits (day), home visits (night), office/practice visits, urgent care/outpatient clinic visits, emergency room visits) and number of days in intensive care and number of days in general hospital wards will be calculated by summing the respective visits and number of days. This will also be calculated for each contact type (COPD exacerbations, COPD not-exacerbation, other healthcare contact).

11.5.4. Safety

11.5.4.1. Exposure

Exposure
Exposure and Post-treatment Duration
• Duration of exposure to study treatment is calculated as: o treatment stop date – treatment start date +1 • Duration of post-treatment time spent on study is calculated as: o study conclusion date – treatment stop date • Duration of total time spent on study is calculated as: o study conclusion date – treatment start date + 1
Exposure Categories
• The following exposure categories will be derived: ≥1 day, ≥4 weeks, ≥8 weeks, ≥12 weeks, ≥16 weeks, ≥20 weeks, ≥24 weeks, ≥28 weeks, ≥32 weeks, ≥36 weeks, ≥40 weeks, ≥44 weeks, ≥48 weeks and ≥52 weeks. An additional category of 51-53 weeks will also be summarized. • For post-treatment duration, the following categories will be derived: 0 days, 1-7 days, >7 days

11.5.4.2. Adverse Events

Adverse Events
Adverse Event Rate
• The event rate per thousand subject-years will be displayed on most AE data displays listed in Section 11.12 (including summaries of AESIs and Serious Adverse Reports). Event rate per thousand subject-years will be calculated as the number of events x 1000 divided by the at risk period during the time-period of interest as defined in Section 11.5.1.5.2.

Adverse Events of Special Interest (AESI)

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

AESI Group	AESI Subgroup	Sub-SMQ
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		
Lower Respiratory Tract Infection (LRTI) excluding pneumonia		
Tremor		
Urinary retention		

Adverse Events Considered of Interest in the Elderly	
• AEs considered of interest in the elderly will be summarized by age category and overall for each treatment group. • SMQs or PTs for these groupings are provided below.	
AE Grouping	**SMQ, PT or System Organ Class (SOC)**
Any AE	
Serious AE	
Results in death	
Life-threatening	
Hospitalization/prolongs existing hospitalization	
Results in disability/incapacity	
Congenital anomaly/birth defect	
Other (medically significant)	
Possible drug-induced liver injury	
Adverse events leading to permanent discontinuation of study treatment or withdrawal from study	
Psychiatric disorders	Psychiatric disorders (SOC)
Nervous system disorders	Nervous system disorders (SOC)
Accidents and injuries	Accidents and injuries (SMQ)
Cardiac disorders	Cardiac disorders (SOC)
Vascular disorders	Vascular disorders (SOC)
Cerebrovascular disorders	Central nervous system vascular disorders (SMQ)
Infections and infestations	Infections and infestations (SOC)
Anticholinergic syndrome	Anticholinergic syndrome (SMQ)
Quality of life decreased	Quality of life decreased (PT)
Postural hypotension, Falls, Black outs/Syncope, Dizziness, Ataxia and Fractures	Postural hypotension (selected PTs*), Falls (PT), Black outs/Syncope (selected PTs*), Dizziness (selected PTs*), Ataxia (selected PTs*) and Fractures (selected PTs*)
* Preferred terms which contribute to each of the groups will be provided by GCSP using the MedDRA version current at the time of reporting. This will be finalised prior to unblinding.	
Association to Serious Adverse Reports	
An event in the pneumonia AESI group is considered associated with an adjudicated Serious Adverse Report if the Serious Adverse Report was classified as 'COPD exacerbation with evidence of pneumonia' or 'Pneumonia/respiratory tract infection without COPD exacerbation' and the onset of the Serious Adverse Report is within -7 to +10 days of the onset of the pneumonia AESI.	

11.5.4.3. Bone Fracture

Bone Fracture
• Bone fracture event rate will be calculated in the same manner as AE rate.
Bone Fracture Incidents
• If a subject suffers fractures in multiple locations with the same date of fracture, this is

Bone Fracture
considered to be one fracture incident. • In the case of multiple fracture types (traumatic/non-traumatic) contributing to one fracture incident, the worst case fracture type (non-traumatic) will be assigned to the fracture incident. E.g. if a subject has a traumatic wrist fracture and a non-traumatic foot fracture on the same date, this will be considered to be one non-traumatic fracture incident. • Bone fracture incident event rate will be calculated in the same manner as AE rate.

11.5.4.4. Maximum/Minimum Post-Baseline and Worst-Case Post-Baseline

Maximum/Minimum Post-Baseline and Worst-Case Post-Baseline	
Definition	**Reporting Details**
Maximum post-baseline (QTcF, QTc B, PR interval, ECG heart rate, pulse rate, systolic BP, diastolic BP and laboratory tests)	Maximum on-treatment value over all time-points (including scheduled and unscheduled assessments)
Minimum post-baseline (Diastolic BP and laboratory tests that do not have a lower limit = 0)	Minimum on-treatment value over all time-points (including scheduled and unscheduled assessments)
Worst case post-baseline (ECG findings)	Including scheduled and unscheduled on-treatment assessments • '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 11.3.3 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), and will include the Week 4 pre-dose ECG for the Pre-dose ECG sub-population. Vital signs (pulse rate, systolic BP and diastolic BP) collected at an assessment associated with a pneumonia event will also be included in derivation of a 'maximum/minimum post-baseline' assessment. The pneumonia event related assessments (e.g. vitals) dates will be assumed to be the same as the event date.

11.5.4.5. Laboratory Parameters

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 (respectively) at any scheduled or

Laboratory Parameters
unscheduled on-treatment visit. • 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. 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 the "any visit post-baseline" row of related summary tables.

11.5.4.6. ECG

ECG Event Rates			
• ECG Abnormality event rates will be calculated in the same manner as AE rate.			
ECG Categories			
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	
Change from Baseline			
Change from Baseline QTcF	msec		<-60
		≥-60	<-30
		≥-30	<0
		≥0	< 30
		≥ 30	<60
		≥ 60	

11.5.4.7. Pneumonia

Pneumonia
Pneumonia Event Rates
Pneumonia event rates (based on the pneumonia eCRF form) will be calculated in the same manner as AE rate.
Association of Chest X-Ray with Pneumonia Event
• Pneumonia is considered to be supported by a chest X-ray if there is an associated X-ray which shows the presence of infiltrates. A chest X-ray is considered associated with pneumonia if it is performed within the duration of the pneumonia or performed between -7 to +10 days (inclusive) of the date of onset of pneumonia.

11.5.4.8. Time to First Event

Time to First Event
• The time to the first event will be calculated as (onset date of first event – date of start of treatment + 1). • Subjects will be represented from their Day 1 date to the start date of their first event or date of censoring. • Subjects that have not experienced an event are censored at the earliest of their date of treatment stop + 1 day or date of death.
Time to First Composite Event
• The time to first composite event will be calculated as the minimum event onset date of all components of the composite endpoint.

11.5.4.9. MACE

MACE	
MACE Event Rates	
MACE event rates will be calculated in the same manner as AE rate.	
Broad MACE criteria	**Narrow MACE criteria**
Ischaemic heart disease SMQ: • Myocardial infarction SMQ (excluding fatalities) • Other ischemic heart disease SMQ (excluding fatalities)	-Myocardial infarction PT (excluding fatalities) -Acute myocardial infarction PT (excluding fatalities)
Central nervous system haemorrhages and cerebrovascular conditions SMQ (excluding fatalities)	
Adjudicated CV deaths	
Note: Adjudication is performed for a serious adverse report (based on the event the adjudicators consider to be the primary medical event if the report includes several adverse events for an individual subject). Summaries for MACE will include any death adjudicated as from a CV cause and non-fatal events recorded in the eCRF. If, for example, a subject has an adjudicated CV death and a non-fatal myocardial infarction in the eCRF, they will be counted once in each category and once in the overall MACE count.	

11.6. Appendix 6: Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a "blank" in subject listing displays unless all data for a specific visit are missing in which case the visit is not displayed in the listing. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and will be displayed as such. ○ 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). ○ No imputation will be made for any missing numerical data, except in the specified sensitivity analyses of the primary and secondary endpoints to assess the impact of missing data on study results.
Responder	• Subjects with a missing baseline will have responder status as missing. • Subjects with missing on-treatment data and a subsequent non-missing on-treatment scheduled assessment will not be considered a responder or non-responder but will be left as missing. • Subjects that have withdrawn from study treatment prior to the visit in question will be imputed as non-responders at all visits post-study treatment discontinuation where the assessment was expected to be performed (regardless of whether the subject has had a post-treatment assessment performed or not). This includes all visits up to and including Week 52. • Subjects with missing on-treatment data and no subsequent non-missing on-treatment scheduled assessments will be imputed as non-responders.

11.6.1. 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 for the imputation of the treatment stop date are provided in Section 11.5.1.2.
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. ○ If the imputed stop date results in a date that is after the date of death, the date of death will be used for the stop date of the medication. • The recorded partial date will be displayed in listings.
Adverse	• Any partial dates will be imputed using the following convention:

Element	Reporting Detail
Events, Exacerbations, Pneumonia	○ 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 this imputation results in a date prior to Day 1 and the event could possibly have occurred during treatment from the partial information, then the Day 1 date will be assumed to be the start date. ○ If it is not certain with the partial date/or no date at all which phase of the study the event started, it 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. ○ If the imputed stop date results in a date that is after the date of death, the date of death will be used for the stop date. ○ For exacerbation data only; ○ If the partial date pertains to a pre-treatment or off-treatment exacerbation then the imputation rules detailed above apply. Please note that having duplicate partial exacerbation start dates or end dates may result in overlapping exacerbations following imputation. However, each exacerbation record will be counted as a unique exacerbation for summaries and analyses. ○ For on-treatment exacerbations only, if the imputation rules detailed above result in overlapping exacerbations, end dates will be imputed as the day prior to the start of the next exacerbation. This is to ensure that all exacerbations are included appropriately in the Andersen-Gill analyses for the Time to Each on-treatment exacerbation endpoints. ○ The recorded partial date will be displayed in listings.
Date of Death	• Any partial date of death will be imputed using the following convention: ○ '01' will be used for the day and 'Jan' will be used for the month. ○ However, if this imputation results in a date prior to a contact/assessment date reported in the eCRF (including adverse event dates, concomitant medication start/end dates), the maximum contact/assessment date will be assumed to be the date of death. ○ The recorded partial date will be displayed in listings.
Date Last Known Alive	• Any partial date last known alive from the survival status eCRF will be imputed using the following convention: ○ '01' will be used for the day and 'Jan' will be used for the month. ○ However, if this imputation results in a date prior to a contact/assessment date reported in the eCRF (including adverse event dates, concomitant medication start/end dates), the maximum contact/assessment date will be assumed to be the date last known alive. • The recorded partial date will be displayed in listings.

11.6.1.1. Missing Data for Statistical Analysis

Details regarding the sensitivity analyses that will be performed for the primary and key secondary endpoints can be found in Section 7 & Section 8.

11.7. Appendix 7: Multicenter Studies

11.7.1. Geographical Region

Due to the large number of centers participating in this study, a geographical region will be used rather than adjusting for center in the statistical analyses. The center grouping will be created based on geographical region and number of randomized subjects in a country, in order to define groups of roughly similar size.

Geographical Region	Countries
Western Europe	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Netherlands, Norway, Poland, Romania, Spain, Sweden, United Kingdom
Eastern Europe	Israel, Russia, Turkey, Ukraine
Asia	China, Hong Kong, Japan, Korea, Philippines, Singapore, Thailand, Viet Nam
North America	Canada, Puerto Rico, United States
South America	Argentina, Brazil, Chile, Colombia, Peru
Other	Australia, New Zealand, South Africa

11.8. Appendix 8: Examination of Covariates, Subgroups & Other Strata

11.8.1. Handling of Covariates, Subgroups & Other Strata

Covariates will be included in statistical analyses as detailed in the statistical model specifications in Section 7 and Section 8.

11.9. Appendix 9: Handling Multiple Comparisons and Multiplicity

The study has been powered at the 1% significance level in order to satisfy regulatory requirements of substantial evidence of efficacy for a single study. However, type I error is controlled at the 5% significance level.

In order to account for multiplicity, the truncated Hochberg procedure (Dmitrienko, 2008) with a truncation parameter of γ=0.6 will be used to control overall type I error at α=0.05.

For the co-primary treatment comparisons (pairwise comparison of FF/UMEC/VI with FF/VI and FF/UMEC/VI with UMEC/VI for the annual rate of on-treatment moderate/severe exacerbations), both comparisons will be declared statistically significant if the unadjusted p-value for both comparisons is significant at the 0.04 level. Should the largest p-value for the two comparisons be above 0.04, the other comparison will be declared statistically significant if the smaller unadjusted p-value is below 0.025.

Pairwise comparisons of FF/UMEC/VI versus FF/VI and FF/UMEC/VI versus UMEC/VI will be performed for the secondary efficacy and other endpoints and for UMEC/VI vs. FF/VI on all endpoints. These comparisons will not be adjusted for multiplicity. If at least one of the co-primary treatment comparisons is considered statistically significant, inferences will be drawn from p-values for the treatment comparisons on secondary and other endpoints. If neither of the co-primary comparisons is considered statistically significant, testing on the secondary and other endpoints will be performed and presented for descriptive purposes only.

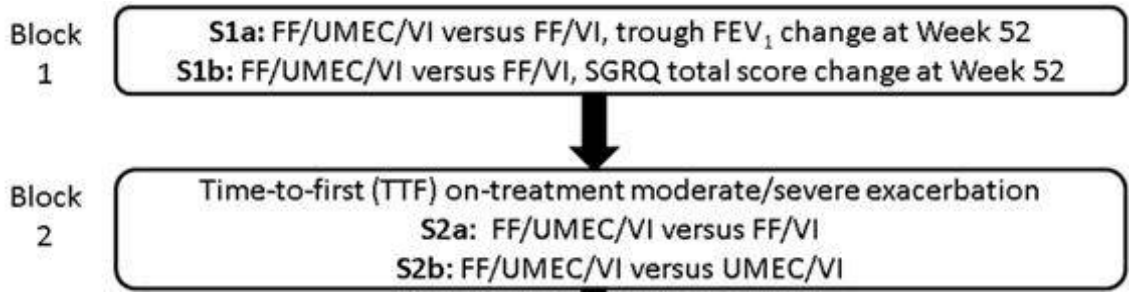
If both co-primary treatment comparisons are statistically significant, these secondary and other treatment comparisons will be declared significant if the unadjusted p-value is <0.05. If only one co-primary treatment comparison is statistically significant, these secondary and other treatment comparisons will be declared significant if the unadjusted p-value is <0.01.

Where strong control of type I error is required, multiplicity across selected treatment comparisons and secondary endpoints will be controlled using a hierarchical, closed testing procedure. The secondary hypothesis tests will be grouped sequentially in two blocks of two comparisons each, grouped according to specific clinical concepts (lung function and symptoms, and time to first exacerbation event).

Each block of comparisons will also be adjusted for multiplicity using the truncated Hochberg method as described for the primary endpoint analysis with a truncation parameter of γ=0.6 for the first block and a truncation parameter of γ=1 for the second block.

At least one endpoint must be statistically significant in the first block in order to make inferences in the second block. As shown in Figure 1, at least one of endpoints S1a and S1b would need to be significant in order to make inferences for the S2a and S2b comparisons contained in the next block.

Figure 1 Secondary endpoint hierarchy



Note that the reference level required to determine statistical significance for each block within the secondary hierarchy will depend on whether one or both comparisons were significant at the prior step:

	Reference level for statistical significance based on unadjusted p-value for comparisons of FF/UMEC/VI versus FF/VI (all co-primary, block 1 and block 2 endpoints) and FF/UMEC/VI versus UMEC/VI (co-primary and block 2 endpoint)			
Co-primary treatment comparisons	Both $p<0.04$	Both $p<0.04$	One $p\geq0.04$ and one $p<0.025$	One $p\geq0.04$ and one $p<0.025$
Block 1	Both $p<0.04$	One $p\geq0.04$ and one $p<0.025$	Both $p<0.008$	One $p\geq0.008$ and one $p<0.005$
Block 2	Both $p<0.05$ or One $p\geq0.05$ and one $p<0.025$	Both $p<0.01$ or One $p\geq0.01$ and one $p<0.005$	Both $p<0.008$ or One $p\geq0.008$ and one $p<0.005$	Both $p<0.002$ or One $p\geq0.002$ and one $p<0.001$

All further efficacy endpoints/treatment comparisons not in the above testing hierarchy will be considered statistically significant at the relevant reference level as detailed in Block 2 if at least one treatment comparison is considered to be statistically significant in Block 2.

11.10. Appendix 10: Model Checking and Diagnostics for Statistical Analysis

Model checking will only be performed for the primary analysis for each endpoint. If the model assumptions are met for the primary analysis then we will assume that the model assumptions were also met for any subgroup analyses.

11.10.1. Statistical Analysis Assumptions

11.10.1.1. Negative Binomial Regression and Poisson Regression

Endpoint(s)	• Annual rate of on-treatment moderate/severe exacerbations • Annual rate of on-treatment severe exacerbations • Annual rate of all on-treatment exacerbations (mild, moderate, severe) • Annual rate of on-treatment moderate exacerbations • Annual rate of on-treatment exacerbations requiring systemic/oral corticosteroids • Annual rate of on-treatment exacerbations requiring antibiotics
Analysis	• Negative binomial regression • Poisson regression (moderate/severe exacerbations)
• The fit of the regression models will be examined using "Q-Q" plots of the standardized residuals. Interpretation of these plots will be aided by the addition of simulated envelopes as proposed by Atkinson (Atkinson,1985).	

11.10.1.2. Cox Proportional Hazards

Endpoint(s)	• Time to first on-treatment moderate/severe exacerbation • Time to death from any cause (on-treatment) • Time to first on-treatment severe exacerbation • Time to first on-treatment event in the pneumonia AESI group • Time to first on-treatment event in the pneumonia AESI group resulting in hospitalization, prolonged hospitalization or death • Time to first on-treatment event in the pneumonia AESI group or moderate/severe exacerbation • Time to first on-treatment event in the pneumonia AESI group resulting in hospitalization, prolonged hospitalization or death or severe exacerbation • Time to first on-treatment event in the pneumonia AESI group resulting in hospitalization, prolonged hospitalization or death or severe exacerbation or event in the CV AESI group resulting in hospitalization, prolonged hospitalization or death
Analysis	• Cox's proportional hazard model
• The proportional hazards assumption will be examined by obtaining the Kaplan-Meier estimates of the survival function S(t) over time separately for each treatment group. In addition, the ln {-ln[S(t)]} plot will be produced.	

11.10.1.3. Andersen-Gill

Endpoints	• Time to onset of each on-treatment moderate/severe exacerbations • Time to onset of each severe exacerbation
Analysis	• Andersen-Gill model for recurrent events
• The proportional hazards assumption will be assessed by plotting the estimated log cumulative hazard function against the log of the time to event by treatment group.	

11.10.1.4. Mixed Model Repeated Measures

Endpoint(s)	• Trough FEV1 • SGRQ total score • Trough FVC • Post-bronchodilator FEV1 • FEV1 reversibility • Post-bronchodilator FVC • TDI focal score • CAT score • Mean number of occasions of rescue use per day • Percentage of rescue-free days • Mean number of nighttime awakenings per night • Percentage of days symptoms stopped usual activities • Pulse rate • Systolic BP • Diastolic BP • QTcF
Analysis	• MMRM
• 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.	

11.10.1.5. Generalized Linear Model

Endpoint(s)	• Proportion of responders according to FEV1, SGRQ total score, CAT score, and TDI focal score
Analysis	• Generalized linear model
• Pearson residuals will be plotted by using PLOTS=PEARSONPANEL option for the model statement in SAS.	

11.10.1.6. Analysis of Covariance

Endpoint(s)	• QTc(F), Trough FEV1 (Sensitivity), SGRQ Total Score(Sensitivity)
Analysis	• ANCOVA
• 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	

11.10.1.7. Logistic Regression

Endpoint(s)	• Subject global rating of change in activity limitation • Subject global rating of change in COPD severity
Analysis	• Logistic regression
• . • The score test will be used to assess the proportional odds assumption.	

11.11. Appendix 11: Abbreviations & Trademarks

11.11.1. Abbreviations

Abbreviation	Description
ADAE	ADaM Dataset for Adverse Events
ADaM	Analysis Data Model
ADCM	ADaM Dataset for Concomitant Medications
AE	Adverse Event
AESI	Adverse Event of Special Interest
ASE	All Subjects Enrolled
ATC	Anatomical Therapeutic Chemical Classification
BDI	Baseline Dyspnea Index
BMI	Body Mass Index
BP	Blood Pressure
bpm	Beats Per Minute
CAT	COPD Assessment Test
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRT	Case Report Tabulation
CSR	Clinical Study Report
CV	Cardiovascular
DBF	Database Freeze
DM	Data Management
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	Eosinophil
EQ-5D-5L	EuroQol Questionnaire (five level)
FEV1	Forced Expiratory Volume in One Second
FF	Fluticasone Furoate
FVC	Forced Vital Capacity
GCSP	Global Clinical Safety and Pharmacovigilance
GLM	General Linear Model
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
HRQoL	Health Related Quality of Life
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroid
IDMC	Independent Data and Monitoring Committee
IDSL	Integrated Data Standards Library
ITT	Intent-To-Treat
IVRS	Interactive Voice Recognition System

Abbreviation	Description
kg	Kilogram
KR	Kenward and Roger
L	Liter
LABA	Long-Acting Beta-Agonist
LAMA	Long-Acting Muscarinic Receptor Antagonist
LLN	Lower Limit of Normal
LRTI	Lower Respiratory Tract Infection
LS	Least-square
m	Meter
MACE	Major Adverse Cardiac Event
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
mmHg	Millimeters of Mercury
MMRM	Mixed Model Repeated Measures
msec	Millisecond
NA	Not Applicable
NQ	Not Quantifiable
PD	Protocol Deviation
PDE4	Phosphodiesterase-4
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PT	Preferred Term
QC	Quality Control
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
RTF	Rich Text Format
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SDAC	Statistical Data Analysis Center
SDL	Source Data Lock
SDTM	Study Data Tabulation Model
SE	Standard Error
SGRQ	St. George's Respiratory Questionnaire
SGRQ-C	SGRQ for COPD patients
SI	System Independent
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TDI	Transitional Dyspnea Index
TFL	Tables, Figures & Listings
TSCG	Tibco Spotfire Clinical Graphics software

Abbreviation	Description
TTF	Time to First
ULN	Upper Limit of Normal
UMEC	Umeclidinium
VAS	Visual Analog Scale
VI	Vilanterol Trifenatate

11.11.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
CAT
ELLIPTA

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
TSCG

11.12. Appendix 12: List of Data Displays

11.12.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.01 to 1.xx	1.01 to 1.xx
Efficacy	2.001 to 2.xxx	2.01 to 2.xx
Safety	3.001 to 3.xxx	3.01 to 3.xx
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	x+1 to z	

11.12.2. Deliverable

Delivery [Priority]	Description
SAC [1]	Final Statistical Analysis Complete. These displays should be created first and will be provided to the clinical team as headline results.
SAC	Final Statistical Analysis Complete. These displays should be created once the high priority displays marked SAC [1] have been completed.

11.12.3. Study Population Tables

Study Population Tables			
No.	**Popu-lation**	**Title**	**Deliverable [Priority]**
Subject Disposition			
1.01	ASE	Summary of Study Populations and Reasons for Screen Failure	SAC
1.02	ITT	Summary of Attendance/Telephone Contact at Each Visit	SAC
1.03	ITT	Summary of Completion and Premature Discontinuation of Study Treatment	SAC
1.04	ITT	Summary of Study Completion and Withdrawal	SAC
1.05	ASE	Summary of Number of Subjects Enrolled by Country	SAC
1.06	ASE	Summary of Number of Subjects Enrolled by Age Category	SAC
1.07	ITT	Summary of Number of Subjects by Geographical Region, Country and Center	SAC
1.08	ECG	Summary of Number of Subjects by Geographical Region, Country and Center	SAC
1.09	TDI	Summary of Number of Subjects by Geographical Region, Country and Center	SAC
1.10	ASE	Summary of Inclusion/Exclusion Criteria Deviations For Screen Failures	SAC
1.11	ITT	Summary of Inclusion/Exclusion Criteria Deviations	SAC
1.12	ITT	Summary of Important Protocol Deviations	SAC
Demography			
1.13	ITT	Summary of Demographic Characteristics	SAC [1]
1.14	ITT	Summary of Demographic Characteristics by Eosinophil Subgroup	SAC [1]
1.15	ECG	Summary of Demographic Characteristics	SAC
1.16	TDI	Summary of Demographic Characteristics	SAC
1.17	ITT	Summary of Demographic Characteristics by Country	SAC
1.18	ITT	Summary of Race and Racial Combinations	SAC
1.19	ITT	Summary of Race and Racial Combinations by Eosinophil Subgroup	SAC
1.20	ECG	Summary of Race and Racial Combinations	SAC
1.21	TDI	Summary of Race and Racial Combinations	SAC
Medical Conditions			
1.22	ITT	Summary of Current Medical Conditions	SAC
1.23	ITT	Summary of Current Medical Conditions by Eosinophil Subgroup	SAC
1.24	ECG	Summary of Current Medical Conditions	SAC
1.25	ITT	Summary of Past Medical Conditions	SAC
1.26	ITT	Summary of Past Medical Conditions by Eosinophil Subgroup	SAC
1.27	ECG	Summary of Past Medical Conditions	SAC
1.28	ITT	Summary of Cardiovascular Risk Factors	SAC
1.29	ITT	Summary of Cardiovascular Risk Factors by Eosinophil Subgroup	SAC
1.30	ECG	Summary of Cardiovascular Risk Factors	SAC
1.31	ITT	Summary of Family History of Cardiovascular Risk Factors	SAC
1.32	ITT	Summary of Family History of Cardiovascular Risk Factors by Eosinophil Subgroup	SAC
1.33	ECG	Summary of Family History of Cardiovascular Risk Factors	SAC
1.34	ITT	Summary of Smoking History at Screening	SAC
1.35	ITT	Summary of Smoking History at Screening by Eosinophil Subgroup	SAC
1.36	ECG	Summary of Smoking History at Screening	SAC

Study Population Tables			
No.	**Popu-lation**	**Title**	**Deliverable [Priority]**
1.37	ITT	Summary of Smoking Status	SAC
1.38	ITT	Summary of Smoking Status by Eosinophil Subgroup	SAC
1.39	ECG	Summary of Smoking Status	SAC
1.40	ITT	Summary of Pneumonia Risk Factors at Screening	SAC
1.41	ITT	Summary of Pneumonia Risk Factors at Screening by Eosinophil Subgroup	SAC
Disease Characteristics			
1.42	ITT	Summary of COPD Duration at Screening	SAC
1.43	ITT	Summary of COPD Duration at Screening by Eosinophil Subgroup	SAC
1.44	ITT	Summary of COPD Exacerbation History at Screening	SAC [1]
1.45	ITT	Summary of COPD Exacerbation History at Screening by Eosinophil Subgroup	SAC
1.46	ITT	Summary of COPD Exacerbation History at Screening by Country	SAC
1.47	ITT	Summary of COPD Exacerbation History Details at Screening	SAC
1.48	ITT	Summary of COPD Exacerbation History Details at Screening by Eosinophil Subgroup	SAC
1.49	ITT	Summary of COPD Exacerbation History Details at Screening by Country	SAC
1.50	ITT	Summary of Screening Lung Function	SAC [1]
1.51	ITT	Summary of Screening Lung Function by Eosinophil Subgroup	SAC
1.52	ITT	Summary of Screening Lung Function by Country	SAC
1.53	ITT	Summary of Reversibility and GOLD Grade (1-4) at Screening	SAC
1.54	ITT	Summary of Reversibility and GOLD Grade (1-4) at Screening by Eosinophil Subgroup	SAC
1.55	ITT	Summary of Reversibility and GOLD Grade (1-4) at Screening by Country	SAC
1.56	ITT	Summary of CAT Score at Screening	SAC
1.57	ITT	Summary of CAT Score at Screening by Eosinophil Subgroup	SAC
1.58	ITT	Summary of Shift in CAT Score Categories from Screening to Baseline	SAC
1.59	ITT	Summary of Shift in CAT Score Categories from Screening to Baseline by Eosinophil Subgroup	SAC
Pulse Oximetry			
1.60	ITT	Summary of Percent Oxygen in Blood at Visit 2, Pre-Dose	SAC
Concomitant Medications			
1.61	ITT	Summary of COPD Concomitant Medications Taken Prior to Screening	SAC
1.62	ITT	Summary of COPD Concomitant Medications Taken in the Run-in, Medications Given for Reasons other than an Exacerbation	SAC
1.63	ITT	Summary of On-treatment COPD Concomitant Medications, Medications Given for Reasons other than an Exacerbation	SAC
1.64	ITT	Summary of Post-treatment COPD Concomitant Medications, Medications Given for Reasons other than an Exacerbation	SAC
1.65	ITT	Summary of On-treatment Concomitant Medications Given for an Exacerbation	SAC
1.66	ITT	Summary of Post-treatment Concomitant Medications Given for an Exacerbation	SAC
1.67	ITT	Summary of COPD Concomitant Medication Combinations Taken at Screening	SAC

Study Population Tables			
No.	**Popu-lation**	**Title**	**Deliverable [Priority]**
1.68	ITT	Summary of COPD Concomitant Medication Combinations Taken at Screening by Eosinophil Subgroup	SAC
1.69	ITT	Summary of COPD Concomitant Medication Combinations Taken at Screening by Country	SAC
1.70	ITT	Summary of COPD Concomitant Medication Combinations Taken at Treatment Discontinuation	SAC
1.71	ITT	Summary of COPD Concomitant Medication Combinations Taken at Treatment Discontinuation for Those Subjects Providing Post-treatment Information	SAC
1.72	ITT	Summary of On-treatment Non-COPD Concomitant Medications	SAC
1.73	ITT	Summary of Post-treatment Non-COPD Concomitant Medications	SAC
1.74	ITT	Summary of Influenza and Pneumonia Vaccination Taken at Any Time up to the End of Study Treatment	SAC
Treatment Compliance			
1.75	ITT	Summary of Treatment Compliance (%)	SAC

11.12.4. Study Population Figures

Study Population figures			
No.	**Popu-lation**	**Title**	**Deliverable**
1.01	ITT	Kaplan-Meier Plot of Time to Premature Discontinuation of Study Treatment	SAC
1.02	ITT	Kaplan-Meier Plot of Time to Premature Discontinuation of Study Treatment – UMEC/VI and FF/VI treatment groups only	SAC
1.03	ITT	Kaplan-Meier Plot of Time to Study Withdrawal	SAC
1.04	ITT	Kaplan-Meier Plot of Time to Study Withdrawal– UMEC/VI and FF/VI treatment groups only	SAC

11.12.5. Efficacy Tables

Efficacy: Tables			
No.	**Popul ation**	**Title**	**Deliverable [Priority]**
COPD Exacerbations – Primary Endpoint			
2.001	ITT	Summary of On-treatment Moderate/Severe COPD Exacerbations	SAC
2.002	ITT	Summary of On-treatment Details of Moderate/Severe COPD Exacerbations	SAC
2.003	ITT	Summary of On-treatment Moderate/Severe COPD Exacerbations by Country	SAC
2.004	ITT	Analysis of On-treatment Moderate/Severe COPD Exacerbations - Negative Binomial Model (Primary Analysis of the Primary Endpoint)	SAC [1]
2.005	ITT	Analysis of On-treatment Moderate/Severe COPD Exacerbations – Poisson Model (Supportive Analysis of the Primary Endpoint)	SAC
2.006	ITT	P-values for Interactions of Treatment with Covariates for Negative Binomial Analysis of On-treatment Moderate/Severe COPD Exacerbations (Supportive Analysis of the Primary Endpoint)	SAC

Efficacy: Tables			
No.	**Population**	**Title**	**Deliverable [Priority]**
2.007	ITT	Analysis of Moderate/Severe COPD Exacerbations - Negative Binomial Model, Analysis Including Off-treatment Data (Sensitivity Analysis of the Primary Endpoint)	SAC
2.008	ITT	Analysis of On-treatment Moderate/Severe COPD Exacerbations - Negative Binomial Model, Imputing Data Following FF/UMEC/VI Discontinuation Using Jump to Reference Assumption (FF/VI as Reference) (Sensitivity Analysis of the Primary Endpoint)	SAC
2.009	ITT	Analysis of On-treatment Moderate/Severe COPD Exacerbations - Negative Binomial Model, Imputing Data Following FF/UMEC/VI Discontinuation Using Jump to Reference Assumption (UMEC/VI as Reference) (Sensitivity Analysis of the Primary Endpoint)	SAC
2.010	ITT	Analysis of On and Off-treatment Moderate/Severe COPD Exacerbations - Negative Binomial Model, Imputing Data Following FF/UMEC/VI Discontinuation Using Jump to Reference Assumption (FF/VI as Reference) (Sensitivity Analysis of the Primary Endpoint)	SAC
2.011	ITT	Analysis of On and Off-treatment Moderate/Severe COPD Exacerbations - Negative Binomial Model, Imputing Data Following FF/UMEC/VI Discontinuation Using Jump to Reference Assumption (UMEC/VI as Reference) (Sensitivity Analysis of the Primary Endpoint)	SAC
COPD Exacerbations – Secondary Endpoints			
2.012	ITT	Summary and Analysis of Time to First On-treatment Moderate/Severe COPD Exacerbation (Primary Analysis of Secondary Endpoint)	SAC [1]
2.013	ITT	Summary and Analysis of Time to First Moderate/Severe COPD Exacerbation Including Off-treatment Data (Sensitivity Analysis of Secondary Endpoint)	SAC
2.014	ITT	Summary and Analysis of Time to First On-treatment Moderate/Severe COPD Exacerbation or Premature Treatment Discontinuation (Sensitivity Analysis of Secondary Endpoint)	SAC
2.015	ITT	Summary of On-treatment Moderate/Severe COPD Exacerbations by Eosinophil Subgroup	SAC
2.016	ITT	Summary and Analysis of Time to First On-treatment Moderate/Severe COPD Exacerbation by Eosinophil Subgroup (Primary Analysis of Secondary Endpoint)	SAC
2.017	ITT	Analysis of On-treatment Moderate/Severe COPD Exacerbations by Eosinophil Subgroup - Negative Binomial Model (Primary Analysis of Secondary Endpoint)	SAC [1]
2.018	ITT	Summary of On-treatment Severe COPD Exacerbations	SAC
2.019	ITT	Analysis of On-treatment Severe COPD Exacerbations - Negative Binomial Model (Primary Analysis of Secondary Endpoint)	SAC
COPD Exacerbations – Other Efficacy Endpoints			
2.020	ITT	Summary of Off-treatment Moderate/Severe COPD Exacerbations	SAC
2.021	ITT	Summary of On-treatment Mild/Moderate/Severe COPD Exacerbations	SAC
2.022	ITT	Analysis of On-treatment Mild/Moderate/Severe COPD Exacerbations - Negative Binomial Model	SAC
2.023	ITT	Summary of On-treatment Moderate COPD Exacerbations	SAC
2.024	ITT	Analysis of On-treatment Moderate COPD Exacerbations - Negative Binomial Model	SAC

Efficacy: Tables			
No.	**Population**	**Title**	**Deliverable [Priority]**
2.025	ITT	Summary of On-treatment Moderate/Severe COPD Exacerbations Requiring Systemic/Oral Corticosteroids	SAC
2.026	ITT	Analysis of On-treatment Moderate/Severe COPD Exacerbations Requiring Systemic/Oral Corticosteroids – Negative Binomial Model	SAC
2.027	ITT	Summary of On-treatment Moderate/Severe COPD Exacerbations Requiring Antibiotics	SAC
2.028	ITT	Analysis of On-treatment Moderate/Severe COPD Exacerbations Requiring Antibiotics – Negative Binomial Model	SAC
2.029	ITT	Summary of On-treatment Severe COPD Exacerbations by Eosinophil Subgroup	SAC
2.030	ITT	Analysis of On-treatment Severe COPD Exacerbations by Eosinophil Subgroup – Negative Binomial Model	SAC
2.031	ITT	Analysis of Time to Each On-treatment Moderate/Severe COPD Exacerbation	SAC
2.032	ITT	Analysis of Time to Each On-treatment Severe COPD Exacerbation	SAC
2.033	ITT	Summary and Analysis of Time to First On-treatment Severe COPD Exacerbation	SAC
2.034	ITT	Summary and Analysis of Time to First On-treatment Severe COPD Exacerbation by Eosinophil Subgroup	SAC
2.035	ITT	Summary and Analysis of Time to First On-treatment Mild/Moderate/ Severe COPD Exacerbation	SAC
2.036	ITT	Summary and Analysis of Time to First On-treatment Moderate COPD Exacerbation	SAC
2.037	ITT	Summary and Analysis of Time to First On-treatment Moderate/Severe COPD Exacerbation Requiring Systemic/Oral Corticosteroids	SAC
2.038	ITT	Summary and Analysis of Time to First On-treatment Moderate/Severe COPD Exacerbation Requiring Antibiotics	SAC
Spirometry – Secondary Endpoint			
2.039	ITT	Summary of Baseline FEV1 (L)	SAC
2.040	ITT	Summary of Trough FEV1 (L)	SAC
2.041	ITT	Analysis of Trough FEV1 (L) (Primary Analysis of Secondary Endpoint)	SAC [1]
2.042	ITT	Analysis of Trough FEV1 (L) Imputing Data Following FF/UMEC/VI Discontinuation Using Jump to Reference Assumption (FF/VI as Reference) (Sensitivity Analysis of Secondary Endpoint)	SAC
2.043	ITT	Analysis of Trough FEV1 (L) Imputing Data Following FF/UMEC/VI Discontinuation Using Jump to Reference Assumption (UMEC/VI as Reference) (Sensitivity Analysis of Secondary Endpoint)	SAC
Spirometry – Other Efficacy Endpoints			
2.044	ITT	Summary of Baseline Pre-bronchodilator FEV1 (L) by Eosinophil Subgroup	SAC
2.045	ITT	Summary of Trough FEV1 (L) by Eosinophil Subgroup	SAC
2.046	ITT	Analysis of Trough FEV1 (L) by Eosinophil Subgroup	SAC
2.047	ITT	Summary of Post-bronchodilator FEV1 (L)	SAC
2.048	ITT	Analysis of Post-bronchodilator FEV1 (L)	SAC
2.049	ITT	Summary and Analysis of Proportion of Subjects Obtaining at Least 100mL Increase from Baseline in Trough FEV1	SAC
2.050	ITT	Summary and Analysis of Proportion of Subjects Obtaining at Least 100mL Increase from Baseline in Trough FEV1 by Eosinophil Subgroup	SAC

Efficacy: Tables			
No.	**Population**	**Title**	**Deliverable [Priority]**
2.051	ITT	Summary of Baseline FEV1 Reversibility (mL)	SAC
2.052	ITT	Summary of FEV1 Reversibility (mL)	SAC
2.053	ITT	Analysis of FEV1 Reversibility (mL)	SAC
2.054	ITT	Summary of Baseline FVC (L)	SAC
2.055	ITT	Summary of Trough FVC (L)	SAC
2.056	ITT	Analysis of Trough FVC (L)	SAC
2.057	ITT	Summary of Post-bronchodilator FVC (L)	SAC
2.058	ITT	Analysis of Post-bronchodilator FVC (L)	SAC
SGRQ – Secondary Endpoint			
2.059	ITT	Summary of Baseline SGRQ Scores	SAC
2.060	ITT	Summary of SGRQ Scores	SAC
2.061	ITT	Analysis of SGRQ Total Score (Primary Analysis of Secondary Endpoint)	SAC [1]
2.062	ITT	Analysis of SGRQ Total Score Imputing Data Following FF/UMEC/VI Discontinuation Using Jump to Reference Assumption (FF/VI as Reference) (Sensitivity Analysis of Secondary Endpoint)	SAC
2.063	ITT	Analysis of SGRQ Total Score Imputing Data Following FF/UMEC/VI Discontinuation Using Jump to Reference Assumption (UMEC/VI as Reference) (Sensitivity Analysis of Secondary Endpoint)	SAC
SGRQ – Other Efficacy Endpoint			
2.064	ITT	Summary of Baseline SGRQ Total Score by Eosinophil Subgroup	SAC
2.065	ITT	Summary of SGRQ Total Score by Eosinophil Subgroup	SAC
2.066	ITT	Analysis of SGRQ Total Score by Eosinophil Subgroup	SAC
2.067	ITT	Summary of SGRQ Total Score at Week 52 by Global Rating of Change in COPD Severity at Week 52, Combined Treatment Groups	SAC
2.068	ITT	Summary of SGRQ Total Score at Week 52 by Global Rating of Change in COPD Severity at Week 52	SAC
2.069	ITT	Summary and Analysis of Proportion of Responders According to SGRQ Total Score	SAC [1]
2.070	ITT	Summary and Analysis of Proportion of Responders According to SGRQ Total Score by Eosinophil Subgroup	SAC
2.071	ITT	Summary and Analysis of Proportion of Moderate/Major Responders According to SGRQ Total Score	SAC
2.072	ITT	Summary and Analysis of Proportion of Major Responders According to SGRQ Total Score	SAC
BDI/TDI			
2.073	TDI	Summary of BDI Focal Score	SAC
2.074	TDI	Summary of BDI Focal Score by Eosinophil Subgroup	SAC
2.075	TDI	Summary of TDI Focal Score	SAC
2.076	TDI	Summary of TDI Focal Score by Eosinophil Subgroup	SAC
2.077	TDI	Analysis of TDI Focal Score	SAC
2.078	TDI	Analysis of TDI Focal Score by Eosinophil Subgroup	SAC
2.079	TDI	Summary of TDI Focal Score Categories of Improvement and Deterioration	SAC
2.080	TDI	Summary and Analysis of Proportion of Responders According to TDI Focal Score	SAC
2.081	TDI	Summary and Analysis of Proportion of Responders According to TDI Focal Score by Eosinophil Subgroup	SAC

Efficacy: Tables			
No.	**Population**	**Title**	**Deliverable [Priority]**
2.082	TDI	Summary and Analysis of Proportion of Moderate/Major Responders According to TDI Focal Score	SAC
2.083	TDI	Summary and Analysis of Proportion of Major Responders According to TDI Focal Score	SAC
All Cause Mortality			
2.084	ITT	Summary of On-treatment Adjudicated Cause of Death	SAC
2.085	ITT	Summary of On-treatment Adjudicated Cause of Death by Eosinophil Subgroup	SAC
2.086	ITT	Summary of Adjudicated Cause of Death Including Off-treatment Data	SAC
2.087	ITT	Summary of Adjudicated Cause of Death Including Off-treatment Data by Eosinophil Subgroup	SAC
2.088	ITT	Summary and Analysis of Time to On-treatment All Cause Mortality	SAC
2.089	ITT	Summary and Analysis of Time to All Cause Mortality Including Off-treatment Data	SAC
CAT			
2.090	ITT	Summary of Baseline CAT Score	SAC
2.091	ITT	Summary of Baseline CAT Score by Eosinophil Subgroup	SAC
2.092	ITT	Summary of CAT Score	SAC
2.093	ITT	Summary of CAT Score by Eosinophil Subgroup	SAC
2.094	ITT	Analysis of CAT Score	SAC
2.095	ITT	Analysis of CAT Score by Eosinophil Subgroup	SAC
2.096	ITT	Summary and Analysis of Proportion of Responders According to CAT Score	SAC
2.097	ITT	Summary and Analysis of Proportion of Responders According to CAT Score by Eosinophil Subgroup	SAC
Subject Global Ratings			
2.098	ITT	Summary of Subject Global Rating of Activity Limitation	SAC
2.099	ITT	Summary and Analysis of Subject Global Rating of Change in Activity Limitation	SAC
2.100	ITT	Summary of Subject Global Rating of COPD Severity	SAC
2.101	ITT	Summary and Analysis of Subject Global Rating of Change in COPD Severity	SAC
Daily Diary Assessments			
2.102	ITT	Summary of Mean Number of Occasions of Rescue Use per Day	SAC
2.103	ITT	Analysis of Mean Number of Occasions of Rescue Use per Day by Four Weekly Period	SAC
2.104	ITT	Summary of Percentage of Rescue-Free Days	SAC
2.105	ITT	Analysis of Percentage of Rescue-Free Days by Four Weekly Period	SAC
2.106	ITT	Summary of Mean Number of Nighttime Awakenings per Night	SAC
2.107	ITT	Analysis of Mean Number of Nighttime Awakenings per Night by Four Weekly Period	SAC
2.108	ITT	Summary of Percentage of Days Symptoms Stopped Usual Activities	SAC
2.109	ITT	Analysis of Percentage of Days Symptoms Stopped Usual Activities by Four Weekly Period	SAC
EQ-5D-5L			
2.110	ITT	Summary of EQ-5D-5L VAS Scores	SAC
2.111	ITT	Summary of EQ-5D-5L Utility Indices	SAC

Efficacy: Tables			
No.	**Population**	**Title**	**Deliverable [Priority]**
Healthcare Resource Utilization			
2.112	ITT	Summary of Unscheduled Healthcare Resource Utilization	SAC
2.113	ITT	Summary of Unscheduled Healthcare Resource Utilization by Contact Type	SAC
Additional Sensitivity Analysis of Primary Endpoint (to be performed only if ≥2% of the ITT population are enrolled at sites that are withdrawn from the study due to concerns over protocol deviations)			
2.114	ITT	Analysis of On-treatment Moderate/Severe COPD Exacerbations - Negative Binomial Model, Excluding Subjects from Sites that were Withdrawn from the Study (Sensitivity Analysis of the Primary Endpoint)	

11.12.6. Efficacy Figures

Efficacy: Figures			
No.	**Population**	**Title**	**Deliverable [Priority]**
COPD Exacerbations – Primary Endpoint			
2.01	ITT	Adjusted On-treatment Moderate/Severe COPD Exacerbation Rate Ratios	SAC
2.02	ITT	Box Plot of On-treatment Moderate/Severe Annual Raw COPD Exacerbation Rates	SAC
2.03	ITT	Forest Plot of Adjusted On-treatment Moderate/Severe COPD Exacerbation Rate Ratios and Associated Sensitivity Analyses	SAC
COPD Exacerbations – Secondary Endpoints			
2.04	ITT	Kaplan-Meier Plot of Time to First On-treatment Moderate/Severe COPD Exacerbation	SAC
2.05	ITT	Kaplan-Meier Plot of Time to First On-treatment Moderate/Severe COPD Exacerbation – UMEC/VI and FF/VI treatment groups only	SAC
2.06	ITT	Hazard Ratios for Time to First On-treatment Moderate/Severe COPD Exacerbation	SAC
2.07	ITT	Kaplan-Meier Plot of Time to First Moderate/Severe COPD Exacerbation, Including Off-treatment Data	SAC
2.08	ITT	Kaplan-Meier Plot of Time to First Moderate/Severe COPD Exacerbation, Including Off-treatment Data – UMEC/VI and FF/VI treatment groups only	SAC
2.09	ITT	Forest Plot of Hazard Ratios for Time to First On-treatment Moderate/Severe COPD Exacerbation and Associated Sensitivity Analyses	SAC

Efficacy: Figures			
No.	**Popu-lation**	**Title**	**Deliverable [Priority]**
2.10	ITT	Kaplan-Meier Plot of Time to First On-treatment Moderate/Severe COPD Exacerbation or Premature Treatment Discontinuation	SAC
2.11	ITT	Kaplan-Meier Plot of Time to First On-treatment Moderate/Severe COPD Exacerbation or Treatment Discontinuation - UMEC/VI and FF/VI treatment groups only	SAC
2.12	ITT	Kaplan-Meier Plot of Time to First On-treatment Moderate/Severe COPD Exacerbation by Eosinophil Subgroup	SAC
2.13	ITT	Kaplan-Meier Plot of Time to First On-treatment Moderate/Severe COPD Exacerbation by Eosinophil Subgroup - UMEC/VI and FF/VI treatment groups only	SAC
2.14	ITT	Hazard Ratios for Time to First On-treatment Moderate/Severe COPD Exacerbation by Eosinophil Subgroup	SAC
2.15	ITT	Adjusted On-treatment Moderate/Severe COPD Exacerbation Rate Ratios by Eosinophil Subgroup	SAC
2.16	ITT	Adjusted On-treatment Severe COPD Exacerbation Rate Ratios	SAC
COPD Exacerbations – Other Endpoint			
2.17	ITT	Kaplan-Meier Plot of Time to First On-treatment Mild/Moderate/Severe COPD Exacerbation	SAC
2.18	ITT	Kaplan-Meier Plot of Time to First On-treatment Mild/Moderate/Severe COPD Exacerbation- UMEC/VI and FF/VI treatment groups only	SAC
2.19	ITT	Kaplan-Meier Plot of Time to First On-treatment Moderate COPD Exacerbation	SAC
2.20	ITT	Kaplan-Meier Plot of Time to First On-treatment Moderate COPD Exacerbation- UMEC/VI and FF/VI treatment groups only	SAC
2.21	ITT	Kaplan-Meier Plot of Time to First On-treatment Moderate/Severe COPD Exacerbation Requiring Systemic/Oral Corticosteroids	SAC
2.22	ITT	Kaplan-Meier Plot of Time to First On-treatment Moderate/Severe COPD Exacerbation Requiring Systemic/Oral Corticosteroids- UMEC/VI and FF/VI treatment groups only	SAC
2.23	ITT	Kaplan-Meier Plot of Time to First On-treatment Moderate/Severe COPD Exacerbation Requiring Antibiotics	SAC
2.24	ITT	Kaplan-Meier Plot of Time to First On-treatment Moderate/Severe COPD Exacerbation Requiring Antibiotics- UMEC/VI and FF/VI treatment groups only	SAC
2.25	ITT	Kaplan-Meier Plot of Time to First On-treatment Severe COPD Exacerbation	SAC
2.26	ITT	Kaplan-Meier Plot of Time to First On-treatment Severe COPD Exacerbation- UMEC/VI and FF/VI treatment groups only	SAC
2.27	ITT	Kaplan-Meier Plot of Time to First On-treatment Severe COPD Exacerbation by Eosinophil Subgroup	SAC
2.28	ITT	Kaplan-Meier Plot of Time to First On-treatment Severe COPD Exacerbation by Eosinophil Subgroup- UMEC/VI and FF/VI treatment groups only	SAC
Spirometry – Secondary Endpoint			
2.29	ITT	Least Squares Mean (95% CI) Change from Baseline in Trough FEV1 (L)	SAC

Efficacy: Figures			
No.	**Popu-lation**	**Title**	**Deliverable [Priority]**
2.30	ITT	Least Squares Mean (95% CI) Change from Baseline in Trough FEV1 (L) – UMEC/VI and FF/VI treatment groups only	SAC
2.31	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Trough FEV1 (L)	SAC
2.32	ITT	Forest Plot of Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Trough FEV1 (L) and Associated Sensitivity Analyses at Week 52	SAC
Spirometry – Other Efficacy Endpoints			
2.33	ITT	Least Squares Mean (95% CI) Change from Baseline in Post-bronchodilator FEV1 (L)	SAC
2.34	ITT	Least Squares Mean (95% CI) Change from Baseline in Post-bronchodilator FEV1 (L) – UMEC/VI and FF/VI treatment groups only	SAC
2.35	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Post-bronchodilator FEV1 (L)	SAC
2.36	ITT	Least Squares Mean (95% CI) Change from Baseline in Trough FVC (L)	SAC
2.37	ITT	Least Squares Mean (95% CI) Change from Baseline in Trough FVC (L) – UMEC/VI and FF/VI treatment groups only	SAC
2.38	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Trough FVC (L)	SAC
2.39	ITT	Least Squares Mean (95% CI) Change from Baseline in Post-bronchodilator FVC (L)	SAC
2.40	ITT	Least Squares Mean (95% CI) Change from Baseline in Post-bronchodilator FVC (L) – UMEC/VI and FF/VI treatment groups only	SAC
2.41	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in Post-bronchodilator FVC (L)	SAC
SGRQ – Secondary Endpoint			
2.42	ITT	Box Plot of Change from Baseline in SGRQ Total Score at Week 52	SAC
2.43	ITT	Empirical Distribution Function Plot of Change from Baseline in SGRQ Total Score at Week 52	SAC
2.44	ITT	Least Squares Mean (95% CI) Change from Baseline in SGRQ Total Score	SAC
2.45	ITT	Least Squares Mean (95% CI) Change from Baseline in SGRQ Total Score – UMEC/VI and FF/VI treatment groups only	SAC
2.46	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in SGRQ Total Score	SAC
2.47	ITT	Forest Plot of Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in SGRQ Total Score and Associated Sensitivity Analyses at Week 52	SAC
SGRQ – Other Efficacy Endpoint			
2.48	ITT	Box Plot of Change from Baseline in SGRQ Total Score at Week 52 by Global Rating of Change in COPD Severity at Week 52, Combined Treatment Groups	SAC
2.49	ITT	Box Plot of Change from Baseline in SGRQ Total Score at Week 52 by Global Rating of Change in COPD Severity at Week 52	SAC
All-Cause Mortality			
2.50	ITT	Kaplan-Meier Plot of Time to On-treatment All Cause Mortality	SAC
2.51	ITT	Kaplan-Meier Plot of Time to On-treatment All Cause Mortality – UMEC/VI and FF/VI treatment groups only	SAC

Efficacy: Figures			
No.	**Popu-lation**	**Title**	**Deliverable [Priority]**
2.52	ITT	Kaplan-Meier Plot of Time to All Cause Mortality Including Off-treatment Data	SAC
2.53	ITT	Kaplan-Meier Plot of Time to All Cause Mortality Including Off-treatment Data – UMEC/VI and FF/VI treatment groups only	SAC
BDI/TDI			
2.54	ITT	Least Squares Means (95% CI) TDI Focal Score	SAC
2.55	ITT	Least Squares Means (95% CI) TDI Focal Score – UMEC/VI and FF/VI treatment groups only	SAC
2.56	ITT	Least Squares Mean (95% CI) Treatment Difference in TDI Focal Score	SAC
CAT			
2.57	ITT	Least Squares Mean (95% CI) Change from Baseline in CAT Score	SAC
2.58	ITT	Least Squares Mean (95% CI) Change from Baseline in CAT Score – UMEC/VI and FF/VI treatment groups only	SAC
2.59	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline in CAT Score	SAC
Daily Diary			
2.60	ITT	Least Squares Mean (95% CI) Change from Baseline in Mean Number of Occasions of Rescue use per Day by Four Weekly Period	SAC
2.61	ITT	Least Squares Mean (95% CI) Change from Baseline in Mean Number of Occasions of Rescue use per Day by Four Weekly Period – UMEC/VI and FF/VI treatment groups only	SAC
2.62	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline Mean Number of Occasions of Rescue Use per Day by Four Weekly Period	SAC
2.63	ITT	Least Squares Mean (95% CI) Change from Baseline in Percentage of Rescue-Free Days by Four Weekly Period	SAC
2.64	ITT	Least Squares Mean (95% CI) Change from Baseline in Percentage of Rescue-Free Days by Four Weekly Period – UMEC/VI and FF/VI treatment groups only	SAC
2.65	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline Percentage of Rescue-Free Days by Four Weekly Period	SAC
2.66	ITT	Least Squares Mean (95% CI) Change from Baseline in Mean Number of Nighttime Awakenings per Night by Four Weekly Period	SAC
2.67	ITT	Least Squares Mean (95% CI) Change from Baseline in Mean Number of Nighttime Awakenings per Night by Four Weekly Period – UMEC/VI and FF/VI treatment groups only	SAC
2.68	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline Mean Number of Nighttime Awakenings per Night by Four Weekly Period	SAC
2.69	ITT	Least Squares Mean (95% CI) Change from Baseline in Percentage of Days Symptoms Stopped Usual Activities by Four Weekly Period	SAC
2.70	ITT	Least Squares Mean (95% CI) Change from Baseline in Percentage of Days Symptoms Stopped Usual Activities by Four Weekly Period – UMEC/VI and FF/VI treatment groups only	SAC
2.71	ITT	Least Squares Mean (95% CI) Treatment Difference in Change from Baseline Percentage of Days Symptoms Stopped Usual Activities by Four Weekly Period	SAC

11.12.7. Safety Tables

Safety Tables			
No.	**Popu-lation**	**Title**	**Deliverable [Priority]**
Exposure			
3.001	ITT	Summary of Study Treatment Exposure	SAC
3.002	ITT	Summary of Study Treatment Exposure by Eosinophil Subgroup	SAC
3.003	ITT	Summary of Post-treatment Duration on Study	SAC
3.004	ITT	Summary of Post-treatment Duration on Study by Eosinophil Subgroup	SAC
3.005	ITT	Summary of On- and Post-treatment Duration on Study	SAC
3.006	ITT	Summary of On- and Post-treatment Duration on Study by Eosinophil Subgroup	SAC
Adverse Events			
3.007	ITT	Overview of On-treatment Adverse Events	SAC
3.008	ITT	Summary of On-treatment Adverse Events	SAC [1]
3.009	ITT	Summary of On-treatment Adverse Events by Country	SAC
3.010	ITT	Summary of On-treatment Drug-related Adverse Events	SAC
3.011	ITT	Summary of On-treatment Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study	SAC
3.012	ITT	Summary of the 10 Most Frequent On-treatment Adverse Events in Each Treatment Group	SAC
3.013	ITT	Summary of On-treatment Common Non-serious Adverse Events Reported by 3% Or More of Subjects in Any Treatment Group	SAC
3.014	ITT	Summary of On-treatment Adverse Event Categories of Interest in the Elderly by Age	SAC
3.015	ASE	Relationship of Adverse Event System Organ Class, Preferred Term and Verbatim Text	SAC
Serious Adverse Events			
3.016	ASE	Summary of Pre-treatment Serious Adverse Events	SAC
3.017	ITT	Summary of Pre-treatment Serious Adverse Events	SAC
3.018	ASE	Summary of Pre-treatment Fatal Serious Adverse Events	SAC
3.019	ASE	Summary of Pre-treatment Serious Adverse Events Leading to Withdrawal from Study	SAC
3.020	ITT	Summary of Subjects and Number of Occurrences of On-treatment Serious, Drug-related Serious, Fatal and Drug-related Serious Adverse Events	SAC
3.021	ITT	Summary of On-treatment Serious Adverse Events	SAC [1]
3.022	ITT	Summary of On-treatment Non-fatal Serious Adverse Events	SAC
3.023	ITT	Summary of On-treatment Fatal Serious Adverse Events	SAC [1]
3.024	ITT	Summary of On-treatment Drug-related Serious Adverse Events	SAC

Safety Tables			
No.	**Popu-lation**	**Title**	**Deliverable [Priority]**
3.025	ITT	Summary of On-treatment Drug-related Fatal Serious Adverse Events	SAC
3.026	ITT	Summary of Post-treatment Serious Adverse Events	SAC
3.027	ITT	Summary of Post-treatment Fatal Serious Adverse Events	SAC
Adjudicated Serious Adverse Events			
3.028	ITT	Summary of Adjudicated On-treatment Serious Adverse Reports	SAC
3.029	ITT	Summary of Adjudicated On-treatment Non-fatal Serious Adverse Reports	SAC
3.030	ITT	Summary of Adjudicated On-treatment Fatal Serious Adverse Reports	SAC
3.031	ITT	Summary of Adjudicated Post-treatment Serious Adverse Reports	SAC
3.032	ITT	Summary of Adjudicated Post-treatment Non-fatal Serious Adverse Reports	SAC
3.033	ITT	Summary of Adjudicated Post-treatment Fatal Serious Adverse Reports	SAC
Adverse Events of Special Interest			
3.034	ITT	Summary of On-treatment Adverse Events of Special Interest	SAC [1]
3.035	ITT	Summary of On-treatment Adverse Events of Special Interest by Eosinophil Subgroup	SAC
3.036	ITT	Summary and Analysis of Time to First On-treatment Event in the Pneumonia AESI Group	SAC
3.037	ITT	Summary and Analysis of Time to First On-treatment Event in the Pneumonia AESI Group by Eosinophil Subgroup	SAC
3.038	ITT	Summary of Pneumonia Risk Factors at Screening for Subjects with an Event in the Pneumonia AESI Group	SAC
3.039	ITT	Summary of Pneumonia Risk Factors at Screening for Subjects with an Event in the Pneumonia AESI Group by Eosinophil Subgoup	SAC
3.040	ITT	Summary and Analysis of Time to First On-treatment Event in the Cardiovascular AESI Group	SAC
3.041	ITT	Summary of Incidence of On-treatment Pneumonia AESI and Adjudicated Pneumonia	SAC
Serious Adverse Events of Special Interest			
3.042	ITT	Summary of On-treatment Serious Adverse Events of Special Interest	SAC
3.043	ITT	Summary of On-treatment Fatal Serious Adverse Events of Special Interest	SAC
3.044	ITT	Summary and Analysis of Time to First On-treatment Event in the Pneumonia AESI Group Resulting in Hospitalization/Prolonged Hospitalization or Death	SAC

Safety Tables			
No.	**Popu-lation**	**Title**	**Deliverable [Priority]**
3.045	ITT	Summary and Analysis of Time to First On-treatment Event in the Cardiovascular AESI Group Resulting in Hospitalization/Prolonged Hospitalization or Death	SAC
MACE			
3.046	ITT	Summary of On-treatment Major Adverse Cardiac Events (MACE) – Narrow Definition	SAC
3.047	ITT	Summary of On-treatment Major Adverse Cardiac Events (MACE) – Broad Definition	SAC
Pneumonia (eCRF Pneumonia Form)			
3.048	ITT	Summary of On-treatment Pneumonia Incidence	SAC
3.049	ITT	Summary of On-treatment Details of Pneumonia	
3.050	ITT	Summary of On-treatment Pneumonia Incidence Resulting in Hospitalization/Prolonged Hospitalization or Death	SAC
3.051	ITT	Summary of On-treatment Details of Pneumonia Resulting in Hospitalization/Prolonged Hospitalization or Death	SAC
Composite Endpoints			
3.052	ITT	Summary and Analysis of Time to First On-treatment Event in the Pneumonia AESI Group or On-treatment Moderate/Severe COPD Exacerbation	SAC
3.053	ITT	Summary and Analysis of Time to First On-treatment Severe COPD Exacerbation or On-treatment Event in the Pneumonia AESI Group Resulting in Hospitalization/Prolonged Hospitalization or Death	SAC
3.054	ITT	Summary and Analysis of Time to First On-treatment Severe COPD Exacerbation or On-treatment Event in the Cardiovascular AESI Group Resulting in Hospitalization/Prolonged Hospitalization or Death or On-treatment Event in the Pneumonia AESI Group Resulting in Hospitalization/Prolonged Hospitalization or Death	SAC
Bone Fractures			
3.055	ITT	Summary of On-treatment Bone Fractures	SAC
Radiography (Chest Imaging)			
3.056	ITT	Summary of On-treatment Chest Imaging (X-ray or CT Scan)	SAC
Liver Event			
3.057	ITT	Summary of Liver Monitoring/Stopping Event Reporting	SAC
3.058	ITT	Summary of Hepatobiliary Laboratory Abnormalities	SAC
Laboratory Parameters			
3.059	ITT	Summary of Chemistry Data	SAC
3.060	ITT	Summary of Change from Baseline in Chemistry Data	SAC
3.061	ITT	Summary of Chemistry Data Outside the Normal Range	SAC

Safety Tables			
No.	**Popu-lation**	**Title**	**Deliverable [Priority]**
3.062	ITT	Summary of Chemistry Changes from Baseline Relative to the Normal Range	SAC
3.063	ITT	Summary of Hematology Data	SAC
3.064	ITT	Summary of Change from Baseline in Hematology Data	SAC
3.065	ITT	Summary of Hematology Data Outside the Normal Range	SAC
3.066	ITT	Summary of Hematology Changes from Baseline Relative to the Normal Range	SAC
Vitals Signs			
3.067	ITT	Summary of Vital Signs	SAC
3.068	ITT	Summary of Change from Baseline in Vital Signs	SAC
3.069	ITT	Analysis of Pulse Rate (bpm)	SAC
3.070	ITT	Analysis of Systolic Blood Pressure (mmHg)	SAC
3.071	ITT	Analysis of Diastolic Blood Pressure (mmHg)	SAC
ECGs			
3.072	ITT	Summary of ECG Values	SAC
3.073	ECG	Summary of ECG Values	SAC
3.074	ITT	Summary of Change from Baseline in ECG Values	SAC
3.075	ECG	Summary of Change from Baseline in ECG Values	SAC
3.076	ITT	Summary of ECG Findings	SAC
3.077	ECG	Summary of ECG Findings	SAC
3.078	ITT	Summary of ECG Findings Shifts from Baseline	SAC
3.079	ECG	Summary of ECG Findings Shifts from Baseline	SAC
3.080	ECG	Summary of ECG Findings Shifts from Pre-dose to Post-dose at Week 4	SAC
3.081	ITT	Summary of ECG Abnormalities	SAC
3.082	ECG	Summary of ECG Abnormalities	SAC
3.083	ITT	Summary of ECG Abnormalities >3% of Subjects in Any Treatment Group	SAC
3.084	ITT	Summary of QTc(F) (msec) Categories	SAC
3.085	ECG	Summary of QTc(F) (msec) Categories	SAC
3.086	ITT	Summary of Change From Baseline in QTc(F) (msec) Categories	SAC
3.087	ECG	Summary of Change From Baseline in QTc(F) (msec) Categories	SAC
3.088	ITT	Analysis of Post-dose QTc(F) (msec)	SAC
3.089	ECG	Analysis of Pre-dose QTc(F) (msec)	SAC
3.090	ECG	Summary of Change from Pre-dose to Post-Dose ECG Heart Rate at Week 4	SAC

11.12.8. Safety Figures

Safety Figures			
No.	**Popu-lation**	**Title**	**Deliverable [Priority]**
Exposure			
3.01	ITT	Plot of Exposure to Study Treatment	SAC
Adverse Events of Special Interest			
3.02	ITT	Kaplan-Meier Plot of Time to First On-treatment Event in the Pneumonia AESI Group	SAC
3.03	ITT	Kaplan-Meier Plot of Time to First On-treatment Event in the Pneumonia AESI Group– UMEC/VI and FF/VI treatment groups only	SAC
3.04	ITT	Kaplan-Meier Plot of Time to First On-treatment Event in the Cardiovascular AESI Group	SAC
3.05	ITT	Kaplan-Meier Plot of Time to First On-treatment Event in the Cardiovascular AESI Group– UMEC/VI and FF/VI treatment groups only	SAC
Serious Adverse Events of Special Interest			
3.06	ITT	Kaplan-Meier Plot of Time to First On-treatment Event in the Pneumonia AESI Group Resulting in Hospitalization/Prolonged Hospitalization or Death	SAC
3.07	ITT	Kaplan-Meier Plot of Time to First On-treatment Event in the Pneumonia AESI Group Resulting in Hospitalization/Prolonged Hospitalization or Death– UMEC/VI and FF/VI treatment groups only	SAC
3.08	ITT	Kaplan-Meier Plot of Time to First On-treatment Event in the Cardiovascular AESI Group Resulting in Hospitalization/Prolonged Hospitalization or Death	SAC
3.09	ITT	Kaplan-Meier Plot of Time to First On-treatment Event in the Cardiovascular AESI Group Resulting in Hospitalization/Prolonged Hospitalization or Death– UMEC/VI and FF/VI treatment groups only	SAC

Safety Figures			
No.	**Popu-lation**	**Title**	**Deliverable [Priority]**
Composite Endpoints			
3.10	ITT	Kaplan-Meier Plot of Time to First On-treatment Event in the Pneumonia AESI Group or On-treatment Moderate/Severe COPD Exacerbation Composite	SAC
3.11	ITT	Kaplan-Meier Plot of Time to First On-treatment Event in the Pneumonia AESI Group or On-treatment Moderate/Severe COPD Exacerbation Composite– UMEC/VI and FF/VI treatment groups only	SAC
3.12	ITT	Kaplan-Meier Plot of Time to First On-treatment Severe COPD Exacerbation or On-treatment Event in the Pneumonia AESI Group Resulting in Hospitalization/Prolonged Hospitalization or Death	SAC
3.13	ITT	Kaplan-Meier Plot of Time to First On-treatment Severe COPD Exacerbation or On-treatment Event in the Pneumonia AESI Group Resulting in Hospitalization/Prolonged Hospitalization or Death– UMEC/VI and FF/VI treatment groups only	SAC
3.14	ITT	Kaplan-Meier Plot of Time to First On-treatment Severe COPD Exacerbation or On-treatment Event in the CV AESI Group Resulting in Hospitalization or Prolonged Hospitalization or Death or On-treatment Event in the Pneumonia AESI Group Resulting in Hospitalization/Prolonged Hospitalization or Death	SAC
3.15	ITT	Kaplan-Meier Plot of Time to First On-treatment Severe COPD Exacerbation or On-treatment Event in the CV AESI Group Resulting in Hospitalization or Prolonged Hospitalization or Death or On-treatment Event in the Pneumonia AESI Group Resulting in Hospitalization/Prolonged Hospitalization or Death– UMEC/VI and FF/VI treatment groups only	SAC
3.16	ITT	Percentage of Subjects with an On-treatment Event in the Pneumonia AESI Group and Percentage of Subjects with an On-treatment Moderate/Severe COPD Exacerbation	SAC
3.17	ITT	Percentage of Subjects with an On-treatment Event in the Pneumonia AESI Group and Percentage of Subjects with an On-treatment Moderate/Severe COPD Exacerbation– UMEC/VI and FF/VI treatment groups only	SAC
Laboratory Parameters			
3.18	ITT	Trellis Display of Maximum Post-baseline Liver Function Test Values, Versus Baseline Liver Function Test Values	SAC
3.19	ITT	Scatter Plots of Maximum Post-baseline Versus Baseline For Chemistry Data	SAC
3.20	ITT	Box Plots of Change from Baseline to Maximum Post-baseline Values for Chemistry Data	SAC
3.21	ITT	Scatter Plots of Minimum Post-baseline Versus Baseline For Chemistry Data	SAC
3.22	ITT	Box Plots of Change from Baseline to Minimum Post-baseline Values for Chemistry Data	SAC
3.23	ITT	Scatter Plots of Maximum Post-baseline Versus Baseline For Hematology Data	SAC

Safety Figures			
No.	**Popu-lation**	**Title**	**Deliverable [Priority]**
3.24	ITT	Box Plots of Change from Baseline to Maximum Post-baseline Values for Hematology Data	SAC
3.25	ITT	Scatter Plots of Minimum Post-baseline Versus Baseline For Hematology Data	SAC
3.26	ITT	Box Plots of Change from Baseline to Minimum Post-baseline Values for Hematology Data	SAC
ECGs			
3.27	ITT	Empirical Distribution Function Plot of Maximum Post-baseline QTcF (msec)	SAC
3.28	ITT	Empirical Distribution Function Plot of Change from Baseline in Maximum Post-baseline QTcF (msec)	SAC
3.29	ECG	Empirical Distribution Function Plot of Maximum Post-baseline QTcF (msec)	SAC
3.30	ECG	Empirical Distribution Function Plot of Change from Baseline in Maximum Post-baseline QTcF (msec)	SAC

11.12.9. ICH Listings

ICH : Listings			
No.	**Popu-lation**	**Title**	**Deliverable [Priority]**
Study Population			
1.	ASE	Listing of Reasons for Screen Failure	SAC
2.	ITT	Listing of Reasons for Study Withdrawal	SAC
3.	ITT	Listing of Reasons for Study Treatment Discontinuation	SAC
4.	ITT	Listing of Subjects for Whom the Treatment Blind was Broken during the Study	SAC
5.	ITT	Listing of Randomized and Actual Treatments	SAC
6.	ITT	Listing of Important Protocol Deviations	SAC
7.	ASE	Listing of Subjects with Inclusion and Exclusion Criteria Deviations for Screen Failures	SAC
8.	ITT	Listing of Subjects with Inclusion and Exclusion Criteria Deviations	SAC
9.	ITT	Listing of Subjects Excluded from the ITT Population	SAC
10.	ITT	Listing of Demographic Characteristics	SAC
11.	ITT	Listing of Race	SAC
12.	ITT	Listing of COPD Duration and Exacerbation History	SAC
Prior and Concomitant Medications			
13.	ITT	Listing of COPD Concomitant Medications	SAC
COPD Exacerbations			
14.	ITT	Listing of COPD Exacerbations	SAC
Spirometry			
15.	ITT	Listing of Derived FEV1 (L) Endpoints	SAC
SGRQ			
16.	ITT	Listing of SGRQ Domain Scores	SAC
Exposure			
17.	ITT	Listing of Exposure and Post-treatment Duration on Study	SAC
Adverse Events			
18.	ASE	Listing of All Adverse Events	SAC

ICH : Listings			
No.	**Popu-lation**	**Title**	**Deliverable [Priority]**
19.	ASE	Listing of Subject Numbers for Individual Adverse Events	SAC
20.	ASE	Listing of Fatal Serious Adverse Events	SAC
21.	ASE	Listing of Non-fatal Serious Adverse Events	SAC
22.	ASE	Listing of Reasons for Considering as a Serious Adverse Event	SAC
23.	ITT	Listing of Adverse Events leading to Withdrawal from the Study / Permanent Discontinuation of Study Treatment	SAC
Liver Events			
24.	ITT	Listing of Medical Conditions for Subjects with Liver Stopping Events	SAC
25.	ITT	Listing of Substance Use for Subjects with Liver Stopping Events	SAC
Laboratory Parameters			
26.	ITT	Listing of Chemistry Values for Subjects with at Least One Value outside the Normal Range	SAC
27.	ITT	Listing of Hematology Values for Subjects with at Least One Value outside the Normal Range	SAC
12-Lead ECGs			
28.	ITT	Listing of ECG Values for Subjects with Any Abnormal ECG Finding	SAC
29.	ITT	Listing of ECG Abnormalities	SAC

11.12.10. Non-ICH Listings

Non-ICH : Listings			
No.	**Popu-lation**	**Title**	**Deliverable [Priority]**
Study Population			
30.	ASE	Listing of Study Treatment Misallocations	SAC
Spirometry			
31.	ITT	Listing of Raw FEV1 (L) and FVC (L) Data	SAC
SGRQ			
32.	ITT	Listing of SGRQ Individual Responses	SAC