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

Title	:	Reporting and Analysis Plan for Phase IIb, Randomized (Stratified), Double-Blind (Sponsor Open), Parallel-Group, Placebo-Controlled, Dose-Finding Study of Nemiralisib (GSK2269557) Added to Standard of Care (SoC) Versus SoC Alone in Participants Diagnosed with an Acute Moderate or Severe Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)
Compound Number	:	GSK2269557
Effective Date	:	10-OCT-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 200879 and at the planned interim analyses.
- This RAP is intended to describe the efficacy, safety and pharmacokinetic analyses required for the study.
- This version of the RAP includes amendments to the originally approved RAP.
- 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. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol 200879.

2. SUMMARY OF KEY PROTOCOL INFORMATION

This study will be undertaken in participants who present with an acute moderate or severe exacerbation of COPD requiring Standard of Care (SoC), referred to as the index exacerbation.

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To characterise the dose response of nemiralisib administered in addition to SoC compared with placebo and SoC in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Change from baseline in Clinic Visit trough forced expiratory volume in one second (FEV_1) at Day 84 measured post-bronchodilator
Secondary Objectives	**Secondary Endpoints**
• To characterise the dose response and efficacy of nemiralisib administered in addition to SoC compared with placebo and SoC in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Rate of moderate and severe exacerbations over the 12-Week Treatment Period • Time to next moderate/severe exacerbation following index exacerbation • Change from baseline in Clinic Visit trough FEV_1 measured pre- and post-bronchodilator at Days 14, 28, 56, and 84 (Day 84: post-bronchodilator is the primary endpoint; pre-bronchodilator is a secondary endpoint) and at hospital discharge (only for participants who are hospitalized for the index exacerbation) • Change from hospital discharge in clinic visit trough FEV_1 measured pre- and post-bronchodilator at Days, 14, 28, 56, and 84 (in participants hospitalized for index exacerbation only)
• To evaluate the treatment effect of nemiralisib in addition to SoC compared with placebo and SoC on symptoms indicative of an exacerbation and on health status using Patient-Reported Outcomes (PROs) in participants diagnosed with an acute moderate or severe exacerbation of COPD	<u>EXAcerbations of Chronic Pulmonary Disease Tool (EXACT-PRO)</u> • Proportion of participants achieving the EXACT definition of recovery from the index exacerbation by Days 14, 28, 56, and 84 • Time to recovery from index exacerbation • Severity of subsequent HCRU-defined exacerbation(s) defined by EXACT <u>COPD Assessment Test (CAT)</u> • Proportion of responders using the CAT at Treatment Days 28, 56, and 84, and following EXACT defined

Objectives	Endpoints
	recovery from the index exacerbation • Change from baseline (Day 1) in CAT total score at Days 28, 56, and 84 and following EXACT defined recovery from the index exacerbation <u>St. George's Respiratory Questionnaire (SGRQ) Total Score</u> • Proportion of responders on the SGRQ total score as measured by the SGRQ for COPD Patients (SGRQ-C) at Days 28, 56, and 84 • Change from baseline (Day 1) in SGRQ total score at Days 28, 56, and 84
• To evaluate the usage of rescue medication in patients diagnosed with an acute moderate or severe exacerbation of COPD	• Rescue medication use (occasions/day), averaged over each week of treatment and over the 84-day treatment period • The percentage of rescue-free days (24-hour periods) during each week of treatment and over the 84-day treatment period
• To evaluate the population pharmacokinetics of nemiralisib in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Plasma nemiralisib concentrations and derived PK parameters (e.g., area under the curve [AUC (0-24) and AUC(0-t)], maximum concentration [Cmax], time at maximum concentration [Tmax], Ctrough) as appropriate will be collected in a subset of randomized participants (approximately 300) at selected sites as follows: trough (pre-dose) for the study treatment and post-dose for the study treatment from 0-1 hour and >1 to 6 hours on Days 14 and 28 of the 12-Week Treatment Period
• To assess the safety and tolerability of nemiralisib and placebo in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Incidence of adverse events (AEs; including serious AEs and AE of Special Interest [AESI]) • Vital signs (pulse rate, systolic and diastolic blood pressure) (measured at each clinic visit up through Visit 7 [Day 112] or Early Withdrawal Visit) • 12-lead electrocardiogram (ECG) assessments (performed at clinic Visits 1 [Screening], 3 [Day 14], 6 [Day 84], and 7 [Day 112] or Early Withdrawal Visit) • Clinical laboratory tests (hematology and chemistry; performed at each clinic visit up through Visit 7 [Day 112] or Early Withdrawal Visit) • Incidence of COPD exacerbations
Exploratory Objectives	**Exploratory Endpoints**
• To further characterize the dose response, and efficacy, of nemiralisib administered in addition to SoC compared with placebo and SoC in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Rate of mild exacerbations over the 12-Week Treatment Period • Rate of all exacerbations (mild, moderate and severe combined) over the 12-Week Treatment Period • Time to next exacerbation (mild, moderate and severe combined)

Objectives	Endpoints
• To evaluate the treatment effect of nemiralisib in addition to SoC compared with placebo and SoC on symptom stability following an exacerbation using Patient-Reported Outcomes in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Stability of symptoms post recovery measured using E-RS:COPD (Evaluating Respiratory Symptoms in COPD) and subscales from Randomization (Visit 2) to Day 84 (Visit 6)
• To explore the PK/PD relationship for nemiralisib	• Relationship between drug exposure and Pharmacodynamic responses (e.g. efficacy, heart rate, clinical laboratory analytes and blood biomarkers) in the PK subset of participants (approximately 300) at selected sites
• To evaluate the treatment effect of nemiralisib in addition to SoC compared with placebo and SoC on HCRU in participants who experience a severe exacerbation of COPD	• Measures of HCRU related to severe exacerbations (e.g., hospitalizations, length of hospital stay, re-hospitalization within 30 days, number of Emergency Room [ER] visits, etc.)
• To evaluate compliance with study treatment	• Number of actuations of the double-blind study treatment as measured by the clip-on Propeller Sensor (for countries where the Propeller Sensor for ELLIPTA is available)
• To evaluate inflammatory markers in blood in relation to acute exacerbation of COPD	• Blood samples collected at Screening through Visit 7 (as part of the clinical laboratory blood samples) for analysis of blood eosinophil counts and inflammatory mediators • Blood samples for analysis of inflammatory biomarkers (including but not limited to: high sensitivity C-reactive protein [hs-CRP], chemokine interferon-γ inducible protein 10 kDa (CXCL10)], and procalcitonin) collected at Visit 1 (Screening)
• To evaluate inflammatory and infective markers in sputum in relation to acute exacerbation of COPD	• Spontaneous sputum sample for analysis of inflammatory and infective markers collected at Screening/Day 1 (pre-dose) and Day 56 in participants who are willing and able to provide a sample
• To evaluate the potential post-treatment impact of double-blind study treatment during the 12-Week Post-Treatment Follow-Up Period	• Change from baseline (Day 84) in Clinic Visit trough FEV1 measured pre- and postbronchodilator at Day 112, 140 and 168 • Rate of moderate and severe COPD exacerbation(s) during the 12-Week Follow-Up Period • Rate of moderate and severe COPD exacerbation(s) over the 24 week study duration • Time to next exacerbation following cessation of double blind study treatment • Proportion of responders using the CAT at Days 112 and 168 • Change from baseline (Day 1) in CAT Total score at Days 112 and 168 • Proportion of responders on the SGRQ Total Score as measured by the SGRQ-C at Days 112 and 168 • Change from baseline (Day 1) in SGRQ total score at

Objectives	Endpoints
	Days 112 and 168 • Severity of subsequent HCRU exacerbation defined by EXACT • E-RS: COPD and subscales from last dose of double-blind study treatment • Rescue medication use up to Day 112

2.2. Study Design

This is a Phase IIb, multicenter, randomized, stratified (by index COPD exacerbation severity [moderate or severe] and by whether or not the participant is in the PK Subgroup), double-blind (Sponsor Open), placebo-controlled, parallel-group study in participants who present with an acute moderate or severe exacerbation of COPD requiring Standard of Care (SoC).

This study consists of a Screening Period, a 12-Week Treatment Period and a 12-Week Post-Treatment Follow-Up Period. Randomization and the first dose of the double-blind study treatment administration (Visit 2/Day 1) should take place in the morning, as soon as possible following determination of eligibility and completion of the baseline measures, including the EXACT-PRO questionnaire for the day of randomization, and FEV_1 measurement and no later than 48 hours after the start of SoC.

PK Subgroup: Sparse PK sampling will be conducted in a subgroup of participants at selected sites. The PK Subgroup will be identical to the main study in terms of the study population, design, and conduct, with the exception of blood draws (3 per visit on Days 14 and 28) for PK analysis.

3. PLANNED ANALYSES

3.1. Interim Analyses

Ongoing data reviews of unblinded safety data, conducted by an Internal Safety Review Committee (iSRC), will be performed throughout the trial. Details will be documented in the iSRC charter.

Interim analyses of the primary endpoint and key secondary endpoints to inform internal decision making will be conducted periodically throughout the trial. The first analysis (Interim Analysis 1) is planned to occur when approximately 170 participants complete 28 days of treatment, where approximately 50 of the 170 participants have an index exacerbation defined as severe. A change that could arise from this interim analysis is a specification of the stratification proportions by index exacerbation severity status (moderate or severe). This decision will be based on inspection of all available endpoints at the interim analysis.

Further interim analyses will be performed, depending on the observed recruitment rate. At least one interim analysis of the primary endpoint of change from baseline in clinic visit trough FEV_1 at Day 84 measured post-bronchodilator will be performed to

determine whether or not any adjustments to the randomization ratio across doses would help optimize the characterization of the dose response profile for nemiralisib. This analysis (Interim Analysis 2) is planned to occur when approximately 300 participants complete 84 days of treatment or when approximately 400 participants remain to be randomized, whichever occurs first. Adjustments could include ceasing randomization to an existing dose(s) of nemiralisib and/or modification of the allocation ratios for the existing nemiralisib doses and/or addition of a 25mcg dose. Other changes may include specification of the stratification proportions by index exacerbation severity status.

An interim analysis of efficacy and safety data collected during the Double-Blind Treatment Period will be conducted when the last participant in the study has completed the 12-week Double-Blind Treatment Period (End of Treatment Interim Analysis). The aim of this analysis is to provide GSK with timely data to inform internal decision making, prior to the end of study.

The following table describes the endpoints that will be analysed/summarised at each interim:

Interim	Purpose of interim	Endpoints
Interim Analysis 1	To inform internal decision making	• Change from baseline in FEV_1 at Days 14, 28, and 56 measured pre- and post-bronchodilator • Other spirometry measures (percent predicted FEV_1, Forced Vital Capacity (FVC), percent predicted FVC and FEV/FVC ratio • On-treatment exacerbations • Proportion of participants achieving EXACT-defined recovery by Days 14, 28, 56 and 84

Interim	Purpose of interim	Endpoints
Interim Analysis 2	To determine if any adjustments to the randomization ratio would help characterize the dose response profile for nemiralisib	Endpoints listed for Interim Analysis 1 and also: • Change from baseline in FEV_1 at Day 84 measured pre- and post-bronchodilator • Rate of (on-treatment) exacerbations over the 12-Week Treatment Period • Time to next (on-treatment) exacerbation during the 12-Week Treatment Period • Proportion of responders using the CAT • Change from baseline in CAT Total Score • Proportion of responders using the SGRQ • Change from baseline in SGRQ Total Score • Rescue medication use, as measured in eDiary
End of Treatment Interim Analysis	To inform internal decision making	Selected Efficacy and Safety endpoints as defined in Appendix 11: List of Data Displays

The statistical methods of analyses are described in Section 7.

The Respiratory Data Sciences Group will apply machine learning techniques to the interim data to determine if identifiable phenotypic sub-population(s) of COPD participants are present at baseline, and if they result in different responses to Nemiralisib, to predict which participants will respond to Nemiralisib therapy, and to identify/quantify relationship(s) between different endpoints and response measures. Details of these analyses will be described in a separate RAP and results will be reported separately to the Clinical Study Report (CSR).

The following functions will be unblinded to interim analysis data: Clinical Statistics, Clinical Programming and Respiratory Data Sciences Group. Other member of GSK will be unblinded to group level summary data following the interim analyses (as documented internally).

3.1.1. Futility analyses

At least one interim analysis for futility will be performed. The first analysis will occur at Interim Analysis 2, i.e. when 300 participants complete 84 days of treatment, or when approximately 400 participants remain to be randomized, whichever occurs first.

Futility will be assessed in a sequential manner.

1)Futility will first be assessed for the primary endpoint of change from baseline in FEV_1 at Day 84 by fitting a suitable dose response model, as described in Section 7.1.2.
2)If the posterior predictive probability of declaring success for this endpoint is low across all doses, then futility will be assessed for the rate of (on-treatment) exacerbations endpoint.
3)If the posterior predictive probability of declaring success for this endpoint is low, then the study may be stopped.

Any decision to stop will be made after a review of all the data summarised/analysed at the time of the interim, including the proportion of participants achieving the EXACT-defined recovery.

3.1.1.1. Futility rules

The decision rules for futility are defined as follows.

Change from baseline in FEV_1 at Day 84

Stop study for futility if the predictive probability of success at the end of the trial, given the data at the interim is <20%, across all doses, where success at the end of the trial for change from baseline in FEV_1 is defined as demonstrating >90% posterior probability that the true difference from placebo for any dose of nemiralisib is greater than 0.

Rate of on-treatment (moderate/severe) exacerbations

Stop study for futility if the predictive probability of success at the end of the trial, given the data at the interim is <20%, where success at the end of the trial for rate of exacerbations is defined as demonstrating >80% posterior probability that the true rate reduction on 750 mcg dose versus placebo > 0%.

If a different dose arm appears to be more efficacious than the 750 mcg arm, then futility may be assessed using the rate reduction for this arm versus placebo.

The pre-determined rules will act as guidelines for stopping the study for futility. All of the data summarised/analysed at the time of the interim will be reviewed prior to any decision to stop the study.

3.2. Final Analyses

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

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

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Participants Enrolled (APE) Population	• All participants who are screened for eligibility.	• Study Population
Modified Intent To treat (MITT) Population	• All randomized participants who receive at least one dose of study treatment. • Participants will be analyzed according to the treatment that they were randomized to.	• Study Population • Efficacy
Per Protocol (PP) Population	• All randomized participants who receive at least one dose of study treatment, excluding any participants with an important protocol deviation. • Participants will be analyzed according to the treatment that they were randomized to.	• Sensitivity analyses of efficacy
Safety Population	• All randomized participants who received at least one dose of study treatment. • Participants will be summarised according to the treatment that they actually received. o If participants receive >1 treatment, then they will be summarised according to the most frequently dosed treatment. In cases where the frequency is equal, the participant will be assigned the lowest dose strength of nemiralisib	• Safety
Pharmacokinetic (PK) Population	• All participants in the Safety population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). • Participants will be summarised according to the treatment that they actually received	• PK

Refer to Appendix 11: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

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

Important deviations which result in exclusion from the analysis population will also be summarised and listed. (Please refer to Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).

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

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

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

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG Randomization System		Data Displays for Reporting	
Code	Description	Description	Order in TLF
A	Placebo	Placebo	1
B	GSK2269557 12.5 mcg	NEMI 12.5 mcg	2
C	GSK2269557 25 mcg*	NEMI 25 mcg	3
D	GSK2269557 50 mcg	NEMI 50 mcg	4
E	GSK2269557 100 mcg	NEMI 100 mcg	5
F	GSK2269557 250 mcg	NEMI 250 mcg	6
G	GSK2269557 500 mcg	NEMI 500 mcg	7
H	GSK2269557 750 mcg	NEMI 750 mcg	8

* The nemiralisib dose of 25 mcg may be added following the results of an un-blinded interim analysis if further characterization of the lower end of the dose response curve is required.

Treatment comparisons will be displayed as follows using the descriptors as specified:

1. NEMI 12.5 mcg vs Placebo
2. NEMI 25 mcg vs Placebo
3. NEMI 50 mcg vs Placebo
4. NEMI 100 mcg vs Placebo
5. NEMI 250 mcg vs Placebo
6. NEMI 500 mcg vs Placebo
7. NEMI 750 mcg vs Placebo

5.2. Baseline Definitions

For all endpoints, the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Post-bronchodilator Baseline FEV_1 is defined as the latest FEV_1 measured prior to the first dose of study treatment and post-bronchodilator.

Pre-bronchodilator Baseline FEV_1 is defined as the latest FEV_1 measured prior to the first dose of study treatment and pre-bronchodilator.

Baseline CAT Total Score is defined as CAT Total Score measured prior to the first dose of study treatment on Day 1.

Baseline SGRQ Total Score is defined as SGRQ Total Score measured prior to the first dose of study treatment on Day 1.

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

A centred baseline will be derived for each participant by subtracting the mean baseline across all participants from each participant's baseline value. The 'centred' baseline may be used instead of Baseline in the statistical analyses to aid convergence.

5.3. Multicentre Studies

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

5.4. Examination of Covariates and Subgroups

5.4.1. Covariates

The list of covariates may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses. The key covariates of interest are Index exacerbation severity, Smoking history and Region. Additional covariates of clinical interest may also be considered. The decision to include covariates in the model will be based on their impact on the model fit and/or convergence and will be detailed in the CSR.

A centred covariate will be derived for each participant by subtracting the mean covariate across all participants from each participant's covariate value. The 'centred' covariate may be used in place of the covariate in the statistical analyses to aid convergence.

Covariate	Details
Index exacerbation severity	Categorical variable (Moderate or Severe) derived using the stratification variable from the randomisation system.
Age (at screening)	Continuous variable derived as described in Section 13.6.2.1
BMI	Continuous variable derived using Height and Weight variables collected in eCRF: BMI = Weight (kg) / (Height (m))^2
Gender	Categorical variable (Male or Female), collected in eCRF
Country	Categorical variable
Region	Categorical variable derived using Country as: • Americas: Canada, Mexico, United States • Asia: Australia, Korea • Eastern Europe: Poland, Romania, Russia • Western Europe: France, Germany, Italy, Netherlands, Spain, Sweden, U.K.
Smoking history	Categorical variable (Current or Former), collected in eCRF
Baseline COPD maintenance therapy type	Categorical variable derived depending on data observed. Possible categories of interest are: Monotherapy vs. Dual therapy vs. Triple therapy
Index exacerbation type	Categorical variable: New or Relapse, derived using the question: "Other than the current prescription, for the index exacerbation, has the subject received oral/systemic corticosteroids and/or antibiotics for a COPD exacerbation within the last 7 days?" in the eCRF: New = No Relapse = Yes
Number of exacerbations in the previous 12 months	Categorical variable derived from "Total number of COPD exacerbations in the last 12 months" in the eCRF. Possible categories of interest are: 0 vs. 1 vs. ≥2
Baseline COPD ICS therapy use	Categorical variable (ICS Use or Non-ICS Use) derived from review of concomitant medications
Baseline Blood Biomarker Status	Categorical variable derived from Screening time-point for the following: High sensitivity CRP • Bacterial: >10 mg/L • Non-Bacterial: ≤10 mg/L Procalcitonin • Bacterial: >0.1 µg/L • Non-Bacterial: ≤ 0.1 µg/L Eosinophils • High: ≥0.15 GI/L • Low: <0.15 GI/L

5.4.2. Examination of Subgroups

The list of subgroups may be used in descriptive summaries and statistical analyses. Additional subgroups of clinical interest may also be considered.

- If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined.
- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup.

Subgroup	Categories
Index exacerbation severity	Moderate vs. Severe
Baseline COPD maintenance therapy type	Possible categories of interest are: Monotherapy vs. Dual therapy vs. Triple therapy
Index exacerbation type	New vs. Relapse
Number of exacerbations in the previous 12 months	Possible categories of interest are: 0 vs. 1 vs. ≥2
Gender	Male vs. Female
Smoking status	Current vs. Former
Baseline COPD ICS therapy use	ICS Use vs. Non-ICS Use
Baseline Blood Biomarker Status	• For High sensitivity CRP: Bacterial vs. Non-Bacterial • For Procalcitonin: Bacterial vs. Non-Bacterial • For Eosinophils: High vs. Low

5.5. Other Considerations for Data Analyses and Data Handling Conventions

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

Section	Component
Section 13.2	Appendix 2: Assessment Windows
Section 13.3	Appendix 3: Study Phases and Treatment Emergent Adverse Events
Section 13.4	Appendix 4: Data Display Standards & Handling Conventions
Section 13.5	Appendix 5: Derived and Transformed Data
Section 13.6	Appendix 6: Reporting Standards for Missing Data
Section 13.7	Appendix 7: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the "APE" and/or "MITT" populations, unless otherwise specified.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, and exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 11: List of Data Displays.

6.1.1. Concomitant medications

Concomitant medications will be summarised by treatment group. Separate summaries of Baseline and On-treatment (Step-up) COPD Maintenance Therapy, and duration of OCS use will also be presented.

Additional summaries or sensitivity analyses of on-treatment COPD maintenance therapy (step-up therapy) may be performed if the data indicate that further investigation is warranted.

7. EFFICACY ANALYSES

Details of the outputs are provided in Appendix 11: List of Data Displays and will be based on GSK data standards and statistical principles.

Further details for use in the endpoint derivations below can be found in Appendix 5: Derived and Transformed Data.

7.1. Primary Efficacy Analyses

7.1.1. Primary Endpoint

The primary endpoint of change from baseline in clinic visit trough FEV_1 at Day 84 measured post-bronchodilator is defined as:

FEV_1 measured prior to dosing and post-bronchodilator on Day 84 – Post-bronchodilator Baseline FEV_1

7.1.2. Primary Statistical Analyses

The primary endpoint will be analysed by fitting a suitable dose response model. The following models will be fitted, and the one that gives the best fit to the data will be selected: Bayesian 4-parameter E_{max} dose response model, 3-parameter E_{max} model and a Log-linear model.

The 4-parameter E_{max} dose response model will take the form:

$$\text{Change from baseline } FEV_1 = (E0 + a_1 * baseline) + \frac{(E_{max} + b_1 * baseline) * Dose^{\gamma}}{ED50^{\gamma} + Dose^{\gamma}}$$

The 3-parameter E_{max} dose response model will take the form:

$$\text{Change from baseline } FEV_1 = (E0 + a_1 * baseline) + \frac{(E_{max} + b_1 * baseline) * Dose}{ED50 + Dose}$$

Where: E0 = the response at dose = 0 (placebo)

E_{max} = the maximal response

ED50 = the dose that yields 50% of the maximal response

γ = the slope parameter

a_1, b_1, are covariates for explanatory parameters

Initially, normal non-informative priors will be used for the E0, a_1, a_2, and E_{max} parameters with mean 0 and standard deviation 1E6 L. A functional uniform prior will be used for the ED50 and slope parameters (Bornkamp, 2014), where the prior density for the functional uniform prior is based on all the parameters in the model. An inverse -

gamma prior with shape of 0.001 and scale of 0.001 will be used for the residual variance. However, if a prior distribution appears not to be truly non-informative then alternative prior distributions may be used.

Parameters will be blocked such that the MCMC procedure samples from E0, a_1, b_1, and E_{max}, first, then the ED50 and slope parameters and then finally the residual variance parameter. For the functional uniform priors, the density will be calculated for values of dose from 0.0001 to 750 in steps of 50 (i.e. 0.0001, 50.0001, 100.0001,…, 750.0001). For the continuous covariates, the density will be calculated from the minimum to the maximum in 10 equal steps. For binary covariates the density will be calculated for values 0 and 1. If the model does not converge including covariates, the model may be fitted with covariates removed.

If the log-linear model is fitted an offset of 1 will be used.

The posterior median change from baseline with 95% Highest Posterior Density (HPD) Credible Intervals, will be presented for each dose along with the adjusted median difference from placebo with 95% HPD, calculated at the mean baseline value across the treatment arms. Posterior probabilities that the true improvement is greater than 0 mL and 75 mL will also be presented. Graphical representation of the dose response across the full dose range will also be produced to allow inference to be made for the non-studied doses based upon the model fit.

For the futility analysis:

The predictive probability of success at the end of the study will be calculated (assuming the randomisation ratios remain the same after the interim) for each dose using the formula suggested by Spiegelhalter, 2004 as follows:

$$Predictive\ probability = 1 - \Phi\left[\frac{\sqrt{n_1}}{\sqrt{m_1}} z_{0.9} - \sqrt{\frac{n_1 + m_1}{m_1}} \frac{y_n}{\sigma}\right]$$

Where n_1 is the number of subjects with Day 84 data in the active arm of interest, m_1 is the number of subjects yet to be observed in the active arm of interest, y_n is the posterior mean difference from placebo from the fitted model, and σ is the standard deviation of the posterior mean difference from placebo.

For the possible adaptations at Interim Analysis 2:

If the study is not deemed futile, and either the 4 parameter or 3 parameter E_{max} dose response curves has successfully been fitted to the data then adaptation of the randomisation schedule will be considered, to drop, add or amend doses from the randomisation scheme.

The adaptation will be done by comparing the relative information from alternative randomisation schemes with the original randomisation schemes, such to find the design

that provides the most information about the dose response relationship. The efficiency ratio (ER) for an alternative scheme comparted to the original, will be calculated as:

$$ER(\theta_i) = \left(\frac{|M(\xi_1,\theta_i)|}{|M(\xi_F,\theta_i)|}\right)^{\frac{1}{p}}, \text{ i=1,…,1000}$$

Where $M(\xi,\theta)$ is the information matrix for the design ξ and model parameters $\theta = (e0, emax, ed50, \gamma, a_1, b_1)^T$, ξ_1 is the alternative design one and $\xi_F$is the fixed original design, and p is the number of parameters (Dette, 2008). In order to ensure any adaptation is robust to the variability in the parameter estimates at the interim analysis, 1000 samples will be generated from the posterior distribution of the parameters $\theta_1, \ldots, \theta_{1000}$ and the ER calculated for each set of parameter. Adaptation will then only take place if the median ER is >1.05 and the 10th percentile of the ER is >1. The efficiency ratio will be estimated using the mean baseline value across the population.

The alternative designs that will be considered will depend on the dose response model fitted but could include:

1. Add 25mcg dose
2. Add 25mcg dose, drop 500mcg dose
3. Add 25mcg dose, drop 250 mcg and 500 mcg doses
4. Drop 12.5mcg dose
5. Drop 12.5 mcg and 50mcg doses

The potential adaption may also be verified in the moderate and severe subgroups to ensure the adaption is beneficial across both groups.

7.1.2.1. Model Checking & Diagnostics

The following list of convergence diagnostics will be applied for each parameter:

- The Monte Carlo Standard Errors (MCSE) should be compared with the standard deviation (SD) of the posterior distribution to ensure that only a fraction of the posterior variability is due to the simulation. The number of samples generated and/or the thinning may be increased to reduce the ratio of the MCSE/SD as deemed necessary.
- The Geweke diagnostic test will be used to assess whether the mean estimates have converged by comparing means from the early and latter part of the Markov chain using a z-score t-test. Large absolute values of the z-score statistic indicate rejection of the null hypothesis of no difference between the mean estimates obtained from the early and latter parts of the chain.
- Trace plots of samples versus the simulation index will be visually inspected to assess some aspects of convergence. The centre of the chain should appear stable with very small fluctuations, i.e., the distribution of points should not change as the chain progresses and the posterior mean and variance are relatively constant.
- Autocorrelation plots will be visually inspected to assess degree of autocorrelation (should decline rapidly and show no oscillation patterns).

7.1.3. Sensitivity and Supportive Analyses

If there are greater than 20% of participants with an important protocol deviation that results in exclusion from the Per Protocol Population, the primary analysis may be repeated using the Per Protocol Population.

Change from baseline in clinic visit trough FEV_1 at Day 84 will also be compared between treatment groups using a Bayesian Repeated Measures analysis with covariates for baseline-by-Day interaction and treatment-by-Day interaction. Day will be fitted as a repeated effect within each participant. All post-baseline scheduled visits will be included in the analysis using Day. Non-informative priors will be used for all modelling parameters. Wherever possible conjugate priors will be utilised. An unstructured covariance matrix will be used to model the within-subject error.

A further sensitivity analysis may be performed where Baseline FEV_1 is replaced with the FEV_1 measured post-bronchodilator and prior to dosing on day of hospital discharge for participants who were hospitalised for their index exacerbation, i.e. who were randomized with a Severe index exacerbation but kept as Baseline FEV_1 for participants who were randomized with a Moderate index exacerbation.

7.1.4. Subgroup Analyses

A subgroup analysis of change from baseline in clinic visit trough FEV_1 by index exacerbation severity will be performed by fitting separate models to each level of the severity subgroup.

A subgroup analysis of change from baseline in clinic visit trough FEV_1 by index exacerbation severity will also be performed by including a treatment-by-severity-by-Day interaction term in the Bayesian Repeated Measures model.

7.2. Secondary Efficacy Analyses

7.2.1. Rate of exacerbations

Rate of exacerbation is defined as the frequency of exacerbations (subsequent to the index exacerbation) within the specified time period, for example, the 12-Week Treatment Period or the 24-Week Study Period.

The length of time on treatment or in study, depending on the specified time-period, for each participant will be calculated for each endpoint as follows:

Endpoint	Time period	Length of time derivation
Rate of (on-treatment) exacerbations, summarised by: • Moderate/severe exacerbations • Moderate exacerbations • Severe exacerbations • All (mild, moderate and	12-Week Treatment Period	Time from date of randomisation to date of last dose of study treatment

Endpoint	Time period	Length of time derivation
severe) exacerbations		
Rate of (on-or off-treatment) exacerbations, summarised by: • Moderate/severe exacerbations • All exacerbations	12-Week Treatment Period	Time from date of randomisation to Day 84 (Visit 6) Visit Date. For participants who withdraw early from the study: Time from date of randomisation to date of study withdrawal
Rate of (off-treatment) exacerbations, summarised by: • Moderate/severe exacerbations • Moderate exacerbations • Severe exacerbations	12-Week Follow Up Period	Time from date of last dose of study treatment to date of study withdrawal/completion
Rate of (on- and off- treatment) exacerbations, summarised by: • Moderate/severe exacerbations • Moderate exacerbations • Severe exacerbations	Full 24-Week Study Period	Time from date of randomisation to date of study withdrawal/completion

Refer to Section 13.5 for further details regarding the length of time derivation

7.2.1.1. Statistical analyses

The rate of exacerbations will be analysed using a Bayesian generalized linear model assuming a negative binomial distribution for the underlying exacerbation rate with a log link function. An offset to account for the length of time on treatment or in study, depending on the specified time-period, for each participant (as described above) will be included in the model as $\log_e$ (length of time).

Non-informative priors will be used for all modelling parameters. Wherever possible conjugate priors will be utilised.

The median exacerbation rates for each dose arm per 12 weeks, along with the median ratio in exacerbation rates (nemiralisib/placebo) per 12 weeks for each dose, will be estimated and corresponding 95% HPD credible intervals presented. The probability that the true exacerbation rate ratio is less than 1, in addition to other values appropriately selected based on the data, will be presented.

Based on pharmacological predictions, the 500 mcg and 750 mcg doses are expected to result in similar levels of target inhibition and thus potentially translate to similar clinical benefit, therefore estimates of the exacerbation rates for pooled data from 500 mcg plus 750 mcg will also be presented.

7.2.1.2. Subgroup analyses

A subgroup analysis of exacerbation rate by Index exacerbation severity will be performed by including a treatment-by-severity term in the model.

7.2.1.3. Exploratory analyses

A summary of exacerbation rate by the following groups will be presented and, if feasible, a subgroup analyses may be performed:

- Index exacerbation type (New or Relapse)
- Number of exacerbations in previous 12 months (0, 1 or ≥2).

7.2.2. Time to next exacerbation

Time to next (on-treatment) exacerbation following index exacerbation during the 12-Week Treatment Period is defined as time from the date of randomisation until the date of onset of the first exacerbation whilst on study treatment. Participants who did not have an exacerbation whilst on study treatment will be censored at the date of their last dose of study treatment.

Time to next (on-or off-treatment) exacerbation during the 12-Week Treatment Period is defined as time from the date of randomisation until the date of onset of the first exacerbation occurring up to Day 84. Participants who have not had an exacerbation during the 12-Week Treatment Period will be censored at Day 84 or the date of study withdrawal, for participants who withdrew from the study prior to Day 84.

Time to next exacerbation following cessation of study treatment is defined as time from the date of last dose of study treatment until the date of onset of the next exacerbation whilst off study treatment during the 12-Week Follow Up Period. Participants who have not had an exacerbation off-treatment will be censored at the date of their last follow up assessment.

Time to next exacerbation will be analysed by severity, as follows:

Endpoint	Time period
Time to next (on-treatment) exacerbation, summarised by: • Moderate/severe exacerbations • All (mild, moderate and severe) exacerbations	12-Week Treatment Period
Time to next (on-or off-treatment) exacerbation, summarised by: • Moderate/severe exacerbations • All exacerbations	12-Week Treatment Period
Time to next exacerbation following cessation of treatment, summarised by: • Moderate/severe exacerbations	12-Week Follow Up Period

Refer to Section 13.5 for further details regarding the length of time derivation

7.2.2.1. Statistical analyses

Time to next exacerbation will be analysed using a Bayesian Cox proportional hazards model with the "Efron" method for handling ties.

Kaplan-Meier (KM) estimates of the probability of exacerbation will also be presented.

Non-informative priors will be used for all modelling parameters. Wherever possible conjugate priors will be utilised.

The hazard ratio and corresponding 95% HPD credible intervals for each nemiralisib dose versus placebo will be presented. The probability that the true hazard ratio is less than 1, in addition to other values appropriately selected based on the data, will be presented.

Based on pharmacological predictions, the 500 mcg and 750 mcg doses are expected to result in similar levels of target inhibition and thus potentially translate to similar clinical benefit, therefore an estimate of hazard ratio for pooled data from 500 mcg plus 750 mcg nemiralisib doses versus placebo will also be presented.

7.2.2.2. Subgroup analyses

A subgroup analysis of time to exacerbation by Index exacerbation severity will be performed by including a treatment-by-severity term in the model.

7.2.3. Change from baseline in Clinic Visit trough FEV_1

Change from baseline in clinic visit trough FEV_1 at Day 14, 28, 56 measured post-bronchodilator is defined as:

FEV_1 measured prior to dosing and post-bronchodilator on Day X – Post-bronchodilator Baseline FEV_1

Where Day X is Day 14, 28, and 56.

Change from baseline in clinic visit trough FEV_1 at Day 14, 28, 56, 84 measured pre-bronchodilator is defined as:

FEV_1 measured prior to dosing and pre-bronchodilator on Day X – Pre-bronchodilator Baseline FEV_1

Where Day X is Day 14, 28, 56, and 84.

7.2.3.1. Statistical Analyses

Change from baseline in Clinic Visit trough FEV_1 measured post-bronchodilator will be analysed using a dose response model and repeated measures analysis as described for the primary endpoint in Section 7.1.2.

Change from baseline in Clinic Visit trough FEV_1 measured pre-bronchodilator will be analysed using a repeated measures analysis as described in Section 7.1.2

7.2.3.2. Subgroup analyses

A subgroup analysis of change from baseline in clinic visit trough FEV_1 by index exacerbation severity will be performed.

7.2.4. Change from hospital discharge in clinic visit trough FEV_1

Change from hospital discharge in clinic visit trough FEV_1 will be derived only for participants who were hospitalised for their index exacerbation and who have been subsequently discharged.

Change from hospital discharge in clinic visit trough FEV_1 measured post-bronchodilator is defined as:

FEV_1 measured prior to dosing and post-bronchodilator on Day X – FEV_1 measured post-bronchodilator and prior to dosing on day of hospital discharge.

Where Day X is 14, 28, 56 and 84.

Change from hospital discharge in clinic visit trough FEV_1 measured pre-bronchodilator is defined as:

FEV_1 measured prior to dosing and pre-bronchodilator on Day X – FEV_1 measured prior to dosing and post-bronchodilator on day of hospital discharge.

Where Day X is 14, 28, 56 and 84.

Note, as per Section 5.1 of the Protocol, if discharge takes place between Day 11 and Day 17 (inclusive), the assessments planned for Day 14 may be completed on the day of discharge. In these cases, for this endpoint only, the FEV_1 assessment will be assigned the hospital discharge assessment and the Day 14 assessment will be missing. Refer to Section 13.2.1.1 for further details.

In addition, if discharge takes place after Day 14, the Day 14 assessment will be missing for this analysis.

7.2.4.1. Statistical analyses

Change from hospital discharge in clinic visit trough FEV_1 will be analysed using a repeated measures analysis as described in Section 7.1.2 if there are a sufficient number of participants to provide a meaningful analysis, otherwise the data will be summarised.

7.2.5. EXAcerbations of Chronic Pulmonary Disease Tool - Patient Reported Outcome (EXACT)

The EXACT is a 14-item daily diary designed to provide a measure of patient-reported symptoms of COPD exacerbation. An EXACT Total Score, ranging from 0 to 100, where

higher scores indicate a more severe condition, will be derived for each day of diary collection according to the instructions in the EXACT User Manual (Version 8.0, Evidera, 2016).

The electronic EXACT diary does not allow a study patient to skip individual items, therefore no missing data are expected for individual items. However, if missing values occur for individual items, the Total Score that contains the item will be set to missing for that day. Moderate-to-severe COPD patients are expected to experience symptom(s) each day, and a score of zero on all 14 EXACT items is likely to represent a situation where in order to complete the diary quickly, the respondent did not accurately report their daily symptom(s), therefore if the EXACT Total Score is 0, it will be set to missing.

A 3-day Rolling Average EXACT Total Score will be calculated for each day, X, as:

> (EXACT Total Score on Day X-1 + EXACT Total Score on Day X + EXACT Total Score on Day X+1) / (Number of days with non-missing values)

Note, for Day 1, the Rolling Average EXACT Total Score will be calculated as the average of EXACT Total Score on Days 1 (Randomisation) and 2 only, since no EXACT data is collected prior to randomisation. Similarly, the Rolling Average EXACT Total Score for the last study day will be calculated as the average of EXACT Total Score on the last day and on the day before the last day.

The Rolling Average EXACT Total Score will be calculated for each day as long as at least 1 EXACT total score in the sequence is present. Therefore, only in the case where EXACT total scores are missing for 3 consecutive days in a row (or 2 consecutive days in the case of the first and last day rolling average calculation), will the rolling average score be missing.

The Maximum Observed Value (MOV) is defined as the highest Rolling Average EXACT Total Score observed within the first 14 days of randomisation. Note: this definition differs from the definition in the EXACT User Manual of "the highest rolling average EXACT score observed in the context of an EXACT exacerbation within the first 14 days of the exacerbation", since the date of the index exacerbation is likely to be prior to randomisation.

7.2.5.1. Proportion of participants achieving EXACT-defined recovery from index exacerbation

EXACT-defined recovery from the index exacerbation is defined as a decrease in the Rolling Average EXACT Total Score ≥9 points from the Maximum Observed Value, sustained for ≥7 days, with the first of the 7 days defined as the recovery day.

The proportion of participants achieving EXACT-defined recovery from the index exacerbation by Days 14, 28, 56, and 84 will be calculated as:

> (Number of participants who experience an EXACT-defined recovery on or before Day X) / (Total number of participants in the MITT population)

Where Day X is 14, 28, 56, and 84.

7.2.5.2. Time to EXACT-defined recovery from index exacerbation

Time to EXACT-defined recovery from index exacerbation is defined as time from the date of randomisation until date of the first EXACT-defined recovery day during the 12-Week Treatment Period, where EXACT-defined recovery is described in Section 7.2.5.1. Participants who did not experience EXACT-defined recovery during the 12-Week Treatment Period will be censored at the date of their last dose of study treatment.

7.2.5.3. Severity of subsequent HCRU-defined exacerbation(s) defined by EXACT

Severity of subsequent HCRU-defined exacerbation(s) defined by EXACT is defined as the highest EXACT Total Score (not using the 3-day Rolling Average) during the period from date of onset of the subsequent HCRU-exacerbation until date of EXACT-defined recovery of subsequent exacerbation.

Note, in this case, the Maximum Observed Value and EXACT-defined recovery are derived using the date of onset of the subsequent HCRU-exacerbation.

Severity of subsequent HCRU-defined exacerbation(s) defined by EXACT will only be derived for participants who have had a subsequent exacerbation. If a participant has more than one subsequent exacerbation, severity will be calculated for each subsequent exacerbation.

7.2.5.4. Statistical analyses

The proportion of participants achieving EXACT-defined recovery from the index exacerbation will be analysed using a Bayesian logistic regression model. Separate models will be fitted for each time-point.

Non-informative priors will be used for all modelling parameters. Wherever possible conjugate priors will be utilised.

The results of the analysis will be presented in terms of odds ratios together with its associated 95% HPD credible interval. The probability that the true odds ratio is greater than 1, in addition to other values appropriately selected based on the data, will be presented.

Time to EXACT-defined recovery from index exacerbation will be analysed using the same techniques as described in Section 7.2.2.1.

Severity of subsequent HCRU-defined exacerbation(s) defined by EXACT will be summarised for each treatment group and reported by study period. The severity of subsequent HCRU-defined exacerbation(s) occurring whilst a participant is on treatment will be reported as during the 12-Week Treatment Period and the severity of subsequent HCRU-defined exacerbation(s) occurring after the last dose of study treatment will be reported as during the 12-Week Follow-up Period.

7.2.5.5. Subgroup analyses

A subgroup analysis of the proportion of participants achieving EXACT-defined recovery from the index exacerbation by Index Exacerbation Severity will be performed by including a treatment-by-severity term in the model.

7.2.5.6. Sensitivity and supportive analyses

Sensitivity analyses exploring the impact of any missing data, and changes to the definition of EXACT-defined recovery may be conducted and may be performed post-SAC.

7.2.6. COPD Assessment Test (CAT)

The COPD Assessment Test (CAT) is a patient completed questionnaire developed to measure the health status of patients with COPD. The CAT consists of eight items, each on a six-point scale: 0 (no impact) to 5 (high impact). The CAT Score will be calculated for each study day of collection by summing the scores for all questions. The CAT Score ranges from 0 to 40, where higher scores indicate a more severe condition.

7.2.6.1. Proportion of responders using the CAT

The proportion of responders using the CAT will only be derived for participants with a baseline CAT Total Score ≥2.

The Proportion of responders using the CAT is defined as:

> (Number of participants with a decrease from baseline in CAT Total Score ≥2 on or before Day X)/(Total number of participants in the MITT population)

Where Day X is 28, 56, and 84 and the study day following EXACT-defined recovery from the index exacerbation. See Section 13.2.1.2 for details for cases where the study day following EXACT-defined recovery occurs within a scheduled assessment window.

Note: due to software limitations of the electronic PRO device, the study day following EXACT-defined recovery is not derived according to the EXACT User Manual, see Section 13.2.1.2 for further details.

Exploratory – Follow-Up Period

The Proportion of responders using the CAT at Day 112 and 168 is defined as:

> (Number of participants with a decrease from baseline in CAT Total Score ≥2 on or before Day X)/(Total number of participants in the MITT population)

Where Day X is Day 112 and Day 168 and the study day following EXACT defined recovery, if it occurs during the Follow-up period.

7.2.6.2. Change from baseline in CAT Total Score

Change from baseline in CAT Total Score is defined as:

CAT Total Score on Day X – Baseline CAT Total Score

Where Day X is 28, 56, 84 and the study day following EXACT defined recovery from the index exacerbation. See Section 13.2.1.2 for details for cases where the study day following EXACT-defined recovery occurs within a scheduled assessment window.

Note: due to software limitations of the electronic PRO device, the study day following EXACT-defined recovery is not derived according to the EXACT User Manual, see Section 13.2.1.2 for further details.

Exploratory – Follow-Up Period

The Change from baseline in CAT Total Score at Day 112 and 168 is defined as:

CAT Total Score on Day X – Baseline CAT Total Score

Where Day X is Day 112 and Day 168.

The Change from end of treatment in CAT Total Score at Day 112 and 168 is defined as:

CAT Total Score on Day X – CAT Total Score on Day 84

Where Day X is Day 112 and Day 168.

7.2.6.3. Statistical analyses

The proportion of responders using CAT will be analysed using the same techniques as described in Section 7.2.5.4.

Change from baseline/end of treatment in CAT Total Score will be compared between treatment groups using a Bayesian Repeated Measures analysis with covariates for baseline-by-Day interaction and treatment-by-Day interaction. Day will be fitted as a repeated effect within each participant.

All post-baseline scheduled visits will be included in the analysis using Day.

Non-informative priors will be used for all modelling parameters. Wherever possible conjugate priors will be utilised. An unstructured covariance matrix will be used to model the within-subject error.

Adjusted posterior median change from baseline and corresponding 95% HPD credible intervals will be summarised for each treatment by time-point, together with estimated treatment differences (GSK – Placebo) and corresponding 95% HPD credible intervals. The posterior probability that the true treatment difference is less than 0, in addition to other values appropriately selected based on the data, will also be presented.

7.2.6.4. Subgroup analyses

A subgroup analysis of the proportion of responders using CAT and the change from baseline in CAT Total Score by Index exacerbation severity will be performed by including a treatment-by-severity term and a treatment-by-severity-by-Day term in the Bayesian logistic regression and Bayesian Repeated Measures models, respectively.

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

St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C) is a 40-item questionnaire designed specifically to focus on COPD patients. SGRQ-C will be scored to be equivalent to the SGRQ Total Score, ranging from 0 to 100, where higher scores reflect worse health-related quality of life. SGRQ Total Scores will be calculated for each day of collection according to the instructions in SGRQ-C Manual (Version 1.3, March 2016).

7.2.7.1. Proportion of responders on the SGRQ Total Score

The proportion of responders on the SGRQ Total Score will only be derived for participants with a baseline SGRQ Total Score ≥4.

Proportion of responders on the SGRQ Total Score is defined as:

> (Number of participants with a decrease from baseline in SGRQ Total Score ≥4 on or before Day X)/(Total number of participants in the MITT population)

Where Day X is 28, 56, and 84.

Exploratory – Follow-Up Period

The Proportion of responders on the SGRQ Total Score at Day 112 and 168 is defined as:

> (Number of participants with a decrease from baseline in SGRQ Total Score ≥4 on or before Day X)/(Total number of participants in the MITT population)

Where Day X is Day 112 and Day 168 and the study day following EXACT defined recovery, if it occurs during the Follow-up period.

7.2.7.2. Change from baseline in SGRQ Total Score

Change from baseline in SGRQ Total Score is defined as:

> SGRQ Total Score on Day X – Baseline SGRQ Total Score

Where Day X is Day 28, 56, and 84.

Exploratory – Follow-Up Period

The Change from baseline in SGRQ Total Score at Day 112 and 168 is defined as:

SGRQ Total Score on Day X – Baseline SGRQ Total Score

Where Day X is Day 112 and Day 168.

The Change from end of treatment in SGRQ Total Score at Day 112 and 168 is defined as:

SGRQ Total Score on Day X – SGRQ Total Score on Day 84

Where Day X is Day 112 and Day 168.

7.2.7.3. Statistical analyses

Change from baseline/end of treatment in SGRQ Total Score and the proportion of responders on the SGRQ Total Score will be analysed using the same techniques as described in Section 7.2.6.3.

7.2.7.4. Subgroup analyses

Subgroup analyses of change from baseline in SGRQ Total Score and the proportion of responders on the SGRQ Total Score by Index exacerbation severity will be conducted as described in Section 7.2.6.4.

7.2.8. Rescue medication use

All participants will record rescue medication use in the eDiary. Rescue medication use will be recorded as the number of occasions of rescue medication use each day.

The Mean Number of Occasions of Rescue Medication Use Per Day is defined as:

(Sum of the number of occasions of rescue medication use each day within the time-period) / (Total number of days with non-missing values within the time-period)

The Percentage of Rescue-Free Days is defined as:

(Sum of the number of days where the number of occasions of rescue medication use is zero within the time-period) / (Total number of days with non-missing values within the time-period)*100

Where the time-period is defined as follows:

Week 1 of the 12-Week Treatment Period: Day 1 to Day 7

Week 2 of the 12-Week Treatment Period: Day 8 to Day 14

Week 3 of the 12-Week Treatment Period: Day 15 to Day 21

Week 4 of the 12-Week Treatment Period: Day 22 to Day 28

Week 5 of the 12-Week Treatment Period: Day 29 to Day 35

Week 6 of the 12-Week Treatment Period: Day 36 to Day 42

Week 7 of the 12-Week Treatment Period: Day 43 to Day 49

Week 8 of the 12-Week Treatment Period: Day 50 to Day 56

Week 9 of the 12-Week Treatment Period: Day 57 to Day 63

Week 10 of the 12-Week Treatment Period: Day 64 to Day 70

Week 11 of the 12-Week Treatment Period: Day 71 to Day 77

Week 12 of the 12-Week Treatment Period: Day 78 to Day of last dose

Over the 12-Week Treatment Period: Day 1 to Day of last dose.

Exploratory – Follow-Up Period

Rescue medication use up to Day 112 will also be summarised by including the time-periods:

Week 13 (Follow-up Period): (Day of last dose + 1) to (Day of last dose + 1) + 6 days

Week 14 (Follow-up Period): (Day of last dose + 7) to (Day of last dose + 1) + 13 days

Week 15 (Follow-up Period): (Day of last dose + 14) to (Day of last dose + 1) + 20 days

Week 16 (Follow-up Period): (Day of last dose + 21) to (Day of last dose + 1) + 27 days

For a subject to be counted in the time periods for rescue medication use, they must have at least one eDiary entry recorded during that time period.

7.2.8.1. Rescue medication use via the clip-on Propeller Sensor for MDI

A subset of participants from countries where the Propeller Sensor for MDI is available will also record rescue medication use via the clip-on Propeller Sensor for MDI. A supportive summary of rescue medication use via the clip-on Propeller Sensor for MDI for these participants will be presented.

Rescue medication use via the clip-on Propeller Sensor for MDI is defined in the same way as rescue medication use via the eDiary, except that the number of actuations will be used instead of the number of occasions in accordance with the way the data is captured.

7.2.8.2. Statistical analyses

The Mean Number of (on-treatment) Occasions of Rescue Medication Use Per Day will be summarised between each treatment group using means, standard deviations, medians, minimum and maximum.

The Percentage of (on-treatment) Rescue-Free Days will be summarised between each treatment group using means, standard deviations, medians, minimum and maximum.

Rescue medication use via the clip-on Propeller Sensor for MDI will be summarised in the same way as rescue medication use via the eDiary.

7.3. Exploratory Efficacy Analyses

7.3.1. Change from Day 84 in Clinic Visit trough FEV_1

Change from Day 84 in clinic visit trough FEV_1 measured post-bronchodilator is defined as:

FEV_1 measured prior to dosing and post-bronchodilator on Day X – Day 84 post-bronchodilator FEV_1

Where Day X is Day112, Day 140 and Day 168.

Change from Day 84 in clinic visit trough FEV_1 measured pre-bronchodilator is defined as:

FEV_1 measured prior to dosing and pre-bronchodilator on Day X – Day 84 pre-bronchodilator FEV_1

Where Day X is Day 112, Day 140 and Day 168.

Participants who discontinue study treatment prior to Day 84 will be excluded from this analysis.

7.3.1.1. Statistical analysis

Change from Day 84 in Clinic Visit trough FEV_1 will be analysed using the same techniques as described for Change from baseline in CAT Total Score in Section 7.2.6.3.

A subgroup analysis of change from Day 84 in FEV_1 will be performed by including a treatment-by-severity-by-Day term in the Bayesian Repeated Measures model.

7.3.2. E-RS:COPD (Evaluating Respiratory Symptoms in COPD)

Change from baseline in E-RS: COPD and subscales will be summarised by treatment group. Exploratory analyses related to E-RS: COPD and subscales may be performed post SAC.

7.3.3. Measures of HCRU related to exacerbations

Unscheduled Healthcare Utilisation will be summarised separately for exacerbation-related, COPD-related or non-COPD related; each summary will be presented by all patients (i.e. moderate and severe index exacerbation combined), and separately by index exacerbation severity.

The number of days of hospital admission for the index and subsequent exacerbations will also be summarised by treatment group.

7.3.3.1. Re-hospitalisation within 30 days of index exacerbation

Re-hospitalisation within 30 days of index exacerbation is defined as 30 days from the date of hospital discharge until the date of next hospital admission (+ 1 day, to account for study day derivation), for participants who were hospitalised for their index exacerbation.

Exacerbation-related, COPD-related and Non-COPD-related hospital admissions are collected in separate eCRFs. The date of hospital admission is not collected in the COPD-related eCRF, therefore the date of next hospital admission will be estimated using the earliest of:

- Date of hospital admission for exacerbation-related hospitalisations
- Date of contact for COPD-related hospitalisations, where the number of inpatient hospitalisation days >0
- Date of hospital admission for non-COPD-related hospitalisations.

The proportion of participants who were re-hospitalised within 30 days of the index exacerbation will be summarised by each treatment arm.

7.3.3.2. Time from resolution of index exacerbation to next exacerbation

Time from resolution of index exacerbation to next exacerbation is defined as time from the date of (Investigator-defined) resolution of index exacerbation until the date of onset of the subsequent exacerbation.

A summary of time from resolution of index exacerbation to next exacerbation will be presented. Participants who did not have a subsequent exacerbation or for whom the index exacerbation was not resolved will be excluded from the summary.

Time from resolution of index exacerbation to next exacerbation will only be derived for the first subsequent exacerbation following the index exacerbation.

7.3.3.3. Subsequent exacerbation treatment type

A summary of the type of treatment for subsequent exacerbations (OCS, antibiotics, or both) may also be presented.

7.3.4. Compliance

Compliance with study treatment for all participants is captured from the dose counter on the ELLIPTA and the overall percentage compliance will be summarised by each treatment group.

Reported compliance with study treatment is also captured daily in the eDiary from the question "Did you take this morning’s dose of study medication”?

The percentage of reported compliance for each participant is calculated as:

(Sum of the number of days where the question was answered with 'Y') / (Number of days from first dose of study treatment to last dose of study treatment) x 100

Overall percentage of reported compliance will also be summarised by each treatment group.

7.3.4.1. Number of actuations of double-blind study treatment measured by the clip-on Propeller Sensor

Percentage compliance via the clip-on Propeller Sensor for ELLIPTA in the subset of participants from countries where the Propeller Sensor for ELLIPTA is available is calculated as:

(Sum of the number of days with actuation > 0) / (Number of days from first dose of study treatment to last dose of study treatment) x 100

Overall percentage compliance will be summarised by each treatment group.

7.3.4.2. Missing EXACT-PRO data

Missing EXACT-PRO data will be summarised by treatment group.

7.3.5. Inflammatory/infective markers in blood and sputum in relation to acute exacerbation of COPD

Results of the analysis of blood/spontaneous sputum samples of eosinophil counts and inflammatory/infective mediators/markers will be summarised by treatment group.

Further analyses of inflammatory/infective markers may be performed, for example split by CRP high, CRP low, Procalcitonin high, etc. categories.

7.3.6. Other spirometry measurements

Percent predicted FEV_1, Forced Vital Capacity (FVC), percent predicted FVC and FEV/FVC ratio will be summarised by treatment group.

7.3.7. Other symptoms suggestive of exacerbation

Responses to questions in the eDiary related to symptoms of sputum purulence (colour), fever, sore throat, wheezing and colds collected in the eDiary will be listed by treatment group.

7.3.8. Classification of exacerbating COPD participants and prediction of response to nemiralisib using machine learning techniques

Exploratory analysis of endpoints using machine learning techniques will be performed which will include classification of COPD participants, identification of parameters which describe a responder, and prediction of response to nemiralisib using baseline data. Details of these analyses will be described in a separate RAP and results may be reported separately to the CSR.

8. SAFETY ANALYSES

The safety analyses will be based on the Safety population, unless otherwise specified. The details of the planned displays will be provided in Appendix 11: List of Data Displays.

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs) and Serious (SAEs) will be based on GSK Core Data Standards.

8.1.1. Adverse Events of Special Interest

Adverse events of special interest (AESI) are significant identified or potential risks identified in the nemiralisib clinical development programme.

8.1.1.1. Post-inhalation Cough Immediately Following Dosing

Post-inhalation cough immediately following dosing is an AESI and will be evaluated during study Visits 2-6 in the 12-Week Double-Blind Treatment Period. Investigators (or medically qualified designees) will monitor participants for potential study treatment tolerability issues, including post-inhalation cough, within 5 minutes immediately following dosing.

The percentage of patients experiencing post-inhalation cough following dosing, regardless of whether it was also reported as an AE, overall and by each visit will be summarised for each treatment group. The type of cough, time to onset and duration of cough, and severity will also be summarised.

In addition, any post-inhalation cough immediately following dosing reported as an adverse event during the clinic visit observation or during the course of the study will be summarised by treatment group.

8.1.1.2. Paradoxical bronchospasm

Paradoxical bronchospasm is an AESI, defined using the Preferred Terms Bronchospasm and Bronchospasm paradoxical and will be summarised by treatment group.

8.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Haematology laboratory tests and liver function tests will be based on GSK Core Data Standards.

8.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified.

8.4. Mortality

A summary of all-cause mortality by treatment will be presented.

9. PHARMACOKINETIC ANALYSES

9.1. Population of Interest

The primary pharmacokinetic analyses will be based on the "Pharmacokinetic" population, unless otherwise specified.

9.2. Drug Concentration Measures

Plasma nemiralisib concentrations of GSK2269557 will be listed and summarised by dose, day and time. Drug levels will be summarised by day (14, 28), dose and time intervals (trough, 0-<1h, 1-6h).

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 13.4.3 Reporting Standards for Pharmacokinetic).

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK Data Standards and statistical principles.

10. POPULATION PK ANALYSIS

A dataset for population PK analysis will be provided by Statistics and Programming based on the NONMEM data specifications in Section 13.8.2.

Conduct of the population PK analyses will be based on the current guidance which contains specific recommendations for working practices, processes and standards for population PK and PK/PD analysis conducted by Clinical Pharmacology Modelling and Simulation (CPMS) [Analysis & Reporting, 2017].

The sparse PK samples will be subjected to a validated population PK model for nemiralisib currently under development.

Details of these analyses will be described in a separate CPMS RAP and results will be reported separately to the CSR. Analyses and reporting of the population PK model will be in accordance with the FDA and EMEA guidance on population PK, PK-PD analyses.

10.1. Derived Pharmacokinetic Parameters

The exposure parameters (e.g. AUC, C_{max}) will be derived from the individual post-hoc estimates from the POP PK model. These will be summarized across dose treatments, subgroups (e.g., gender, race) or as a function of a continuous variable (e.g., age).

11. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

If statistical analyses suggest an effect of nemiralisib on primary and other key clinical endpoints, an integrated longitudinal population dose/exposure versus clinical response on analysis key parameters including FEV_1 and exacerbation rate will be undertaken. Participant characteristics influencing the relationship will be evaluated.

Details of these analyses will be described in a separate CPMS RAP and results will be reported separately to the CSR.

12. REFERENCES

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Dette, H., Bretz, F., Pepelyshev, A. & Pinheiro, J., (2008). Optimal Designs for Dose-Finding Studies. Journal of the American Statistical Association, 103:483, 1255-1237. doi: 10.1198/016214508000000427.

Evidera. (2016). The Exacerbations of Chronic Pulmonary Disease Tool (EXACT) Patient-Reported Outcome (PRO) USER MANUAL (Version 8.0).

Spiegelhalter, D.J., Abrams, K.R. & Myles, J.P., (2004). Bayesian Approaches to Clinical Trials and Health-Care Evaluation. John Wiley & Sons, Ltd.

13. APPENDICES

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

13.1.1. Exclusions from Per Protocol Population

Protocol deviations will be reviewed regularly throughout the course of the study, as described in Protocol Deviation Management Plan (PDMP). Deviations which will result in exclusion from the Per Protocol population will be assigned on a case-by-case basis prior to database freeze (DBF).

Decisions on whether or not the subject should be excluded from the PP population because the incorrect treatment was taken, due to the incorrect container being dispensed, will be identified after unblinding (i.e. post DBF). A PD of "incorrect treatment" will be added to the reporting dataset.

13.2. Appendix 2: Assessment Windows

13.2.1. Definitions of Assessment Windows for Analyses

13.2.1.1. Hospital discharge

As per Section 5.1 of the Protocol, if discharge takes place between Day 11 and Day 17 (inclusive), the assessments planned for Day 14 may be completed on the day of discharge. In these cases, for this endpoint only, the FEV_1 assessment will be assigned the hospital discharge FEV_1 assessment and the Day 14 assessment will be missing.

For all other analyses and summaries that include participants who were hospitalised for their index exacerbation, an additional Analysis Timepoint of "HOSPTIAL DISCHARGE" will be derived. However, in the cases where discharge takes place between Day 11 and Day 17 (inclusive), participants will be summarised under DAY 14 and a footnote to say that participants who were discharged at Day 14 are summarised under DAY 14 will be included.

13.2.1.2. EXACT-Defined Recovery for CAT Trigger

If the study day following EXACT-defined recovery for a participant occurs within a scheduled assessment window, an additional analysis time-point will be programmatically created for that scheduled visit. For example, if EXACT-defined recovery occurred on Day 56, then a Day 56 Visit will be programmatically created with the data from the Recovery visit so that it can be summarised/analysed in both the Visit and Recovery categories.

Due to software limitations of the electronic PRO device, the study day following EXACT-defined recovery from the index exacerbation is not derived according to the EXACT User Manual. Instead, it has been derived using a 3-day Rolling Average that is calculated as the mean EXACT score [Day X-2, Day X-1, Day X].

13.3. Appendix 3: Study Phases and Treatment Emergent Adverse Events

13.3.1. Study Periods

13.3.1.1. 12-Week Treatment Period

The 12-Week Treatment Period is assigned from Study Day 1 to Study Day 84.

13.3.1.2. 12-Week Follow-Up Period

The 12-Week Follow-up Period is assigned from Study Day 85 to Study Day 168.

13.3.2. Study Phases

Exacerbation events during the 12-Week Treatment Period will be classified according to their occurrence from randomisation until treatment discontinuation/study withdrawal days, as detailed below.

Study Phase	Occurring from randomisation until
On-Treatment during the 12-Week Treatment Period	Treatment Stop Day
On- or Off-Treatment during the 12-Week Treatment Period	Day 84 or Study Withdrawal Day if Treatment Stop Day is < Day 84

13.3.2.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before Randomisation Date
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 6: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

13.3.3. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date & on or before treatment stop date plus 10 days.

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

13.4. Appendix 4: Data Display Standards & Handling Conventions

13.4.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Compound	: \arprod\gsk2269557\mid200879
Analysis Datasets	
• For all interim analyses, except for the End of Treatment Interim Analysis, datasets will be created according to Legacy GSK A&R dataset standards. • For the End of Treatment Interim Analysis and the final reporting effort, datasets will be created according to current CDISC standards	
Generation of RTF Files	
• RTF files will be generated for the final reporting effort.	

13.4.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 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
  • Figures will be produced using PROC SGPLOT in SAS

Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of decimal places. • For lab parameters results that contain a character value of '<', or '>', e.g. '<X' or '>X', the parameter value will be imputed with X.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.

Unscheduled Visits	
• Unscheduled visits will be included in summary tables of the worst-case results by potential clinical importance criteria only. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principles 7.01 to 7.13.	

13.4.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PK File	Pop-PK file (CSV format) for the POP-PK analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the data specification detailed in Section 13.8.2 Population Pharmacokinetic (PopPK) Dataset Specification.
NONMEM/PK/PD File	PK/PD file (CSV format) for the PK/PD analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the data specification detailed in the CPMS RAP.

13.5. Appendix 5: Derived and Transformed Data

13.5.1. General

Multiple Measurements at One Analysis Time Point
• Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from Randomisation Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Randomisation Date → Study Day = Ref Date – Randomisation Date
  • Ref Data ≥ Randomisation Date → Study Day = Ref Date – (Randomisation Date) + 1

Time from date of randomisation and time from date of last dose of study treatment

• For endpoints that use the time from the date of randomisation to a reference date, time will be calculated as
  • (Ref Date – Randomisation Date) + 1
• For endpoints that use the time from the date of last dose of study treatment to a reference date, time will be calculated as
  • (Ref Date – (Last Dose Date + 1)) +1

13.5.2. Study Population

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1**

13.5.3. Safety

Adverse Events
AE'S of Special Interest
• Post-inhalation cough: Lower level term (LLT) to be included is "coughing after drug inhalation" • Paradoxical bronchospasm: Preferred Terms to be included are "Bronchospasm paradoxical" and "Bronchospasm"

13.6. Appendix 6: Reporting Standards for Missing Data

13.6.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) is defined as completing all phases of the study including the last scheduled study visit • A participant is considered to have completed the Treatment Period, if he/she has completed the last on-treatment study visit (Visit 6) • Withdrawn subjects were not replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Withdrawal visits will not be summarised (and will be listed only).

13.6.2. Handling of Missing Data

Element	Reporting Detail

General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument:
	  • These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table.
	  • Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

13.6.2.1. Handling of Missing and Partial Dates

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

Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event:
	  • Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 3: Study Phases and Treatment Emergent Adverse Events.
	  • Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used.
	• Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

Element	Reporting Detail

Concomitant Medications/Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
	  • If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month
	  • If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.
	• The recorded partial date will be displayed in listings.

Age	• The eCRF collects year of birth only. Day and Month will be imputed by Data Management using a PPD for the day and 'PPD for the month • Age will then be derived referenced to the Screening Date • A footnote to say that age has been imputed will be included in any outputs containing age.

13.7. Appendix 7: Values of Potential Clinical Importance

13.7.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Haemoglobin	G/DL	Male 18-64 years	7.1	19.9
		Male 65+ years	7.1	19.9
		Female 18-64 years	7.1	19.9
		Female 65+ years	7.1	19.9
Lymphocytes	GI/L		0.85	4.1
Total Absolute Neutrophil Count	GI/L		1.5	8
Platelet Count	GI/L		31	1499
White Blood Cell count	GI/L	18-64 years	1.1	10.8
		65+ years	1.1	10.8

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	g/L		32	50
Calcium	mmol/L		1.5	3.24
Creatinine		Male 40-49 years	69	160
		Male 50-59 years	67.2	160
		Male 60-69 years	67.2	160
		Male 70+ years	59.2	160
		Female 40-49 years	52.2	160
		Female 50-59 years	53	160
		Female 60-69 years	53	160
		Female 70+ years	55.7	160
Glucose	mmol/L	13-49 years	2.2	27.8
		50+ years	2.2	27.8
Potassium	mmol/L		2.8	6.5
Sodium	mmol/L		120	160
Urea/BUN	mmol/L	13-64 years	2.5	15
		65+ years	2.5	15

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	≥ 2x ULN
AST/SGOT	U/L	High	≥ 2x ULN
AlkPhos	U/L	High	≥ 2x ULN
T Bilirubin	µmol/L	High	≥ 2x ULN
T. Bilirubin + ALT	µmol/L U/L	High	2xULN T.Bilirubin + ≥ 3x ULN ALT
Direct Bilirubin	µmol/L		0 – 6

13.7.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec		> 530
Absolute PR Interval	msec	< 110	> 240
Absolute QRS Interval	msec	< 75	> 110
Change from Baseline			
Increase from Baseline QTc	msec		> 60

13.7.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 95	> 160
Diastolic Blood Pressure	mmHg	< 55	> 100
Heart Rate	bpm	< 40	> 110

13.8. Appendix 8: Population Pharmacokinetic (PopPK) Analyses

13.8.1. Population Pharmacokinetic (PopPK) Methodology

All analysis will be performed in the validated Modelling and Analysis Platform (MAP). MAP consists of a Linux desktop containing various modelling applications, including NONMEM, PsN, Pirana, R and RStudio. All software versions used will be documented.

The population PK analysis will be performed in the following sequence of steps:

1. Exploratory data analysis/data check out.
2. Base structural model development.
3. Covariate analysis.
4. Model refinement.
5. Model evaluation.
6. Model application using simulation

The above analysis and reporting steps follow EMEA (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003067.pdf) and FDA population PK guidances (https://www.fda.gov/downloads/drugs/guidances/UCM072137.pdf)

Key components of these regulatory guidelines on population PK are also included in the Global CPMS guidance for pop pk RAP (https://connect.gsk.com/sites/cpms/TandD/Guidances).

13.8.2. Population Pharmacokinetic (PopPK) Dataset Specification

Statistics & Programming, in discussion with CPMS, will provide a NONMEM dataset.

Column headings in NONMEM-ready datasets and specifications should be consistent to minimise the programming process, and facilitate a smooth transfer of projects between users as needed. IDSL standards will be followed where possible.

A list of most common standardised variable names for NONMEM datasets can be found in Table below.

List of Variable Names for NONMEM-Ready Datasets for PopPK Analysis

Variable	Label (Variable description)
C	NONMEM line exclusion identifier
ID	NONMEM subject identifier
STUD	Study ID
SUBJID	Subject identifier for study
SITEID	Unique identifier for a study site
AMT	NONMEM Amount of drug administered then EVID =1- dose event record
UAMT	Unit of AMT (mg)
ADDL	NONMEM Additional dose
CONC	Drug Concentration
UCONC	Unit of CONC (ng/mL)
LNCONC	Natural log of CONC column
ANALYTE	Drug label e.g 557
LLQ	Lower Limit of quantification
LNLLQ	Natural log of LLQ column
DAY	Study day number of record or of dosing
TIME	Plasma sample time after last dose
UTIME	Unit of TIME (h)
DOSE	Dose amount
EVID	NONMEM Event ID If row has dose then EVID=1 else EVID =0 If EVID=1 then this is a dose event record If EVID = 0 then this is an observation record
II	NONMEM Inter-dose interval II=24 – dose every day
SS	Steady state item SS= 1 refers to steady state
MDV	NONMEM Missing data value then MDV=1 else MDV=0
AGE	Subject Age (yrs)
SEX	Subject gender 0 = Male 1 =Female
SEXTEXT	Subject gender text Male or Female
BMI	Baseline Body Mass Index
WT	Baseline Subject weight
CONMED1	Identifier for inhibitor CYP3A4 1 =Yes, 0 = No
CONMED1TXT	Inhibitor Name
CONMED2	Identifier for inducer CYP3A4 1 =Yes, 0 = No
CONMED2TXT	Inducer Name

If observation record e.g CONC has “NA” or “NS” then assign CONC cell as “.”
If observation record e.g CONC has “NQ” or “BQL” then assign CONC cell as “.” and MDV = 1 -this means value can be estimated by model
Missing covariate data should be imputed as “-99.

13.9. Appendix 9: Pharmacokinetic / Pharmacodynamic Analyses

13.9.1. Pharmacokinetic/Pharmacodynamic Methodology

PK-PD analysis of Nemiralisib will be guided by the results of the formal statistical analyses on the key clinical endpoints. The aims of the PK-PD analyses will contribute towards the dose selection in future studies using an integrated longitudinal analysis framework.

The objective is to explore an integrated modelling framework to characterise the longitudinal FEV1 response versus dose (average systemic exposure) during on- & off-treatment phases

$$FEV1_i(t_{ij}) = FEV1_{i,base} \cdot (1 + f(t_{ij}, dose_i, x_i) + \varepsilon_{ij} \text{ with } \varepsilon_{ij} \sim N(0, \sigma 2)$$

A longitudinal nonlinear mixed-effects model will be used to describe the FEV1 response over time measured for each patient (i) at each visit (tij) with ε denoting the normal distributed residual variability with mean 0 and variance $\sigma 2$. The function $f()$ describes the relative change from observed FEV1 at baseline ($FEV1_{,base}$) and any influence of patient characteristics on FEV1 response will be assessed.

Joint relationship between time to first exacerbation and FEV1 change as function of dose/exposure and patient covariates will be assessed.

Details of these analyses will be described in a separate CPMS RAP and results will be reported separately to the CSR.

13.10. Appendix 10: Abbreviations & Trade Marks

13.10.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
APE	All Participants Enrolled
AUC	Area Under the Curve
BMI	Body Mass Index
CAT	COPD Assessment Test
CDISC	Clinical Data Interchange Standards Consortium
COPD	Chronic Obstructive Pulmonary Disease
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CSV	Comma Separated Values
CTR	Clinical Trial Register
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
ERS	Evaluating Respiratory Symptoms
EXACT	Exacerbations of Chronic Pulmonary Disease Tool
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
FEV1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GSK	GlaxoSmithKline
HCRU	Health Care Resource Use
HPD	Highest Posterior Density
IA	Interim Analysis
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
iSRC	Independent Safety Review Committee
KM	Kaplan-Meier

LLT	Lower Level Term
MCMC	Markov Chain Monte Carlo
MCSE	Monte Carlo Standard Errors
MDI	Metered Dose Inhaler
MITT	Modified Intent To Treat
OCS	Oral Corticosteroids
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
PRO	Patient Reported Outcomes
PT	Preferred Term
QC	Quality Control
QTcF	Fridericia's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SGRQ	St. George's Respiratory Questionnaire
SGRQ-C	St. George's Respiratory Questionnaire for COPD Patients
SoC	Standard of Care
SOP	Standard Operation Procedure
TFL	Tables, Figures & Listings

13.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
COPD Assessment Test (CAT)
ELLIPTA
HARP

Trademarks not owned by the GlaxoSmithKline Group of Companies
E-RS: COPD
EXACT-PRO
NONMEM
Propeller Sensor
SAS
SGRQ

13.11. Appendix 11: List of Data Displays

13.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays for SAC:

Section	Tables	Figures
Study Population	1.1 to 1.31	1.3
Efficacy	2.1 to 2.107	2.1 to 2.20
Safety	3.1 to 3.33	3.1 to 3.4
Pharmacokinetic	4.1 to 4.2	Not applicable
Section	**Listings**	
ICH Listings	1 to 27	
Other Listings	28 to 30	

13.11.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 12: Example Mock Shells for Data Displays.

13.11.3. Deliverables

Delivery	Description
IA	Interim Analysis (except the End of treatment Phase Interim Analysis)
EOT	End of Treatment Phase Interim Analysis
SAC	Statistical Analysis Complete

13.11.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	MITT	ES8	Summary of Subject Status and Reason for Study Withdrawal		EOT, SAC
1.2.	MITT	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		EOT, SAC
1.3.	APE	ES6	Summary of Screening Status and Reasons for Screen Failure		SAC
1.4.	APE	NS1	Summary of Number of Participants by Country and Site ID	For EOT, use MITT population and summarise country only: Summary of Number of Participants by Country	EOT, SAC
Protocol Deviation					
1.5.	MITT	DV1	Summary of Important Protocol Deviations		SAC
1.6.	MITT	IE1	Summary of Inclusion/Exclusion Criteria Deviations		SAC
Population Analysed					
1.7.	MITT	SP1	Summary of Study Populations		SAC
1.8.	MITT	SP2	Summary of Exclusions from the Per Protocol/Safety Population		SAC
Demographic and Baseline Characteristics					
1.9.	MITT	DM1	Summary of Demographic Characteristics	Use the following ranges for the Age Group row: ≤64; 65-74; ≥75	EOT, SAC
1.10.	APE	DM11	Summary of Age Ranges		SAC
1.11.	MITT	DM5	Summary of Race and Racial Combinations		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.12.	MITT	MH4	Summary of Past Medical Conditions		SAC
1.13.	MITT	MH4	Summary of Current Medical Conditions		SAC
1.14.	MITT	FH1	Summary of Family History of Cardiovascular Risk Factors		SAC
1.15.	MITT	SU1	Summary of Smoking History at Screening		EOT, SAC
1.16.	MITT	SU1	Summary of Smoking Status Over the 12-Week Treatment Period		SAC
1.17.	MITT	SU1	Summary of Smoking Status Over the 12-Week Follow-Up Period		SAC
1.18.	MITT	Example 7	Summary of COPD Duration at Screening		SAC
1.19.	MITT	Example 1	Summary of COPD Exacerbation History at Screening	Use categories 0;1;2;3;≥3. Summarise moderate/severe, moderate; severe Include 7-Day History of COPD Exacerbations	EOT, SAC
1.20.	MITT	Example 1	Summary of COPD Exacerbation History at Screening by Country		SAC
Concomitant Medications					
1.21.	MITT	Example 14	Summary of Baseline COPD Maintenance Therapy	For EOT use categories: Triple, Non-triple	EOT, SAC
1.22.	MITT	Example 14	Summary of Baseline ICS Therapy	For EOT use categories: Yes, No	EOT, SAC
1.23.	MITT	Example 15	Summary of On-Treatment COPD Maintenance (Step-up) Therapy		SAC
1.24.	MITT	CM1	Summary of Concomitant Medications During 12-Week Treatment Period		SAC
1.25.	MITT	Example 16	Summary of Duration of On-Treatment OCS		EOT, SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.26.	MITT	Example 16	Summary of Duration of On-Treatment OCS Excluding Non-COPD medications		EOT, SAC
1.27.	MITT	CM1	Summary of Concomitant Medications During 12-Week Follow-Up Period		SAC
Exposure and Treatment Compliance					
1.28.	MITT	Example 36	Summary of Exposure to Study Treatment		EOT, SAC
1.29.	MITT	Example 2	Summary of Overall Treatment Compliance Measured by the Dose Counter on the ELLIPTA		EOT, SAC
1.30.	MITT	Example 2	Summary of Reported Treatment Compliance from the Daily eDiary		SAC
1.31.	MITT	Example 2	Summary of Overall Treatment Compliance Measured by the Clip-on Propeller Sensor for ELLIPTA		SAC

13.11.5. Study Population Figures

Study Population Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	MITT	Example 4	Plot of COPD Exacerbation History at Screening (Moderate)		EOT
1.2.	MITT	Example 4	Plot of COPD Exacerbation History at Screening (Severe)		EOT
1.3.	MITT	Example 4	Plot of COPD Exacerbation History at Screening (Moderate/Severe)		EOT

13.11.6. Efficacy Tables

13.11.6.1. Efficacy tables for Interim Analysis 1

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in Clinic Visit trough FEV_1					
2.1.	MITT	Example 3	Summary of FEV_1 (L)	Include pre- and post-bronchodilator	IA1
2.2.	MITT	Example 3	Summary of FEV_1 (L) by Index Exacerbation Severity	Include pre- and post-bronchodilator Include additional row for hospital discharge visit for Severe group	IA1
2.3.	MITT	Example 3	Summary of Change from Baseline in FEV_1 (L)	Include pre- and post-bronchodilator	IA1
2.4.	MITT	Example 3	Summary of Change from Baseline in FEV_1 (L) by Index Exacerbation Severity	Include pre- and post-bronchodilator. Include additional row for hospital discharge visit for Severe group	IA1
2.5.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 at Day 14 Measured Post-bronchodilator (Dose Response Model)		IA1
2.6.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 at Day 28 Measured Post-bronchodilator (Dose Response Model)		IA1
2.7.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity (Dose Response Model)		IA1
2.8.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity (Dose Response Model)		IA1
2.9.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) Measured Post-bronchodilator (Repeated Measures Model)		IA1

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.10.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) Measured Pre-bronchodilator (Repeated Measures Model)		IA1
2.11.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) Measured Post-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		IA1
2.12.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) Measured Pre-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		IA1
Rate of Exacerbations					
2.13.	MITT	Example 5	Summary of On-treatment Exacerbations		IA1
2.14.	MITT	Example 5	Summary of On-treatment Exacerbations by Index Exacerbation Severity		IA1
EXAcerbations of Chronic Pulmonary Disease Tool - Patient Reported Outcome (EXACT)					
2.15.	MITT	Example 9	Summary of Proportion of Participants Achieving the EXACT-definition of Recovery by Visit	Exclude statistical analysis information (summary only)	IA1
2.16.	MITT	Example 9	Summary of Proportion of Participants Achieving the EXACT-definition of Recovery by Index Exacerbation Severity	Exclude statistical analysis information (summary only)	IA1
Other Spirometry Measures					
2.17.	MITT	Example 3	Summary of Spirometry Measurements		IA1
2.18.	MITT	Example 3	Summary of Change from Baseline in Spirometry Measurements		IA1

13.11.6.2. Efficacy tables for Interim Analysis 2

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in Clinic Visit trough FEV_1					
2.1.	MITT	Example 3	Summary of FEV_1 (L)	Include pre- and post-bronchodilator	IA2
2.2.	MITT	Example 3	Summary of FEV_1 (L) by Index Exacerbation Severity	Include pre- and post-bronchodilator Include additional row for hospital discharge visit for Severe group	IA2
2.3.	MITT	Example 3	Summary of Change from Baseline in FEV_1 (L)	Include pre- and post-bronchodilator	IA2
2.4.	MITT	Example 3	Summary of Change from Baseline in FEV_1 (L) by Index Exacerbation Severity	Include pre- and post-bronchodilator. Include additional row for hospital discharge visit for Severe group	IA2
2.5.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 14 Measured Post-bronchodilator (Dose Response Model)		IA2
2.6.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 28 Measured Post-bronchodilator (Dose Response Model)		IA2
2.7.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 56 Measured Post-bronchodilator (Dose Response Model)		IA2
2.8.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 84 Measured Post-bronchodilator (Dose Response Model)		IA2
2.9.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate (Dose Response Model)		IA2
2.10.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity: Severe (Dose Response Model)		IA2

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.11.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate (Dose Response Model)		IA2
2.12.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity: Severe (Dose Response Model)		IA2
2.13.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 56 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate (Dose Response Model)		IA2
2.14.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 56 Measured Post-bronchodilator by Index Exacerbation Severity: Severe (Dose Response Model)		IA2
2.15.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 84 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate (Dose Response Model)		IA2
2.16.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 84 Measured Post-bronchodilator by Index Exacerbation Severity: Severe (Dose Response Model)		IA2
2.17.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) Measured Post-bronchodilator (Repeated Measures Model)		IA2
2.18.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) Measured Pre-bronchodilator (Repeated Measures Model)		IA2
2.19.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) Measured Post-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		IA2

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.20.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) Measured Pre-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		IA2
2.21.	MITT	Example 32	Summary of Efficiency Ratio for Possible Adaptions to Randomization Ratio		IA2
Rate of Exacerbations					
2.22.	MITT	Example 5	Summary of On-treatment (Moderate/Severe) Subsequent Exacerbations		IA2
2.23.	MITT	Example 5	Summary of On-treatment (Moderate/Severe) Subsequent Exacerbations by Index Exacerbation Severity		IA2
2.24.	MITT	Example 6	Statistical Analysis of On-treatment (Moderate/Severe) Subsequent Exacerbations		IA2
2.25.	MITT	Example 6	Subgroup Analysis of On-treatment (Moderate/Severe) Subsequent Exacerbations by Index Exacerbation Severity		IA2
EXAcerbations of Chronic Pulmonary Disease Tool - Patient Reported Outcome (EXACT)					
2.26.	MITT	Example 9	Statistical Analysis of Proportion of Participants Achieving the EXACT-definition of Recovery by Visit		IA2
2.27.	MITT	Example 9	Subgroup Analysis of Proportion of Participants Achieving the EXACT-definition of Recovery by Index Exacerbation Severity		IA2
COPD Assessment Test (CAT)					
2.28.)	MITT	Example 3	Summary of Change from Baseline in CAT Total Score		IA2
2.29.	MITT	Example 9	Statistical Analysis of Proportion of Responders Using the CAT Total Score by Visit		IA2
2.30.	MITT	Example 11	Statistical Analysis of Change from Baseline in CAT Total Score (Repeated Measures Model)		IA2

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
St. George's Respiratory Questionnaire (SGRQ)					
2.31.	MITT	Example 3	Summary of Change from Baseline in SGRQ Total Score		IA2
2.32.	MITT	Example 9	Statistical Analysis of Proportion of Responders Using the SGRQ Total Score by Visit		IA2
2.33.	MITT	Example 11	Statistical Analysis of Change from Baseline in SGRQ Total Score (Repeated Measures Model)		IA2
Rescue Medication Use					
2.34.	MITT	RM1	Summary of Mean Number of Occasions of Rescue Medication Use Per Day		IA2
2.35.	MITT	RM1	Summary of Percentage of Rescue-Free Days		IA2
Other Spirometry Measures					
2.36.	MITT	Example 3	Summary of Spirometry Measurements		IA2
2.37.	MITT	Example 3	Summary of Change from Baseline in Spirometry Measurements		IA2

13.11.6.3. Efficacy tables for End of Treatment Interim Analysis and SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in Clinic Visit trough FEV_1					
2.1.	MITT	Example 3	Summary of FEV_1 (L)	Include pre- and post-bronchodilator	EOT, SAC
2.2.	MITT	Example 3	Summary of FEV_1 (L) by Index Exacerbation Severity	Include pre- and post-bronchodilator Include additional row for hospital discharge visit for Severe group	EOT, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.3.	MITT	Example 3	Summary of Change from Baseline in FEV_1 (L)	Include pre- and post-bronchodilator	EOT, SAC
2.4.	MITT	Example 3	Summary of Change from Baseline in FEV_1 (L) by Index Exacerbation Severity	Include pre- and post-bronchodilator. Include additional row for hospital discharge visit for Severe group	EOT, SAC
2.5.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 14 Measured Post-bronchodilator (Dose Response Model)		SAC
2.6.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 28 Measured Post-bronchodilator (Dose Response Model)		SAC
2.7.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 56 Measured Post-bronchodilator (Dose Response Model)		SAC
2.8.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 84 Measured Post-bronchodilator (Dose Response Model)		SAC
2.9.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate (Dose Response Model)		SAC
2.10.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity: Severe (Dose Response Model)		SAC
2.11.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate (Dose Response Model)		SAC
2.12.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity: Severe (Dose Response Model)		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.13.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 56 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate (Dose Response Model)		SAC
2.14.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 56 Measured Post-bronchodilator by Index Exacerbation Severity: Severe (Dose Response Model)		SAC
2.15.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 84 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate (Dose Response Model)		SAC
2.16.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 84 Measured Post-bronchodilator by Index Exacerbation Severity: Severe (Dose Response Model)		SAC
2.17.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) Measured Post-bronchodilator (Repeated Measures Model)		EOT, SAC
2.18.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) Measured Post-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		EOT, SAC
Change from Hospital Discharge in Clinic Visit trough FEV_1					
2.19.	MITT	Example 3	Summary of Change from Hospital Discharge in FEV_1 (L)	Include pre- and post-bronchodilator	SAC
2.20.	MITT	Example 11	Statistical Analysis of Change from Hospital Discharge in FEV_1 (L) Measured Post-bronchodilator (Repeated Measures Model)		SAC
2.21.	MITT	Example 11	Statistical Analysis of Change from Hospital Discharge in FEV_1 (L) Measured Pre-bronchodilator (Repeated Measures Model)		SAC
Change from Day 84 in Clinic Visit trough FEV_1					
2.22.	MITT	Example 3	Summary of Change from Day 84 in FEV_1 (L)	Include pre- and post-bronchodilator	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.23.	MITT	Example 11	Statistical Analysis of Change from Day 84 in FEV_1 (L) Measured Post-bronchodilator (Repeated Measures Model)		SAC
2.24.	MITT	Example 11	Statistical Analysis of Change from Day 84 in FEV_1 (L) Measured Pre-bronchodilator (Repeated Measures Model)		SAC
2.25.	MITT	Example 11	Subgroup Analysis of Change from Day 84 in FEV_1 (L) Measured Post-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		SAC
2.26.	MITT	Example 11	Subgroup Analysis of Change from Day 84 in FEV_1 (L) Measured Pre-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		SAC
Rate of Exacerbations					
2.27.	MITT	Example 5	Summary of On-treatment (Moderate/Severe) Subsequent Exacerbations		EOT, SAC
2.28.	MITT	Example 5	Summary of On-treatment (Mild/Moderate/Severe) Subsequent Exacerbations		SAC
2.29.	MITT	Example 5	Summary of On-treatment (Moderate/Severe) Subsequent Exacerbations by Index Exacerbation Severity		EOT, SAC
2.30.	MITT	Example 6	Statistical Analysis of On-treatment (Moderate/Severe) Subsequent Exacerbations		EOT, SAC
2.31.	MITT	Example 6	Statistical Analysis of On-treatment (Mild/Moderate/Severe) Subsequent Exacerbations		SAC
2.32.	MITT	Example 6	Subgroup Analysis of On-treatment (Moderate/Severe) Subsequent Exacerbations by Index Exacerbation Severity		EOT, SAC
2.33.	MITT	Example 5	Summary of On-treatment Subsequent Exacerbations by Index Exacerbation Type		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.34.	MITT	Example 5	Summary of On-treatment Subsequent Exacerbations by Number of Exacerbations in Previous 12 Months		SAC
2.35.	MITT	Example 5	Summary of On-treatment (Moderate/Severe) Subsequent Exacerbations by Baseline Maintenance Therapy		EOT, SAC
2.36.	MITT	Example 6	Subgroup Analysis of On-treatment (Moderate/Severe) Subsequent Exacerbations by Baseline Maintenance Therapy		EOT, SAC
2.37.	MITT	Example 5	Summary of On-treatment (Moderate/Severe) Subsequent Exacerbations by Baseline ICS Therapy		EOT, SAC
2.38.	MITT	Example 6	Subgroup Analysis of On-treatment (Moderate/Severe) Subsequent Exacerbations by Baseline ICS Therapy		EOT, SAC
2.39.	MITT	Example 6	Subgroup Analysis of On-treatment (Moderate/Severe) Subsequent Exacerbations by EXACT Recovery Status at Day 14		EOT, SAC
2.40.	MITT	Example 12	Summary of Number of On-treatment Subsequent (Moderate/Severe) Exacerbations Treated with Steroids/Antibiotics		EOT, SAC
2.41.	MITT	Example 6	Subgroup Analysis of On-treatment (Moderate/Severe) Subsequent Exacerbations by Baseline Blood Biomarker Status		EOT, SAC
2.42.	MITT	Example 5	Summary of On-or Off-treatment (Moderate/Severe) Subsequent Exacerbations During the 12-Week Treatment Period		SAC
2.43.	MITT	Example 5	Summary of On-or Off-treatment (Mild/Moderate/Severe) Subsequent Exacerbations During the 12-Week Treatment Period		SAC
2.44.	MITT	Example 5	Summary of On-or Off-treatment (Moderate/Severe) Subsequent Exacerbations During the 12-Week Treatment Period by Index Exacerbation Severity		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.45.	MITT	Example 6	Statistical Analysis of On- or Off-treatment (Moderate/Severe) Subsequent Exacerbations During the 12-Week Treatment Period		EOT, SAC
2.46.	MITT	Example 6	Statistical Analysis of On- or Off-treatment (Mild/Moderate/Severe) Subsequent Exacerbations During the 12-Week Treatment Period		SAC
2.47.	MITT	Example 6	Subgroup Analysis of On- or Off-treatment (Moderate/Severe) Subsequent Exacerbations During the 12-Week Treatment Period by Index Exacerbation Severity		SAC
2.48.	MITT	Example 5	Summary of Off-treatment (Moderate/Severe) Subsequent Exacerbations		EOT, SAC
2.49.	MITT	Example 5	Summary of Off-treatment (Moderate/Severe) Subsequent Exacerbations by Index Exacerbation Severity		SAC
2.50.	MITT	Example 6	Statistical Analysis of Off-treatment (Moderate/Severe) Subsequent Exacerbations		EOT, SAC
2.51.	MITT	Example 6	Subgroup Analysis of Off-treatment (Moderate/Severe) Subsequent Exacerbations by Index Exacerbation Severity		SAC
2.52.	MITT	Example 5	Summary of On- and Off-treatment (Moderate/Severe) Subsequent Exacerbations During the 24-Week Study Period		SAC
2.53.	MITT	Example 5	Summary of On- and Off-treatment (Moderate/Severe) Subsequent Exacerbations During the 24-Week Study Period by Index Exacerbation Severity		SAC
2.54.	MITT	Example 6	Statistical Analysis of On- and Off-treatment (Moderate/Severe) Subsequent Exacerbations During the 24-Week Study Period		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.55.	MITT	Example 6	Subgroup Analysis of On- and Off-treatment (Moderate/Severe) Subsequent Exacerbations During the 24-Week Study Period by Index Exacerbation Severity		SAC
Time to Next Exacerbation					
2.56.	MITT	Example 8	Statistical Analysis of Time to next On-treatment Exacerbation		EOT, SAC
2.57.	MITT	Example 8	Subgroup Analysis of Time to next On-treatment Exacerbation by Index Exacerbation Severity		EOT, SAC
2.58.	MITT	Example 8	Statistical Analysis of Time to next On- or Off-treatment Exacerbation During the 12-Week Treatment Period		SAC
2.59.	MITT	Example 8	Statistical Analysis of Time to next On- or Off-treatment Exacerbation During the 12-Week Treatment Period by Index Exacerbation Severity		SAC
2.60.	MITT	Example 8	Statistical Analysis of Time to Next Exacerbation Following Cessation of Study Treatment		SAC
2.61.	MITT	Example 8	Statistical Analysis of Time to Next Exacerbation Following Cessation of Study Treatment by Index Exacerbation Severity		SAC
EXAcerbations of Chronic Pulmonary Disease Tool - Patient Reported Outcome (EXACT)					
2.62.	MITT	Example 9	Statistical Analysis of Proportion of Participants Achieving the EXACT-definition of Recovery by Visit		EOT, SAC
2.63.	MITT	Example 9	Subgroup Analysis of Proportion of Participants Achieving the EXACT-definition of Recovery by Index Exacerbation Severity		EOT, SAC
2.64.	MITT	Example 8	Summary and Statistical Analysis of Time to EXACT-defined Recovery		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.65.	MITT	Example 10	Summary of Severity of Subsequent HCRU-defined Exacerbation During 12-Week Treatment Period	Also split by moderate and severe	SAC
2.66.	MITT	Example 10	Summary of Severity of Subsequent HCRU-Defined Exacerbation During 12-Week Follow-up Period	Also split by moderate and severe	SAC
2.67.	MITT	Example 35	Summary of Missing On-treatment EXACT-PRO data		EOT, SAC
2.68.	MITT	Example 35	Summary of Missing Off-treatment EXACT-PRO data		SAC
COPD Assessment Test (CAT)					
2.69.	MITT	Example 3	Summary of Change from Baseline in CAT Total Score		EOT, SAC
2.70.	MITT	Example 3	Summary of Change from Baseline in CAT Total Score by Index Exacerbation Severity		SAC
2.71.	MITT	Example 9	Statistical Analysis of Proportion of Responders Using the CAT Total Score by Visit		EOT, SAC
2.72.	MITT	Example 9	Subgroup Analysis of Proportion of Responders Using the CAT Total Score by Visit by Index Exacerbation Severity		SAC
2.73.	MITT	Example 11	Statistical Analysis of Change from Baseline in CAT Total Score (Repeated Measures Model)		EOT, SAC
2.74.	MITT	Example 11	Subgroup Analysis of Change from Baseline in CAT Total Score (Repeated Measures Model) by Index Exacerbation Severity		SAC
2.75.	MITT	Example 3	Summary of Change from End of Treatment in CAT Total Score		SAC
2.76.	MITT	Example 3	Summary of Change from End of Treatment in CAT Total Score by Index Exacerbation Severity		SAC
2.77.	MITT	Example 11	Statistical Analysis of Change from End of Treatment in CAT Total Score (Repeated Measures Model)		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.78.	MITT	Example 11	Subgroup Analysis of Change from End of Treatment in CAT Total Score (Repeated Measures Model) by Index Exacerbation Severity		SAC
St. George's Respiratory Questionnaire (SGRQ)					
2.79.	MITT	Example 3	Summary of Change from Baseline in SGRQ Total Score		EOT, SAC
2.80.	MITT	Example 3	Summary of Change from Baseline in SGRQ Total Score by Index Exacerbation Severity		SAC
2.81.	MITT	Example 9	Statistical Analysis of Proportion of Responders on the SGRQ Total Score by Visit		EOT, SAC
2.82.	MITT	Example 9	Subgroup Analysis of Proportion of Responders on the SGRQ Total Score by Index Exacerbation Severity		SAC
2.83.	MITT	Example 11	Statistical Analysis of Change from Baseline SGRQ Total Score (Repeated Measures Model)		EOT, SAC
2.84.	MITT	Example 11	Subgroup Analysis of Change from Baseline SGRQ Total Score (Repeated Measures Model) by Index Exacerbation Severity		SAC
2.85.	MITT	Example 3	Summary of Change from End of Treatment in SGRQ Total Score		SAC
2.86.	MITT	Example 3	Summary of Change from End of Treatment in SGRQ Total Score by Index Exacerbation Severity		SAC
2.87.	MITT	Example 11	Statistical Analysis of Change from End of Treatment in SGRQ Total Score (Repeated Measures Model)		SAC
2.88.	MITT	Example 11	Subgroup Analysis of Change from End of Treatment in SGRQ Total Score (Repeated Measures Model) by Index Exacerbation Severity		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
E-RS: COPD					
2.89.	MITT	Example 3	Summary of Change from Baseline in E-RS: COPD and Subscales		SAC
Rescue Medication Use					
2.90.	MITT	RM1	Summary of Mean Number of Occasions of Rescue Medication Use Per Day		EOT, SAC
2.91.	MITT	RM1	Summary of Percentage of Rescue-Free Days		EOT, SAC
2.92.	MITT	RM1	Summary of Mean Number of Actuations of Rescue Medication Use Per Day Via the Clip-on Propeller Sensor for MDI		SAC
2.93.	MITT	RM1	Summary of Percentage of Rescue-Free Days Via the Clip-on Propeller Sensor for MDI		SAC
Healthcare Resource Utilisation					
2.94.	MITT	Example 19	Summary of Exacerbation Related Unscheduled Healthcare Resource Utilisation		SAC
2.95.	MITT	Example 19	Summary of Exacerbation Related Unscheduled Healthcare Resource Utilization by Index Exacerbation Severity		SAC
2.96.	MITT	Example 21	Summary of Exacerbation Related Hospitalizations		SAC
2.97.	MITT	Example 19	Summary of COPD Related Unscheduled Healthcare Resource Utilisation		SAC
2.98.	MITT	Example 19	Summary of COPD Related Unscheduled Healthcare Resource Utilisation by Index Exacerbation Severity		SAC
2.99.	MITT	Example 20	Summary of Non-COPD Related Unscheduled Healthcare Resource Utilisation		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.100.	MITT	Example 20	Summary of Non-COPD Related Unscheduled Healthcare Resource Utilisation by Index Exacerbation Severity		SAC
2.101.	MITT	Example 22	Summary of Re-hospitalization Within 30 days of Index Exacerbation		SAC
2.102.	MITT	Example 24	Summary of Time from Resolution of Index Exacerbation to Next Exacerbation		SAC
2.103.	MITT	Example 23	Summary of Subsequent Exacerbation Treatment		SAC
Other Spirometry Measures					
2.104.	MITT	Example 3	Summary of Spirometry Measurements		EOT, SAC
2.105.	MITT	Example 3	Summary of Change from Baseline in Spirometry Measurements		EOT, SAC
Inflammatory/infective Markers in Blood and Sputum					
2.106.	MITT	Example 3	Summary of Inflammatory Markers in Blood	For EOT only include Screening timepoint	EOT, SAC
2.107.	MITT	Example 3	Summary of Inflammatory Markers in Sputum		SAC

13.11.7. Efficacy Figures

13.11.7.1. Efficacy Figures for Interim Analysis 1

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in Clinic Visit trough FEV_1					
2.1.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 Measured Post-bronchodilator		IA1
2.2.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 Measured Post-bronchodilator		IA1
2.3.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 56 measured post-bronchodilator		IA1
2.4.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		IA1
2.5.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		IA1
2.6.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		IA1
2.7.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		IA1

13.11.7.2. Efficacy Figures for Interim Analysis 2

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in Clinic Visit trough FEV_1					
2.1.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 Measured Post-bronchodilator		IA2
2.2.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 Measured Post-bronchodilator		IA2
2.3.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 56 Measured Post-bronchodilator		IA2
2.4.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 84 Measured Post-bronchodilator		IA2
2.5.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		IA2
2.6.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		IA2
2.7.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		IA2
2.8.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		IA2
2.9.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 56 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		IA2

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.10.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 56 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		IA2
2.11.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 84 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		IA2
2.12.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 84 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		IA2
2.13.	MITT	Example 31	Plot of Repeated Measures Model of Change from Baseline in FEV_1 Measured Post-bronchodilator		IA2
2.14.	MITT	Example 31	Plot of Repeated Measures Model of Change from Baseline in FEV_1 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		IA2
2.15.	MITT	Example 31	Plot of Repeated Measures Model of Change from Baseline in FEV_1 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		IA2
Time to Next Exacerbation					
2.16.	MITT	Example 30	Kaplan-Meier Plot of Time to Next On-treatment (Moderate/Severe) Exacerbation		IA2
2.17.	MITT	Example 30	Kaplan-Meier Plot of Time to Next On-treatment (Mild/Moderate/Severe) Exacerbation		IA2

13.11.7.3. Efficacy Figures for End of Treatment Interim Analysis and SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in Clinic Visit trough FEV_1					
2.1.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 Measured Post-bronchodilator		SAC
2.2.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 Measured Post-bronchodilator		SAC
2.3.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 56 Measured Post-bronchodilator		SAC
2.4.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 84 Measured Post-bronchodilator		SAC
2.5.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		SAC
2.6.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		SAC
2.7.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		SAC
2.8.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		SAC
2.9.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 56 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.10.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 56 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		SAC
2.11.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 84 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		SAC
2.12.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 84 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		SAC
2.13.	MITT	Example 31	Plot of Adjusted Posterior Medians (95% HPD CrI) of Change from Baseline in FEV_1 Measured Post-bronchodilator		EOT, SAC
2.14.	MITT	Example 31	Plot of Adjusted Posterior Medians (95% HPD CrI) of Change from Baseline in FEV_1 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		EOT, SAC
2.15.	MITT	Example 31	Plot of Adjusted Posterior Medians (95% HPD CrI) of Change from Baseline in FEV_1 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		EOT, SAC
Time to Next Exacerbation					
2.16.	MITT	Example 30	Kaplan-Meier Plot of Time to Next On-treatment (Moderate/Severe) Exacerbation		EOT, SAC
2.17.	MITT	Example 30	Kaplan-Meier Plot of Time to Next On-treatment (Mild/Moderate/Severe) Exacerbation		SAC
2.18.	MITT	Example 30	Kaplan-Meier Plot of Time to Next On-or Off-treatment (Moderate/Severe) Exacerbation During the 12-Week Treatment Period		SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.19.	MITT	Example 30	Kaplan-Meier Plot of Time to Next On-or Off-treatment (Mild/Moderate/Severe) Exacerbation During the 12-Week Treatment Period		SAC
2.20.	MITT	Example 30	Kaplan-Meier Plot of Time to Next (Moderate/Severe) Exacerbation Following Cessation of Study Treatment		SAC

13.11.8. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	Safety	AE1	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term		EOT, SAC
3.2.	Safety	AE1	Summary of Post-Treatment Adverse Events by System Organ Class and Preferred Term		SAC
3.3.	Safety	AE3	Summary of Common (>=5%) Treatment Emergent Adverse Events by Overall Frequency		EOT, SAC
3.4.	Safety	AE1	Summary of Drug-Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term		EOT, SAC
3.5.	Safety	AE15	Summary of Common (>=5%) Non-serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)		SAC
3.6.	Safety	AE5A	Summary of All Adverse Events by Maximum Intensity by System Organ Class and Preferred Term		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.7.	Safety	AE1	Summary of Treatment Emergent Adverse Events for Participants with Absolute Neutrophil Count Below Lower Value of PCI		SAC
Serious and Other Significant Adverse Events					
3.8.	Safety	AE16	Summary of Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)		EOT, SAC
3.9.	Safety	AE16	Summary of Fatal Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	Only with subcategory: Number of Fatal SAEs	EOT, SAC
3.10.	Safety	AE1	Summary of Serious Treatment Emergent Drug-related Adverse Events by System Organ Class and Preferred Term		SAC
3.11.	Safety	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term		EOT, SAC
3.12.	Safety	AE1	Summary of Post-treatment Serious Adverse Events by System Organ Class and Preferred Term		SAC
3.13.	Safety	AE1	Summary of Treatment Emergent Adverse Events of Special Interest by Lower Level Term		EOT, SAC
3.14.	Safety	AE1	Summary of Treatment Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term		EOT, SAC
3.15.	Safety	Example 17	Summary of Post-Inhalation Cough by Visit		EOT, SAC
3.16.	Safety	Example 28	Summary of Post-Inhalation Cough by Visit and Cough Type		EOT, SAC
3.17.	Safety	Example 33	Summary of Post-Inhalation (PI) Cough at Any Visit		EOT, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Chemistry					
3.18.	Safety	LB1	Summary of Chemistry Data	For EOT summarise Alkaline Phosphates at Screening only	EOT, SAC
3.19.	Safety	LB17	Summary of Worst Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline		EOT, SAC
Laboratory: Hematology					
3.20.	Safety	LB1	Summary of Hematology Data	For EOT summarise Eosinophils, Monocytes, Lymphocytes at Screening only	EOT, SAC
3.21.	Safety	LB1	Summary of Change from Baseline in Hematology	Only for WBC, lymphocytes, neutrophils	SAC
3.22.	Safety	LB17	Summary of Worst Case Hematology Results by PCI Criteria Post-Baseline Relative to Baseline		EOT, SAC
Laboratory: Hepatobiliary (Liver)					
3.23.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting		SAC
3.24.	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities		SAC
ECG					
3.25.	Safety	EG1	Summary of ECG Findings	Include Worst Case Post-Baseline row	EOT, SAC
3.26.	Safety	EG2	Summary of ECG Values by Visit	For the following parameters: QTcF, QTcB, PR, Heart rate	EOT, SAC
3.27.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit	For the following parameters: QTcF, QTcB, PR, Heart rate	SAC
3.28.	Safety	Example 27	Summary of QTcF Categories		SAC
3.29.	Safety	Example 27	Summary of QTcB Categories		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.30.	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category		SAC
3.31.	Safety	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category		SAC
3.32.	Safety	Example 25	Summary of ECG Abnormalities for Participants with Any Abnormal ECG Interpretation		EOT, SAC
Vital Signs					
3.33.	Safety	VS1	Summary of Vital Signs		SAC
3.34.	Safety	VS7	Summary of Worst Case Vital Signs Results by PCI Criteria Post-Baseline Relative to Baseline		EOT, SAC

13.11.9. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory					
3.1.	Safety	LB7	LFT Shift from Baseline to Maximum		EOT, SAC
3.2.	Safety	Example 34	Plot of Laboratory Data at Screening		EOT, SAC
3.3.	Safety	Example 13	Median (range) Absolute Neutrophil Count by Time and Treatment		SAC
ECG					
3.4.	Safety	EG8	Distribution of QTcF Change by Time and Treatment		SAC

13.11.10. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic Concentration-Time Data					
4.1.	PK	PK01	Summary of Plasma GSK2269557 Pharmacokinetic Concentration-Time Data		SAC
4.2.	PK	PK05	Summary of Log-Transformed Plasma GSK2269557 Pharmacokinetic Concentration-Time Data		SAC

13.11.11. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	APE	ES7	Listing of Reasons for Screen Failure		SAC
2.	MITT	ES2	Listing of Reasons for Study Withdrawal		SAC
3.	MITT	SD2	Listing of Reasons for Study Treatment Discontinuation		SAC
4.	MITT	BL1	Listing of Participants for Whom the Treatment Blind was Broken		SAC
5.	MITT	TA1	Listing of Planned and Actual Treatments		SAC
Protocol Deviations					
6.	MITT	DV2	Listing of Important Protocol Deviations		SAC
7.	MITT	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations		SAC
Populations Analysed					
8.	MITT	SP3	Listing of Participants Excluded from Per Protocol Population	For participants excluded from MITT population (i.e. participants in the MITT but not in PP)	SAC
Demographic and Baseline Characteristics					
9.	MITT	DM2	Listing of Demographic Characteristics		SAC
10.	MITT	DM9	Listing of Race		SAC
Prior and Concomitant Medications					
11.	MITT	CP_CM3	Listing of Concomitant Medications		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure and Treatment Compliance					
12.	Safety	EX3	Listing of Exposure Data		SAC
Adverse Events					
13.	Safety	AE8	Listing of All Adverse Events		SAC
14.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		SAC
15.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		SAC
Serious and Other Significant Adverse Events					
16.	Safety	AE8	Listing of Fatal Serious Adverse Events		SAC
17.	Safety	AE8	Listing of Non-Fatal Serious Adverse Events		SAC
18.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event		SAC
19.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment		SAC
Hepatobiliary (Liver)					
20.	Safety	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events		SAC
21.	Safety	SU2	Listing of Substance Use for Participants with Liver Stopping Events		SAC
All Laboratory					
22.	Safety	LB5	Listing of All Chemistry Data for Participants with Any Value of Potential Clinical Importance		SAC
23.	Safety	LB14	Listing of Chemistry Data with Character Results		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
24.	Safety	LB5	Listing of All Hematology Data for Participants with Any Value of Potential Clinical Importance		SAC
25.	Safety	LB14	Listing of all Hematology Data with Character Results		SAC
ECG					
26.	Safety	EG3	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance		SAC
27.	Safety	EG5	Listing of All ECG Findings for Participants with an Abnormal Finding		SAC

13.11.12. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
28.	MITT	Example 29	Listing of Subjects who Received Incorrect Medication		SAC
29.	PK	PK07	Listing of Plasma Pharmacokinetic Concentration-Time Data		SAC
30.	Safety	EG5	Listing of All ECG Findings for Subjects with an Abnormal Finding		SAC

13.12. Appendix 12: Example Mock Shells for Data Displays

13.12.1. Example shell 1

Example Shell X
Protocol: XYZ100001 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of COPD Exacerbation History at Screening

	Treatment A (N=100)	Treatment B (N=100)	Total (N=200)
Moderate COPD exacerbations			
n	X	X	X
0	xx (x%)	xx (x%)	xx (x%)
1	xx (x%)	xx (x%)	xx (x%)
>=2	xx (x%)	xx (x%)	xx (x%)
Severe COPD exacerbations			
n	X	X	X
0	xx (x%)	xx (x%)	xx (x%)
1	xx (x%)	xx (x%)	xx (x%)
>=2	xx (x%)	xx (x%)	xx (x%)
Total number of moderate/severe COPD exacerbations			
n	911	899	1810
0	313 (34%)	317 (35%)	630 (35%)
1	252 (28%)	253 (28%)	505 (28%)
>=2	346 (38%)	329 (37%)	675 (37%)

Note: Number of COPD exacerbations reported in the 12 months prior to the Screening Visit.
PPD

13.12.2. Example Shell 2

Protocol: XYZ100001 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Treatment Compliance

	Treatment A (N=100)	Treatment B (N=100)	Total (N=200)
Overall compliance (%)			
n	xx	xx	xx
Mean	xx	xx	xx
SD	xx	xx	xx
Median	xx	xx	xx
Min.	xx	xx	xx
Max.	xx	xx	xx
Compliance interval			
< 80%	xx (x%)	xx (x%)	xx (x%)
80% - < 100%	xx (x%)	xx (x%)	xx (x%)
100% - < 120%	xx (x%)	xx (x%)	xx (x%)
>=120%	xx (x%)	xx (x%)	xx (x%)

PPD

13.12.3. Example shell 3

Example Shell X
Protocol: ABC123456 Page 1 of n
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Change from Baseline in FEV1 (L)
Measured post-bronchodilator

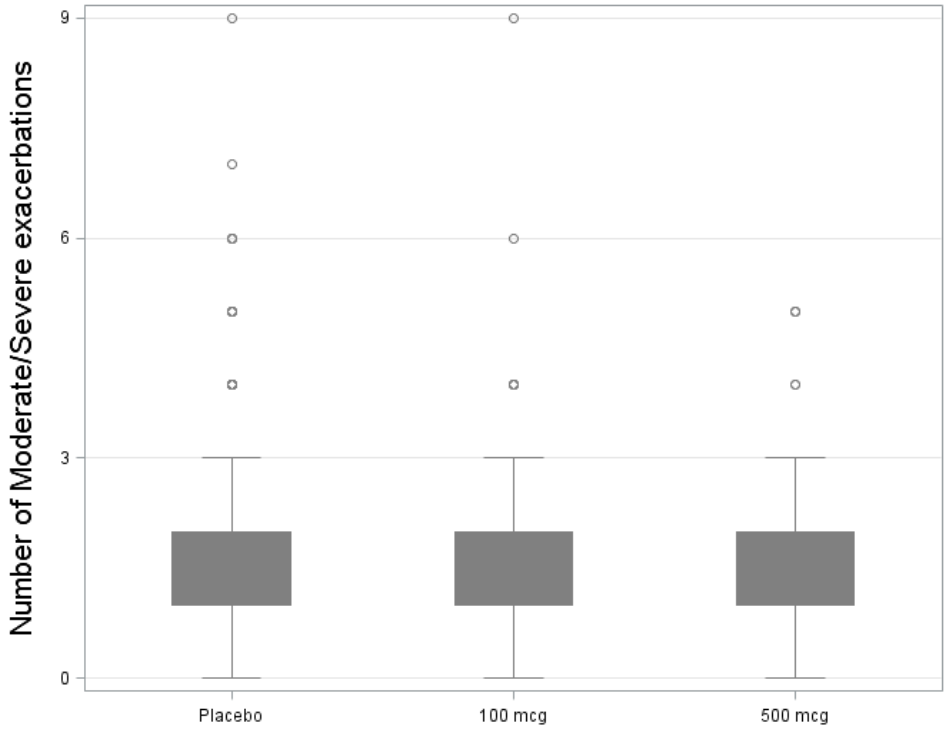
Visit	N	Treatment Arm	n	Mean	SD	Median	Min.	Max.
Day 1	200	Placebo	200	0.111	0.1111	0.100	-0.11	1.11
	200	GSK2269557 12.5 mcg	190	0.222	0.2222	0.200	-0.22	1.22
	200	GSK2269557 50 mcg	195	0.333	0.3333	0.300	-0.33	1.33
	200	GSK2269557 100 mcg	195	0.444	0.4444	0.400	-0.44	1.44
	200	GSK2269557 250 mcg	190	0.555	0.5555	0.500	-0.55	1.55
	200	GSK2269557 500 mcg	190	0.555	0.5555	0.500	-0.55	1.55
	200	GSK2269557 750 mcg	190	0.555	0.5555	0.500	-0.55	1.55
Day 14	200	Placebo	200	0.111	0.1111	0.100	-0.11	1.11
	200	GSK2269557 12.5 mcg	190	0.222	0.2222	0.200	-0.22	1.22
	200	GSK2269557 50 mcg	195	0.333	0.3333	0.300	-0.33	1.33
	200	GSK2269557 250 mcg	195	0.444	0.4444	0.400	-0.44	1.44
	200	GSK2269557 500 mcg	190	0.555	0.5555	0.500	-0.55	1.55
	200	GSK2269557 750 mcg	190	0.555	0.5555	0.500	-0.55	1.55

PPD

13.12.4. Example Shell 4

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Figure X
Plot of Number of Exacerbations in Previous 12 Months
(Moderate/Severe)



PPD

Protocol: ABC123456
Population: Intent-to-Treat/Safety/Other study specific

Table X
Statistical Analysis of Change from Baseline in FEV1 (ml)
Measured post-bronchodilator

Visit	Treatment Comparison	Adjusted Median Difference	Std Dev	95% Credible Interval	Prob Treat. Diff >0 (%)
Day 14	GSK2269557 12.5 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
	GSK2269557 50 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
	GSK2269557 100 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
	GSK2269557 250 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
	GSK2269557 500 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
	GSK2269557 750 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
Day 28	GSK2269557 12.5 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
	GSK2269557 50 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
	GSK2269557 100 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx

13.12.5. Example Shell 5

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of On-treatment Exacerbations

	Treatment A (N=100)	Treatment B (N=100)
Number of moderate/severe exacerbations per subject		
0	50 (50%)	98 (98%)
1	6 (6%)	15 (15%)
2	6 (6%)	9 (9%)
3	1 (1%)	1 (1%)
4	0	2 (2%)
5	0	1 (1%)
>5	0	1 (1%)
Subjects with >=1 moderate/severe exacerbation	13 (13%)	28 (28%)
Total Number of moderate/severe exacerbations	21	49
Number of moderate exacerbations per Subject		
0	50 (50%)	98 (98%)
1	6 (6%)	15 (15%)
2	6 (6%)	9 (9%)
3	1 (1%)	1 (1%)

PPD

13.12.6. Example Shell 6

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Statistical Analysis of On-treatment Exacerbations

	Treatment A (N=100)	Treatment B (N=100)
Moderate/severe exacerbations		
Annual exacerbation rate (95% CrI)	0.35 (x.xx, x.xx)	0.30 (x.xx, x.xx)
Active vs. Placebo		
Ratio		0.85 (x.xx, x.xx)
Pr Diff <1		x.xx
Percent reduction in rate (95% CrI)		15% (x.xx, x.xx)
Predictive probability (%) [1]	xx%	
[*only when required*]		
Moderate exacerbations		
Annual exacerbation rate (95% CrI)	0.35 (x.xx, x.xx)	0.30 (x.xx, x.xx)
Active vs. Placebo		
Ratio		0.85 (x.xx, x.xx)
Pr Diff <1		x.xx
Percent reduction in rate (95% CrI)		15% (x.xx, x.xx)

[1] Predictive posterior probability of success at end of study, where success is Pr(Reduction>0%)>80%

PPD

13.12.7. Example Shell 7

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of COPD Duration at Screening

	Treatment A (N=100)		Treatment B (N=100)		Total (N=200)	
Duration of COPD:						
n	100		99		199	
<1 year	XX	(x%)	XX	(x%)	XX	(x%)
>=1 to <5 years	XX	(x%)	XX	(x%)	XX	(x%)
>=5 to <10 years	XX	(x%)	XX	(x%)	XX	(x%)
>=10 to <15 years	XX	(x%)	XX	(x%)	XX	(x%)
>=15 to <20 years	XX	(x%)	XX	(x%)	XX	(x%)
>=20 to <25 years	XX	(x%)	XX	(x%)	XX	(x%)
>=25 years	XX	(x%)	XX	(x%)	XX	(x%)

PPD

13.12.8. Example Shell 8

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary and Analysis of Time to Next On-treatment Moderate/Severe Exacerbation (days)
up to Day 84

	Treatment A (N=100)	Treatment B (N=100)
Number of Subjects with Event	10 (10%)	14 (14%)
Number of Subjects Censored	90 (90%)	86 (86%)
Treatment A vs. Placebo		
Hazard Ratio	X.XX	
95% Credible Interval	(x.xx, x.xx)	

Note: Hazard ratio and 95% Credible Interval are from a Bayesian Cox proportional hazards model

PPD

13.12.9. Example Shell 9

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Statistical Analysis of Proportion of Participants Achieving EXACT-definition of Response

	Treatment A (N=100)	Treatment B (N=100)
Day 14		
n	x.xx	x.xx
Responder	x.xx (x%)	x.xx (x%)
Non-responder	x.xx (x%)	x.xx (x%)
Active vs. Placebo		
Odds Ratio (OR) (95% CrI)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Pr OR >1	x.xx	x.xx
Day 28		
n	x.xx	x.xx
Responder	x.xx (x%)	x.xx (x%)
Non-responder	x.xx (x%)	x.xx (x%)
Active vs. Placebo		
Odds Ratio (95% CrI)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Pr Diff >1	x.xx	x.xx

PPD

13.12.10. Example Shell 10

Protocol: XYZ100001 Page 1 of n
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of severity of subsequent HCRU-defined exacerbation during 12-Week Treatment Period

Treatment	N	n	Mean	SD	Median	Min.	Max.
Placebo	30	30	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Trt A	30	30	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Trt B	30	30	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

PPD

13.12.11. Example Shell 11

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Mixed Model Repeated Measures Analysis of CAT Total Score

	Treatment A (N=100)	Treatment B (N=100)
Day 28		
n	x.xx	x.xx
Adjusted mean score change (SE)	x.xx (x)	x.xx (x)
Active - Placebo		
Difference (SE)	x.xx (x.xx)	x.xx (x.xx)
95% (CrI)	x.xx	x.xx
Pr Diff >0	x.xx	x.xx
Day 56		
n	x.xx	x.xx
Adjusted mean score change (SE)	x.xx (x)	x.xx (x)
Active - Placebo		
Difference (SE)	x.xx (x.xx)	x.xx (x.xx)
95% (CrI)	x.xx	x.xx
Pr Diff >0	x.xx	x.xx

PPD

13.12.12. Example Shell 12

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of the Number of Subsequent (On-treatment) Exacerbations Treated with Steroids/Antibiotics

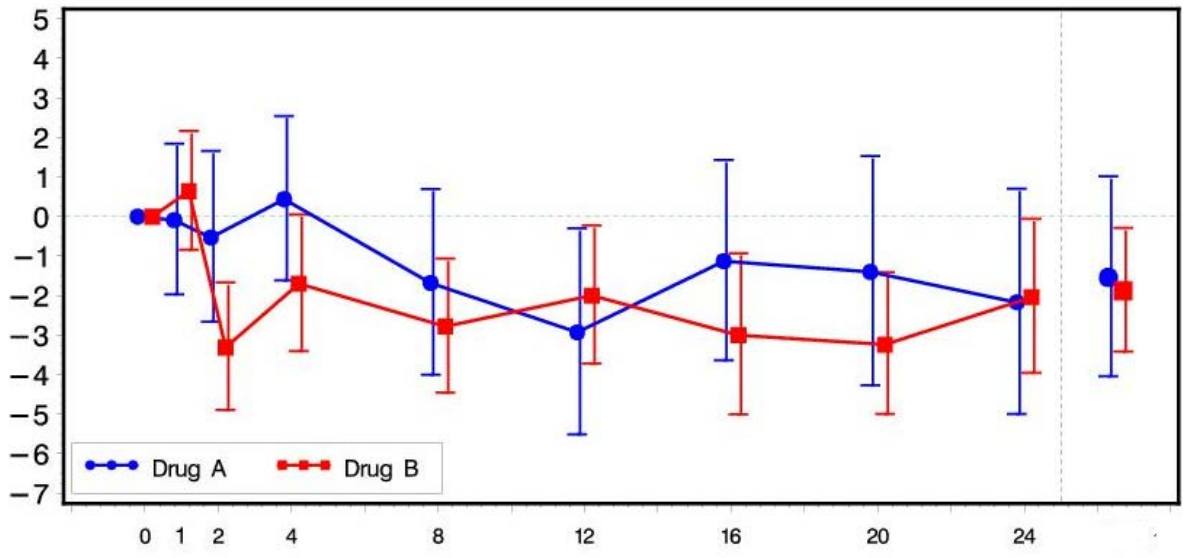
	Treatment A (N=100)	Treatment B (N=100)
Total exacerbations	50	51
Treatment		
Antibiotics	30	40
Steroids	50	40
Both	30	30

PPD

13.12.13. Example shell 13

Protocol: XYZ100001
Population: Intent-to-Treat/Safety/Other study specific

Figure X
Median (range) Absolute Neutrophil Count by Time and Treatment



PPD

13.12.14. Example Shell 14

Protocol: XYZ100001
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Baseline COPD Maintenance Therapy

Therapy category	Treatment A (N=81)	Treatment B (N=79)
Any medication at baseline	70 (86%)	50 (63%)
Monotherapy	X (x%)	X (x%)
LAMA only	x (x%)	x (x%)
Dual therapy	x (x%)	x (x%)
ICS/LABA	x (x%)	x (x%)
Dual bronchodilator	xx (xx%)	xx (xx%)
Triple therapy	X (x%)	X (x%)
LAMA/ICS/LABA	x (x%)	0

PPD

13.12.15. Example Shell 15

Protocol: XYZ100001 Page 1 of n
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of On-Treatment COPD Maintenance (Step-up) Therapy

Therapy category	Treatment A (N=81)	Treatment B (N=79)
Any Step-up Therapy	70 (86%)	50 (63%)

PPD

13.12.16. Example shell 16

Protocol: XYZ100001 Page 1 of n
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of OCS use

	Treatment A (N=81)	Treatment B (N=79)
OCS use for index exacerbation	81 (100%)	79 (100%)
Total number of Days of OCS use		
Mean	Xx	xx
SD	Xx	xx
Median	Xx	xx
Min.	Xx	xx
Max.	Xx	xx
On-treatment OCS use	xx (xx%)	xx (xx%)
Total number of Days of OCS use		
Mean	Xx	xx
SD	Xx	xx
Median	Xx	xx
Min.	Xx	xx
Max.	Xx	xx

PPD

13.12.17. Example Shell 17

Protocol: ABC123456 Page 1 of x
Population: Safety

Table X
Summary of Post-Inhalation Cough by Visit

Visit: VISIT 2 (RANDOMISATION)

	Placebo (N=43)		GSK2269557 50 mcg (N=14)		GSK2269557 100 mcg (N=15)		GSK2269557 250 mcg (N=16)		GSK2269557 500 mcg (N=14)		GSK2269557 750 mcg (N=42)	
Did subject experience PI cough? [1]												
n	20		10		12		15		12		35	
Yes	7	(35%)	4	(40%)	6	(50%)	3	(20%)	6	(50%)	12	(34%)
No	13	(65%)	6	(60%)	6	(50%)	12	(80%)	6	(50%)	23	(66%)
Type of cough												
Single cough	4	(57%)	2	(50%)	1	(17%)	1	(33%)	1	(17%)	2	(17%)
Intermittent cough	2	(29%)	2	(50%)	5	(83%)	1	(33%)	4	(67%)	5	(42%)
Continuous cough	1	(14%)	0		0		1	(33%)	1	(17%)	5	(42%)
Severity of cough												
Mild	5	(71%)	3	(75%)	3	(50%)	2	(67%)	1	(17%)	6	(50%)
Moderate	2	(29%)	1	(25%)	2	(33%)	1	(33%)	5	(83%)	4	(33%)
Severe	0		0		1	(17%)	0		0		2	(17%)
Time to onset of PI cough (minutes)												
0-1	6	(86%)	3	(75%)	6	(100%)	3	(100%)	6	(100%)	12	(100%)
>1-2	1	(14%)	1	(25%)	0		0		0		0	
>2-3	0		0		0		0		0		0	
>3-4	0		0		0		0		0		0	
>4-5	0		0		0		0		0		0	
>5	0		0		0		0		0		0	
Duration of PI cough (minutes)												
<=1	6	(86%)	3	(75%)	5	(83%)	3	(100%)	5	(83%)	11	(92%)
>1-2	1	(14%)	1	(25%)	1	(17%)	0		1	(17%)	1	(8%)
>2-3	0		0		0		0		0		0	
>3-4	0		0		0		0		0		0	
>4-5	0		0		0		0		0		0	

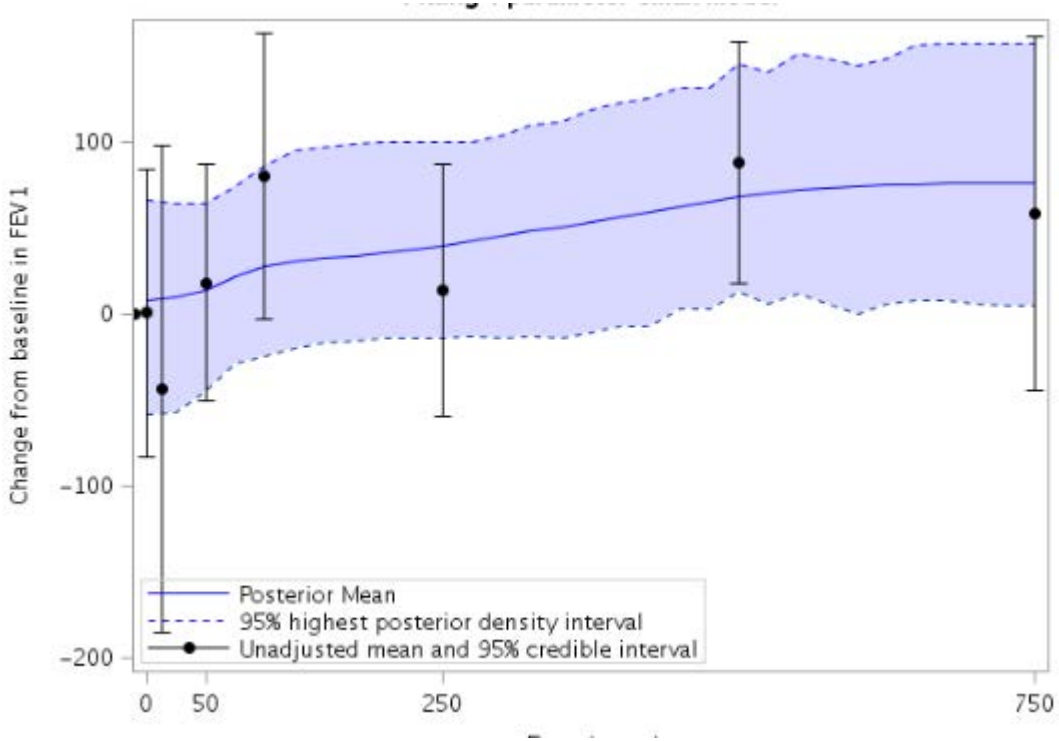
>5-10	x		x								
>10-30	x		x								
>30	x		x								
Number of subjects reporting cough as AE/SAE	2	(29%)	1	(25%)	4	(67%)	0		2	(33%)	3	(25%)
Mild	x	(x%)	x									
Moderate	x	(x%)	x									
Severe	x	(x%)	x									

[1] Percentages are calculated using the number of subjects evaluated at visit as the denominator.
All other percentages are calculated using the number of subjects with a PI cough at visit as the denominator.

13.12.18. Example shell 18

Protocol: ABC123456 Page 1 of x
Population: Intent-to-Treat/Safety/Other study specific

Figure X
Plot of Dose Response Model of Change from Baseline in FEV1



[Footnote to describe the fitted model]

PPD

13.12.19. Example Shell 19

Protocol: ABC123456
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of COPD Related Unscheduled Healthcare Resource Utilization

		Treatment A (N=100)		Treatment B (N=100)	
Unscheduled Healthcare Utilisation	Yes	97	(97%)	19	(19%)
	No	3	(3%)	81	(81%)
Number of Home Visits (day)	n	100		100	
	0	90	(90%)	92	(92%)
	1	4	(4%)	4	(4%)
	2	0		0	
	3	0		0	
	>3	0		2	(<1%)
	Total [1]	4		4	
Number of Home Visits (night)	n	100		100	
	0	100	(100%)	100	(100%)
	1	0		0	
	2	0		0	
	3	0		0	
	>3	0		0	
	Total [1]	0		0	

[1] Total number of contacts across all subjects.
[2] Total number of days across all subjects.
PPD

Protocol: ABC123456
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of COPD Related Unscheduled Healthcare Resource Utilization

		Treatment A (N=100)		Treatment B (N=100)	
Number of Office/Practice Visits	n	911		899	
	0	846	(93%)	808	(90%)
	1	42	(5%)	58	(6%)
	2	13	(1%)	23	(3%)
	3	7	(<1%)	8	(<1%)
	>3	3	(<1%)	2	(<1%)
	Total [1]	103		140	
Number of Urgent Care/Outpatient Visits	n	911		899	
	0	886	(97%)	882	(98%)
	1	15	(2%)	10	(1%)
	2	3	(<1%)	2	(<1%)
	3	3	(<1%)	3	(<1%)
	>3	4	(<1%)	2	(<1%)
	Total [1]	54		37	
Number of Emergency Room Visits	n	911		899	
	0	906	(>99%)	893	(>99%)
	1	5	(<1%)	5	(<1%)
	2	0		1	(<1%)
	3	0		0	
	>3	0		0	
	Total [1]	5		7	

[1] Total number of contacts across all subjects.
[2] Total number of days across all subjects.

PPD

Table X
Summary of COPD Related Unscheduled Healthcare Resource Utilization

		Treatment A (N=100)	Treatment B (N=100)
Number of Days in Intensive Care	n	911	899
	0	910 (>99%)	894 (>99%)
	1	0	0
	2	0	1 (<1%)
	3	0	0
	>3	1 (<1%)	4 (<1%)
	Total [2]	12	40
Number of Days in General Ward	n	911	899
	0	896 (98%)	878 (98%)
	1	0	2 (<1%)
	2	1 (<1%)	1 (<1%)
	3	0	0
	>3	14 (2%)	18 (2%)
	Total [2]	119	258

[1] Total number of contacts across all subjects.
[2] Total number of days across all subjects.

PPD

13.12.20. Example Shell 20

Protocol: ABC123456 Page 1 of x
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Non-COPD Related Unscheduled Healthcare Resource Utilization

		Treatment A (N=100)	Treatment B (N=100)
Unscheduled Healthcare Utilisation	Yes	97 (97%)	19 (19%)
	No	3 (3%)	81 (81%)
Number of Days in Accident and emergency	n	100	100
	0	90 (90%)	92 (92%)
	1	4 (4%)	4 (4%)
	2	0	0
	3	0	0
	>3	0	2 (<1%)
	Total	4	4
Number of Days in General Ward	n	100	100
	0	100 (100%)	100 (100%)
	1	0	0
	2	0	0
	3	0	0
	>3	0	0
	Total	0	0

PPD

13.12.21. Example Shell 21

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Exacerbation Related Hospitalizations

	Treatment A (N=100)	Treatment B (N=100)
Index exacerbation		
Participants with hospitalization	x.xx	x.xx
Number of hospitalizations	x.xx	x.xx
Mean duration (days)	x.xx	x.xx
SD	x.xx	x.xx
Median duration (days)	x.xx	x.xx
Minimum duration (days)	x.xx	x.xx
Maximum duration (days)	x.xx	x.xx
Subsequent exacerbations		
Participants with hospitalization	x.xx	x.xx
Number of hospitalizations	x.xx	x.xx
Mean duration (days)	x.xx	x.xx
SD	x.xx	x.xx
Median duration (days)	x.xx	x.xx
Minimum duration (days)	x.xx	x.xx
Maximum duration (days)	x.xx	x.xx

PPD

13.12.22. Example Shell 22

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Re-hospitalization Within 30 days of Index Exacerbation

		Treatment A (N=100)	Treatment B (N=100)
Re-hospitalization Within 30 days	Yes	97 (97%)	19 (19%)
	No	3 (3%)	81 (81%)

PPD

13.12.23. Example Shell 23

Protocol: XYZ100001
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Subsequent Exacerbation Treatment

	Treatment A (N=81)	Treatment B (N=79)
Subsequent exacerbation	70 (86%)	50 (63%)
OCS	X (x%)	X (x%)
Antibiotics	x (x%)	x (x%)
OCS and antibiotics	X (x%)	X (x%)

PPD

13.12.24. Example Shell 24

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Time from Resolution of Index Exacerbation to Next Exacerbation

	Treatment A (N=100)	Treatment B (N=100)
Subsequent exacerbation	x.xx	x.xx
Mean duration (days)	x.xx	x.xx
SD	x.xx	x.xx
Median duration (days)	x.xx	x.xx
Minimum duration (days)	x.xx	x.xx
Maximum duration (days)	x.xx	x.xx

PPD

13.12.25. Example Shell 25

Protocol: ABC123456 Page 1 of x
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of ECG Abnormalities for Participants with Any Abnormal Clinically Significant ECG Interpretation

	Treatment A (N=100)	Treatment B (N=100)
Visit 2 (Day 1)		
Abnormal – Clinically significant	10 (10%)	15 (15%)
Any finding	5 (50%)	5 (33%)
ST depression	5 (50%)	5 (33%)
Short PR Interval	0	5 (33%)
T wave inversion	0	5 (33%)
…….		

Includes Scheduled, unscheduled and Early Withdrawal visits.
Participants may have more than one abnormality at each visit.

PPD

13.12.26. Example Shell 26

Protocol: ABC123456 Page 1 of n
Population: Intent-to-Treat/Safety/Other study specific

Table X
Statistical Analysis of Change from Baseline in FEV1 (mL) (Dose Response Model)
Measured post-bronchodilator

	Placebo (N=xx)	DNX 5mg (N=xx)	DNX 10mg (N=xx)	DNX 25mg (N=xx)	DNX 35mg (N=xx)	DNX 50mg (N=xx)
n [1]	xx	xx	xx	xx	xx	xx
Posterior Adj. Median Change	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
95% HPD Credible Interval	(x.xx,x.xx)	(x.xx,x.xx)	(x.xx,x.xx)	(x.xx,x.xx)	(x.xx,x.xx)	(x.xx,x.xx)
Active - Placebo						
Posterior Adj. Median Difference		x.xx	x.xx	x.xx	x.xx	x.xx
95% HPD Credible Interval		(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)
Prob(Difference>0)		xx%	xx%	xx%	xx%	xx%
Predictive probability (%) [2] *[only if required]*		xx%	xx%	xx%	xx%	xx%

[1] Number of subjects with data contributing to the analysis.
[2] Predictive posterior probability of success at end of study, where success is Pr(Difference>0)>90%.
Note: Model fitted was a…..[insert as appropriate].

PPD

13.12.27. Example Shell 27

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of QTc(F) (msec) Categories

	Treatment A (N=100)		Treatment B (N=100)	
Screening				
n	xx		xx	
<=450	xx	(xx%)	xx	(xx%)
>450 to <=480	xx	(xx%)	xx	(xx%)
>480 to <=500	xx	(xx%)	xx	(xx%)
>500	xx	(xx%)	xx	(xx%)
Day 1 (Baseline)				
n	xx		xx	
<=450	xx	(xx%)	xx	(xx%)
>450 to <=480	xx	(xx%)	xx	(xx%)
>480 to <=500	xx	(xx%)	xx	(xx%)
>500	xx	(xx%)	xx	(xx%)
Day 14				
n	xx		xx	
<=450	xx	(xx%)	xx	(xx%)
>450 to <=480	xx	(xx%)	xx	(xx%)
>480 to <=500	xx	(xx%)	xx	(xx%)
>500	xx	(xx%)	xx	(xx%)

13.12.28. Example Shell 28

Protocol: ABC123456 Page 1 of x
Population: Safety

Table X
Summary of Post-Inhalation Cough by Visit and Cough Type

Visit 2 (Day 1) Type of cough: Single cough	Treatment A (N=100)
Did subject experience event [1]?	12 (24%)
Cough severity	
Mild	6 (50%)
Moderate	5 (42%)
Severe	1 (8%)
Time to onset of PI cough (minutes)	
0-1	2(17%)
>1-2	3(25%)
>2-3	4(33%)
>3-4	3(25%)
>4-5	0
>5	0
Duration of PI cough (minutes)	
<=1	7(58%)
>1 - 2	2(17%)
>2 - 3	3(25%)
>3 - 4	0
>4 - 5	0
>5 - 10	0
>10 - 30	0
>30	0

[1] Percentages are calculated using the number of subjects evaluated at visit as the denominator.

All other percentages are calculated using the number of subjects with particular cough type at visit as the denominator.

Protocol: ABC123456

Population: Safety

Table X

Summary of Post-Inhalation Cough by Visit and Cough Type

Visit 2 (Day 1) Type of cough: Single cough	Treatment A (N=100)
Number of subjects reporting cough as AE/SAE	4 (33%)
Mild	2 (17%)
Moderate	2 (17%)
Severe	0

Table X
Summary of Post-Inhalation Cough by Visit and Cough Type

Visit 2 (Day 1) Type of cough: Intermittent cough	Treatment A (N=100)
Did subject experience event [1]?	11 (22%)
Cough severity	
Mild	2 (18%)
Moderate	6 (55%)
Severe	3 (27%)
Time to onset of PI cough (minutes)	
0-1	1(9%)
>1-2	4(36%)
>2-3	6(55%)
>3-4	0
>4-5	0
>5	0
Duration of PI cough (minutes)	
<=1	0
>1 - 2	3(27%)
>2 - 3	6(55%)
>3 - 4	1(9%)
>4 - 5	0
>5 - 10	0
>10 - 30	1(9%)
>30	0

Table X
Summary of Post-Inhalation Cough by Visit and Cough Type

Visit 2 (Day 1) Type of cough: Intermittent cough	Treatment A (N=100)
Number of subjects reporting cough as AE/SAE	5 (45%)
Mild	1 (9%)
Moderate	2 (18%)
Severe	2 (18%)

Table X
Summary of Post-Inhalation Cough by Visit and Cough Type

Visit 2 (Day 1) Type of cough: Continuous cough	Treatment A (N=100)
Did subject experience event [1]?	4 (8%)
Cough severity	
Mild	1 (25%)
Moderate	2 (50%)
Severe	1 (25%)
Time to onset of PI cough (minutes)	
0-1	3(75%)
>1-2	1(25%)
>2-3	0
>3-4	0
>4-5	0
>5	0
Duration of PI cough (minutes)	
<=1	0
>1 - 2	0
>2 - 3	0
>3 - 4	1 (25%)
>4 - 5	1 (25%)
>5 - 10	0
>10 - 30	1 (25%)
>30	1 (25%)

Protocol: ABC123456
Population: Safety

Table X
Summary of Post-Inhalation Cough by Visit and Cough Type

Visit 2 (Day 1) Type of cough: Continuous cough	Treatment A (N=100)
Number of subjects reporting cough as AE/SAE	2 (50%)
Mild	1 (25%)
Moderate	1 (25%)
Severe	0

REPEAT FOR EACH VISIT

13.12.29. Example Shell 29

Protocol: MID200879 Page 1 of 1
Population: Intent-to-Treat

Listing X
Listing of Subjects who Received Incorrect Medication

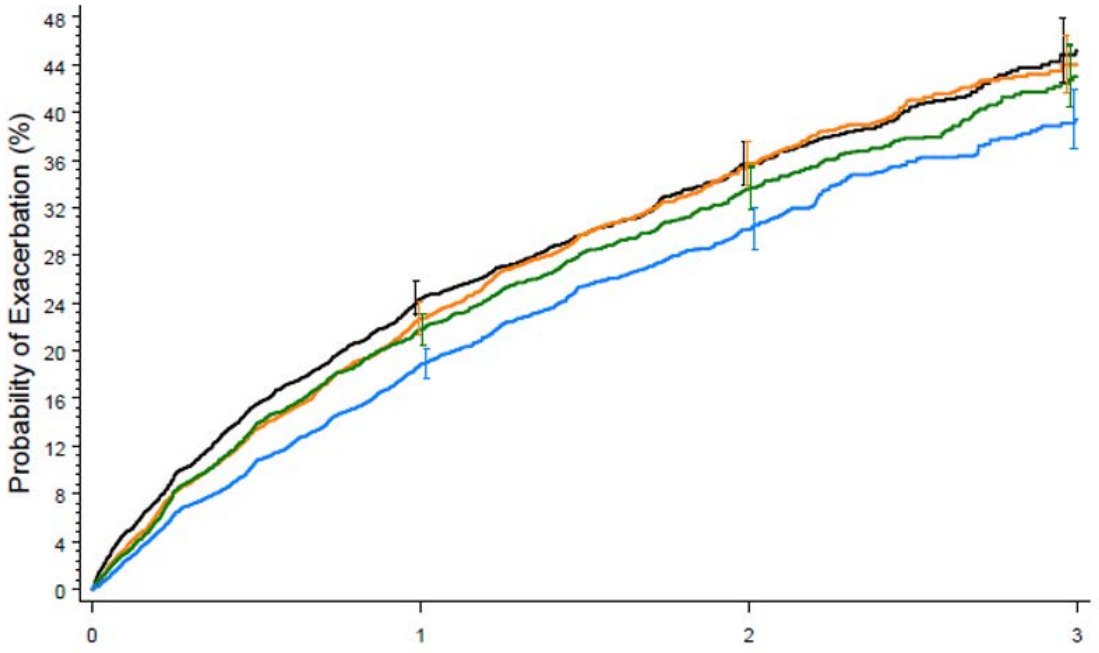
Randomized Treatment	Centre/ Subj	Start Date of Dosing	End Date of Dosing	Duration (Days)	Dispense Visit	Dispense Date	Actual Treatment Dispensed
GSK2269557 500 mcg	PPD	XXXXXXXXX	XXXXXXXXX	XX	Visit 3 (Week 0)	XXFEB2013	GSK2269557 500 mcg
		XXXXXXXXX	XXXXXXXXX	XX	Visit 5 (Week 4)	XXMAR2013	GSK2269557 100 mcg
		XXXXXXXXX	XXXXXXXXX	XX	Visit 6 (Week 8)	XXAPR2013	GSK2269557 500 mcg

PPD

13.12.30. Example Shell 30

Protocol: ABC123456 Page 1 of x
Population: Intent-to-Treat/Safety/Other study specific

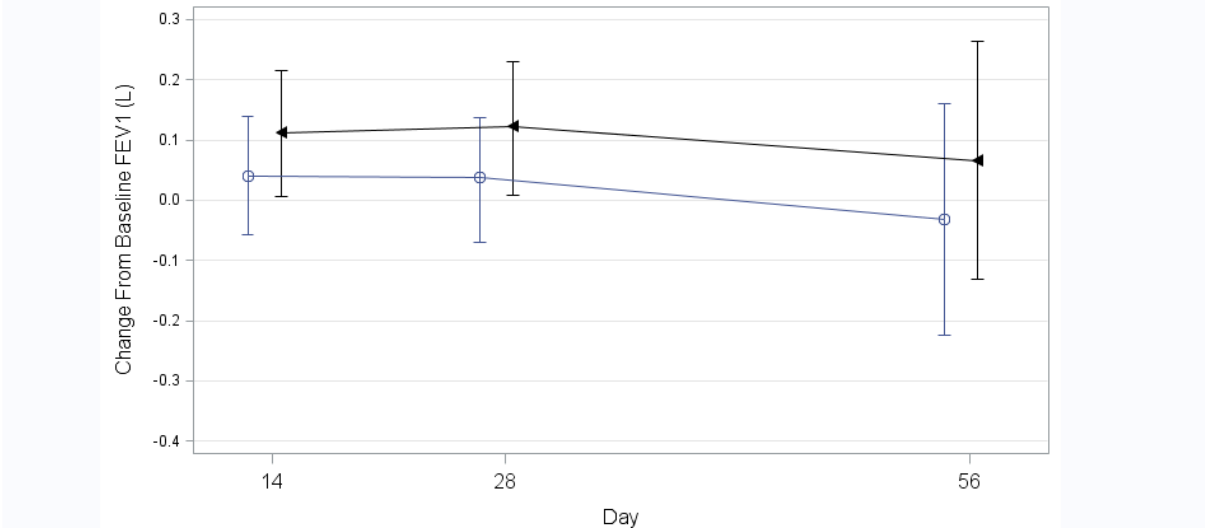
Figure X
Kaplan-Meier Plot of Time to Next On-treatment Exacerbation During the 12-Week Treatment Period



13.12.31. Example Shell 31

Protocol: ABC123456 Page 1 of x
Population: Intent-to-Treat/Safety/Other study specific

Figure X
Plot of Repeated Measures Model of Change from Baseline in FEV1 Measured Post-bronchodilator



13.12.32. Example Shell 32

Protocol: XYZ100001 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Efficiency Ratio for Possible Adaptions to Randomization Ratio

	Median	10th Percentile
Design 1: Add 25mcg dose	xx	xx
Design 2: Add 25mcg dose, drop 500mcg dose	xx	xx
Design 3: Add 25mcg dose, drop 250 mcg and 500 mcg doses	xx	xx
Design 4: Drop 12.5mcg dose	xx	xx
Design 5: Drop 12.5mcg and 50mcg doses	xx	xx

PPD

13.12.33. Example Shell 33

Protocol: ABC123456
Population: Safety

Table X
Summary of Post-Inhalation (PI) Cough at Any Visit

	Placebo (N=43)	GSK2269557 50 mcg (N=14)	GSK2269557 100 mcg (N=15)	GSK2269557 250 mcg (N=16)	GSK2269557 500 mcg (N=14)	GSK2269557 750 mcg (N=42)
Did subject experience PI cough at any visit?						
Yes	X (xx%)	X (xx%)	X (xx%)	X (xx%)	X (xx%)	X (xx%)
No	X (xx%)	X (xx%)	X (xx%)	X (xx%)	X (xx%)	X (xx%)
Maximum Severity of cough						
Mild	X (xx%)	X (xx%)	X (xx%)	X (xx%)	X (xx%)	X (xx%)
Moderate	X (xx%)	X (xx%)	X (xx%)	X (xx)	X (xx%)	X (xx%)
Severe	0	0	X (xx%)	0	0	X (xx%)
Maximum Duration of PI cough (minutes)[1]						
Mean	x	x	x	x	x	x
SD	x	x	x	x	x	x
Median	x	x	x	x	x	x
Minimum	x	x	x	x	x	x
Maximum	x	x	x	x	x	x
Number of occurrences of PI cough						
0	x	x	x	x	x	x
1	x	x	x	x	x	x
2	x	x	x	x	x	x
3	x	x	x	x	x	x
4	x	x	x	x	x	x

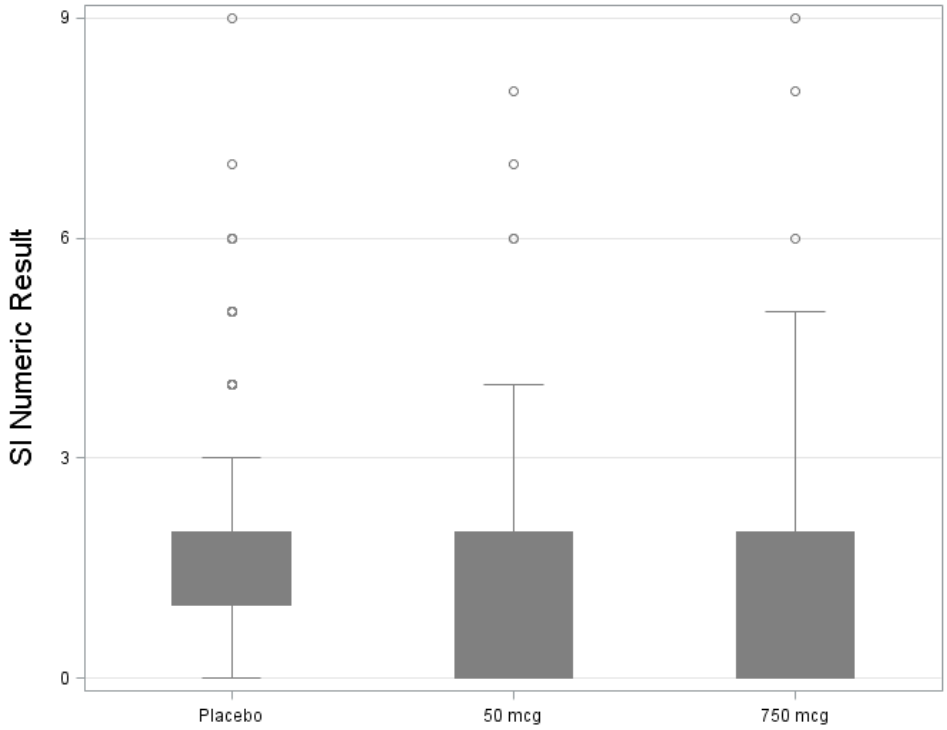
[1] Duration from the maximum severity cough

PPD

13.12.34. Example Shell 34

Protocol: ABC123456
Population: Safety

Figure X
Plot of Laboratory Data at Screening



PPD

13.12.35. Example shell 35

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Missing On-treatment EXACT-PRO data

	Placebo (N=300)	GSK2269557 50 mcg (N=100)	GSK2269557 100 mcg (N=100)	GSK2269557 250 mcg (N=100)	GSK2269557 500 mcg (N=100)	GSK2269557 750 mcg (N=300)
No. subjects missing >4 consecutive days	X (xx%)	X (xx%)	X (xx%)	X (xx%)	X (xx%)	X (xx%)
Number of missing days						
Mean	X.xx	X.xx	X.xx	X.xx	X.xx	X.xx
Median	X.xx	X.xx	X.xx	X.xx	X.xx	X.xx
Minimum	X.xx	X.xx	X.xx	X.xx	X.xx	X.xx
Maximum	X.xx	X.xx	X.xx	X.xx	X.xx	X.xx

PPD

13.12.36. Example Shell 36

Example EX1
Protocol: XYZ100001 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Exposure to Study Treatment

		Treatment A (N=100)	Treatment B (N=100)
Time on Study Treatment(days)	n	97	100
	Mean	15.6	11.2
	SD	13.23	9.46
	Median	11.5	8.0
	Min.	1	1
	Max.	64	50
	< 28 days	20 (21%)	20 (20%)
	28 days to 42 days	50 (52%)	50 (50%)
	43 days to 56 days	10 (10%)	10 (10%)
	57 days to 70 days	xx (xx%)	xx (xx%)
	>70 days	Xx (xx%)	Xx (xx%)

PPD

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

Title	:	Reporting and Analysis Plan for Phase IIb, Randomized (Stratified), Double-Blind (Sponsor Open), Parallel-Group, Placebo-Controlled, Dose-Finding Study of Nemiralisib (GSK2269557) Added to Standard of Care (SoC) Versus SoC Alone in Participants Diagnosed with an Acute Moderate or Severe Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)
Compound Number	:	GSK2269557
Effective Date	:	08-MAY-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 200879 and at the planned interim analyses.
- This RAP is intended to describe the efficacy, safety and pharmacokinetic analyses required for the study.
- This version of the RAP includes amendments to the originally approved RAP.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

RAP Author(s): PPD
Statistics Leader, (Respiratory Clinical Statistics)

Approver	Date	Approval Method
PPD TA Director (Respiratory Clinical Statistics)	08-MAY-2018	Email
PPD Programming Manager (Respiratory Clinical Programming)	03-MAY-2018	Email

RAP Team Approvals:

Approver	Date	Approval Method
PPD Principal Programmer (Respiratory Clinical Programming)	02-MAY-2018	Email
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CONFIDENTIAL

200879

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol 200879.

2. SUMMARY OF KEY PROTOCOL INFORMATION

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To characterise the dose response of nemiralisib administered in addition to SoC compared with placebo and SoC in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Change from baseline in Clinic Visit trough forced expiratory volume in one second (FEV_1) at Day 84 measured post-bronchodilator
Secondary Objectives	**Secondary Endpoints**
• To characterise the dose response and efficacy of nemiralisib administered in addition to SoC compared with placebo and SoC in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Rate of moderate and severe exacerbations over the 12-Week Treatment Period • Time to next moderate/severe exacerbation following index exacerbation • Change from baseline in Clinic Visit trough FEV_1 measured pre- and post-bronchodilator at Days 14, 28, 56, and 84 (Day 84: post-bronchodilator is the primary endpoint; pre-bronchodilator is a secondary endpoint) and at hospital discharge (only for participants who are hospitalized for the index exacerbation) • Change from hospital discharge in clinic visit trough FEV_1 measured pre- and post-bronchodilator at Days, 14, 28, 56, and 84 (in participants hospitalized for index exacerbation only)
• To evaluate the treatment effect of nemiralisib in addition to SoC compared with placebo and SoC on symptoms indicative of an exacerbation and on health status using Patient-Reported Outcomes (PROs) in participants diagnosed with an acute moderate or severe exacerbation of COPD	<u>EXAcerbations of Chronic Pulmonary Disease Tool (EXACT-PRO)</u> • Proportion of participants achieving the EXACT definition of recovery from the index exacerbation by Days 14, 28, 56, and 84 • Time to recovery from index exacerbation • Severity of subsequent HCRU-defined exacerbation(s) defined by EXACT <u>COPD Assessment Test (CAT)</u> • Proportion of responders using the CAT at Treatment Days 28, 56, and 84, and following EXACT defined recovery from the index exacerbation • Change from baseline (Day 1) in CAT total score at Days 28, 56, and 84 and following EXACT defined recovery from the index exacerbation

Objectives	Endpoints
	<u>St. George's Respiratory Questionnaire (SGRQ) Total Score</u> • Proportion of responders on the SGRQ total score as measured by the SGRQ for COPD Patients (SGRQ-C) at Days 28, 56, and 84 • Change from baseline (Day 1) in SGRQ total score at Days 28, 56, and 84
• To evaluate the usage of rescue medication in patients diagnosed with an acute moderate or severe exacerbation of COPD	• Rescue medication use (occasions/day), averaged over each week of treatment and over the 84-day treatment period • The percentage of rescue-free days (24-hour periods) during each week of treatment and over the 84-day treatment period
• To evaluate the population pharmacokinetics of nemiralisib in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Plasma nemiralisib concentrations and derived PK parameters (e.g., area under the curve [AUC (0-24) and AUC(0-t)], maximum concentration [Cmax], time at maximum concentration [Tmax], Ctrough) as appropriate will be collected in a subset of randomized participants (approximately 300) at selected sites as follows: trough (pre-dose) for the study treatment and post-dose for the study treatment from 0-1 hour and >1 to 6 hours on Days 14 and 28 of the 12-Week Treatment Period
• To assess the safety and tolerability of nemiralisib and placebo in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Incidence of adverse events (AEs; including serious AEs and AE of Special Interest [AESI]) • Vital signs (pulse rate, systolic and diastolic blood pressure) (measured at each clinic visit up through Visit 7 [Day 112] or Early Withdrawal Visit) • 12-lead electrocardiogram (ECG) assessments (performed at clinic Visits 1 [Screening], 3 [Day 14], 6 [Day 84], and 7 [Day 112] or Early Withdrawal Visit) • Clinical laboratory tests (hematology and chemistry; performed at each clinic visit up through Visit 7 [Day 112] or Early Withdrawal Visit) • Incidence of COPD exacerbations
Exploratory Objectives	**Exploratory Endpoints**
• To further characterize the dose response, and efficacy, of nemiralisib administered in addition to SoC compared with placebo and SoC in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Rate of mild exacerbations over the 12-Week Treatment Period • Rate of all exacerbations (mild, moderate and severe combined) over the 12-Week Treatment Period • Time to next exacerbation (mild, moderate and severe combined)

Objectives	Endpoints
• To evaluate the treatment effect of nemiralisib in addition to SoC compared with placebo and SoC on symptom stability following an exacerbation using Patient-Reported Outcomes in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Stability of symptoms post recovery measured using E-RS:COPD (Evaluating Respiratory Symptoms in COPD) and subscales from Randomization (Visit 2) to Day 84 (Visit 6)
• To explore the PK/PD relationship for nemiralisib	• Relationship between drug exposure and Pharmacodynamic responses (e.g. efficacy, heart rate, clinical laboratory analytes and blood biomarkers) in the PK subset of participants (approximately 300) at selected sites
• To evaluate the treatment effect of nemiralisib in addition to SoC compared with placebo and SoC on HCRU in participants who experience a severe exacerbation of COPD	• Measures of HCRU related to severe exacerbations (e.g., hospitalizations, length of hospital stay, re-hospitalization within 30 days, number of Emergency Room [ER] visits, etc.)
• To evaluate compliance with study treatment	• Number of actuations of the double-blind study treatment as measured by the clip-on Propeller Sensor (for countries where the Propeller Sensor for ELLIPTA is available)
• To evaluate inflammatory markers in blood in relation to acute exacerbation of COPD	• Blood samples collected at Screening through Visit 7 (as part of the clinical laboratory blood samples) for analysis of blood eosinophil counts and inflammatory mediators • Blood samples for analysis of inflammatory biomarkers (including but not limited to: high sensitivity C-reactive protein [hs-CRP], chemokine interferon-γ inducible protein 10 kDa (CXCL10)], and procalcitonin) collected at Visit 1 (Screening)
• To evaluate inflammatory and infective markers in sputum in relation to acute exacerbation of COPD	• Spontaneous sputum sample for analysis of inflammatory and infective markers collected at Screening/Day 1 (pre-dose) and Day 56 in participants who are willing and able to provide a sample
• To evaluate the potential post-treatment impact of double-blind study treatment during the 12-Week Post-Treatment Follow-Up Period	• Change from baseline (Day 84) in Clinic Visit trough FEV1 measured pre- and postbronchodilator at Day 112, 140 and 168 • Rate of moderate and severe COPD exacerbation(s) during the 12-Week Follow-Up Period • Rate of moderate and severe COPD exacerbation(s) over the 24 week study duration • Time to next exacerbation following cessation of double blind study treatment • Proportion of responders using the CAT at Days 112 and 168 • Change from baseline (Day 1) in CAT Total score at Days 112 and 168 • Proportion of responders on the SGRQ Total Score as measured by the SGRQ-C at Days 112 and 168 • Change from baseline (Day 1) in SGRQ total score at

Objectives	Endpoints
	Days 112 and 168 • Severity of subsequent HCRU exacerbation defined by EXACT • E-RS: COPD and subscales from last dose of double-blind study treatment • Rescue medication use up to Day 112

2.2. Study Design

This is a Phase IIb, multicenter, randomized, stratified (by index COPD exacerbation severity [moderate or severe] and by whether or not the participant is in the PK Subgroup), double-blind (Sponsor Open), placebo-controlled, parallel-group study in participants who present with an acute moderate or severe exacerbation of COPD requiring Standard of Care (SoC).

This study consists of a Screening Period, a 12-Week Treatment Period and a 12-Week

Post-Treatment Follow-Up Period. Randomization and the first dose of the double-blind study treatment administration (Visit 2/Day 1) should take place in the morning, as soon as possible following determination of eligibility and completion of the baseline measures, including the EXACT-PRO questionnaire for the day of randomization, and FEV_1 measurement and no later than 48 hours after the start of SoC.

PK Subgroup: Sparse PK sampling will be conducted in a subgroup of participants at selected sites. The PK Subgroup will be identical to the main study in terms of the study population, design, and conduct, with the exception of blood draws (3 per visit on Days 14 and 28) for PK analysis.

3. PLANNED ANALYSES

3.1. Interim Analyses

Ongoing data reviews of unblinded safety data, conducted by an Internal Safety Review Committee (iSRC), will be performed throughout the trial. Details will be documented in the iSRC charter.

Interim analyses of the primary endpoint and key secondary endpoints to inform internal decision making will be conducted periodically throughout the trial. The first analysis (Interim Analysis 1) is planned to occur when approximately 170 participants complete 28 days of treatment, where approximately 50 of the 170 participants have an index exacerbation defined as severe. A change that could arise from this interim analysis is a specification of the stratification proportions by index exacerbation severity status (moderate or severe). This decision will be based on inspection of all available endpoints at the interim analysis.

Further interim analyses will be performed, depending on the observed recruitment rate. At least one interim analysis of the primary endpoint of change from baseline in clinic visit trough FEV_1 at Day 84 measured post-bronchodilator will be performed to determine whether or not any adjustments to the randomization ratio across doses would help optimize the characterization of the dose response profile for nemiralisib. This analysis (Interim Analysis 2) is planned to occur when approximately 300 participants

complete 84 days of treatment or when approximately 400 participants remain to be randomized, whichever occurs first. Adjustments could include ceasing randomization to an existing dose(s) of nemiralisib and/or modification of the allocation ratios for the existing nemiralisib doses and/or addition of a 25mcg dose. Other changes may include specification of the stratification proportions by index exacerbation severity status.

An interim analysis of efficacy data collected during the Double-Blind Treatment Period will be conducted when the last participant in the study has completed the 12-week Double-Blind Treatment Period (End of Treatment Interim Analysis). The aim of this analysis is to provide GSK with timely data to inform internal decision making, prior to the end of study.

The following table describes the endpoints that will be analysed/summarised at each interim:

Interim	Purpose of interim	Endpoints
Interim Analysis 1	To inform internal decision making	• Change from baseline in FEV_1 at Days 14, 28, and 56 measured pre- and post-bronchodilator • Other spirometry measures (percent predicted FEV_1, Forced Vital Capacity (FVC), percent predicted FVC and FEV/FVC ratio • On-treatment exacerbations • Proportion of participants achieving EXACT-defined recovery by Days 14, 28, 56 and 84
Interim Analysis 2	To determine if any adjustments to the randomization ratio would help characterize the dose response profile for nemiralisib	Endpoints listed for Interim Analysis 1 and also: • Change from baseline in FEV_1 at Day 84 measured pre- and post-bronchodilator • Rate of (on-treatment) exacerbations over the 12-Week Treatment Period • Time to next (on-treatment) exacerbation during the 12-Week Treatment Period • Proportion of responders using the CAT • Change from baseline in CAT Total Score • Proportion of responders using the SGRQ • Change from baseline in SGRQ Total Score • Rescue medication use, as measured in eDiary
End of Treatment Interim Analysis	To inform internal decision making	Selected Efficacy and Safety endpoints as defined in Appendix 11: List of Data Displays

The statistical methods of analyses are described in Section 7.

The Respiratory Data Sciences Group will apply machine learning techniques to the interim data to determine if identifiable phenotypic sub-population(s) of COPD participants are present at baseline, and if they result in different responses to Nemiralisib, to predict which participants will respond to Nemiralisib therapy, and to identify/quantify relationship(s) between different endpoints and response measures. Details of these analyses will be described in a separate RAP and results will be reported separately to the Clinical Study Report (CSR).

The following functions will be unblinded to interim analysis data: Clinical Statistics, Clinical Programming and Respiratory Data Sciences Group. Other member of GSK will be unblinded to group level summary data following the interim analyses (as documented internally).

3.1.1. Futility analyses

At least one interim analysis for futility will be performed. The first analysis will occur at Interim Analysis 2, i.e. when 300 participants complete 84 days of treatment, or when approximately 400 participants remain to be randomized, whichever occurs first.

Futility will be assessed in a sequential manner.

1) Futility will first be assessed for the primary endpoint of change from baseline in FEV_1 at Day 84 by fitting a suitable dose response model, as described in Section 7.1.2.
2) If the posterior predictive probability of declaring success for this endpoint is low across all doses, then futility will be assessed for the rate of (on-treatment) exacerbations endpoint.
3) If the posterior predictive probability of declaring success for this endpoint is low, then the study may be stopped.

Any decision to stop will be made after a review of all the data summarised/analysed at the time of the interim, including the proportion of participants achieving the EXACT-defined recovery.

3.1.1.1. Futility rules

The decision rules for futility are defined as follows.

Change from baseline in FEV_1 at Day 84

Stop study for futility if the predictive probability of success at the end of the trial, given the data at the interim is <20%, across all doses, where success at the end of the trial for change from baseline in FEV_1 is defined as demonstrating >90% posterior probability that the true difference from placebo for any dose of nemiralisib is greater than 0.

Rate of on-treatment (moderate/severe) exacerbations

Stop study for futility if the predictive probability of success at the end of the trial, given the data at the interim is <20%, where success at the end of the trial for rate of exacerbations is defined as demonstrating >80% posterior probability that the true rate reduction on 750 mcg dose versus placebo > 0%.

If a different dose arm appears to be more efficacious than the 750 mcg arm, then futility may be assessed using the rate reduction for this arm versus placebo.

The pre-determined rules will act as guidelines for stopping the study for futility. All of the data summarised/analysed at the time of the interim will be reviewed prior to any decision to stop the study.

3.2. Final Analyses

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

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

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Participants Enrolled (APE) Population	• All participants who are screened for eligibility.	• Study Population
Modified Intent To treat (MITT) Population	• All randomized participants who receive at least one dose of study treatment. • Participants will be analyzed according to the treatment that they were randomized to.	• Study Population • Efficacy
Per Protocol (PP) Population	• All randomized participants who receive at least one dose of study treatment, excluding any participants with an important protocol deviation. • Participants will be analyzed according to the treatment that they were randomized to.	• Sensitivity analyses of efficacy
Safety Population	• All randomized participants who received at least one dose of study treatment. • Participants will be summarised according to the treatment that they actually received. o If participants receive >1 treatment, then they will be summarised according to the most frequently dosed treatment. In cases where the frequency is equal, the participant will be assigned the lowest dose strength of nemiralisib	• Safety
Pharmacokinetic (PK) Population	• All participants in the Safety population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). • Participants will be summarised according to the treatment that they actually received	• PK

Refer to Appendix 11: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

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

Important deviations which result in exclusion from the analysis population will also be summarised and listed. (Please refer to Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).

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

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

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

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG Randomization System		Data Displays for Reporting	
Code	Description	Description	Order in TLF
A	Placebo	Placebo	1
B	GSK2269557 12.5 mcg	NEMI 12.5 mcg	2
C	GSK2269557 25 mcg*	NEMI 25 mcg	3
D	GSK2269557 50 mcg	NEMI 50 mcg	4
E	GSK2269557 100 mcg	NEMI 100 mcg	5
F	GSK2269557 250 mcg	NEMI 250 mcg	6
G	GSK2269557 500 mcg	NEMI 500 mcg	7
H	GSK2269557 750 mcg	NEMI 750 mcg	8

* The nemiralisib dose of 25 mcg may be added following the results of an un-blinded interim analysis if further characterization of the lower end of the dose response curve is required.

Treatment comparisons will be displayed as follows using the descriptors as specified:

1. NEMI 12.5 mcg vs Placebo
2. NEMI 25 mcg vs Placebo
3. NEMI 50 mcg vs Placebo
4. NEMI 100 mcg vs Placebo
5. NEMI 250 mcg vs Placebo
6. NEMI 500 mcg vs Placebo
7. NEMI 750 mcg vs Placebo

5.2. Baseline Definitions

For all endpoints, the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Post-bronchodilator Baseline FEV_1 is defined as the latest FEV_1 measured prior to the first dose of study treatment and post-bronchodilator.

Pre-bronchodilator Baseline FEV_1 is defined as the latest FEV_1 measured prior to the first dose of study treatment and pre-bronchodilator.

Baseline CAT Total Score is defined as CAT Total Score measured prior to the first dose of study treatment on Day 1.

Baseline SGRQ Total Score is defined as SGRQ Total Score measured prior to the first dose of study treatment on Day 1.

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

A centred baseline will be derived for each participant by subtracting the mean baseline across all participants from each participant's baseline value. The 'centred' baseline may be used instead of Baseline in the statistical analyses to aid convergence.

5.3. Multicentre Studies

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

5.4. Examination of Covariates and Subgroups

5.4.1. Covariates

The list of covariates may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses. Additional covariates of clinical interest may also be considered. The decision to include covariates in the model will be based on their impact on the model fit and will be detailed in the CSR.

A centred covariate will be derived for each participant by subtracting the mean covariate across all participants from each participant's covariate value. The 'centred' covariate may be used in place of the covariate in the statistical analyses to aid convergence.

Covariate	Details
Index exacerbation severity	Categorical variable (Moderate or Severe) derived using the stratification variable from the randomisation system.
Age (at screening)	Continuous variable derived as described in Section 13.6.2.1
BMI	Continuous variable derived using Height and Weight variables collected in eCRF: BMI = Weight (kg) / (Height (m))^2
Gender	Categorical variable (Male or Female), collected in eCRF
Country	Categorical variable
Smoking status	Categorical variable (Current or Former), collected in eCRF
Baseline COPD maintenance therapy type	Categorical variable derived depending on data observed. Possible categories of interest are: Monotherapy vs. Dual therapy vs. Triple therapy
Index exacerbation type	Categorical variable: New or Relapse, derived using the question: "Other than the current prescription, for the index exacerbation, has the subject received oral/systemic corticosteroids and/or antibiotics for a COPD exacerbation within the last 7 days?" in the eCRF: New = No Relapse = Yes
Number of exacerbations in the previous 12 months	Categorical variable derived from "Total number of COPD exacerbations in the last 12 months" in the eCRF. Possible categories of interest are: 0 vs. 1 vs. ≥2

5.4.2. Examination of Subgroups

The list of subgroups may be used in descriptive summaries and statistical analyses. Additional subgroups of clinical interest may also be considered.

- If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined.
- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup.

Subgroup	Categories
Index exacerbation severity	Moderate vs. Severe
Baseline COPD maintenance therapy type	Possible categories of interest are: Monotherapy vs. Dual therapy vs. Triple therapy
Index exacerbation type	New vs. Relapse
Number of exacerbations in the previous 12 months	Possible categories of interest are: 0 vs. 1 vs. ≥2
Gender	Male vs. Female
Smoking status	Current vs. Former

5.5. Other Considerations for Data Analyses and Data Handling Conventions

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

Section	Component
Section 13.2	Appendix 2: Assessment Windows
Section 13.3	Appendix 3: Study Phases and Treatment Emergent Adverse Events
Section 13.4	Appendix 4: Data Display Standards & Handling Conventions
Section 13.5	Appendix 5: Derived and Transformed Data
Section 13.6	Appendix 6: Reporting Standards for Missing Data
Section 13.7	Appendix 7: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the "APE" and/or "MITT" populations, unless otherwise specified.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, and exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 11: List of Data Displays.

6.1.1. Concomitant medications

Concomitant medications will be summarised by treatment group. Separate summaries of Baseline and On-treatment (Step-up) COPD Maintenance Therapy, and duration of OCS use will also be presented.

Additional summaries or sensitivity analyses of on-treatment COPD maintenance therapy (step-up therapy) may be performed if the data indicate that further investigation is warranted.

7. EFFICACY ANALYSES

Details of the outputs are provided in Appendix 11: List of Data Displays and will be based on GSK data standards and statistical principles.

Further details for use in the endpoint derivations below can be found in Appendix 5: Derived and Transformed Data.

7.1. Primary Efficacy Analyses

7.1.1. Primary Endpoint

The primary endpoint of change from baseline in clinic visit trough FEV_1 at Day 84 measured post-bronchodilator is defined as:

FEV_1 measured prior to dosing and post-bronchodilator on Day 84 – Post-bronchodilator Baseline FEV_1

7.1.2. Primary Statistical Analyses

The primary endpoint will be analysed by fitting a suitable dose response model. The following models will be fitted, and the one that gives the best fit to the data will be selected: Bayesian 4-parameter E_{max} dose response model, 3-parameter E_{max} model and a Log-linear model.

The 4-parameter E_{max} dose response model will take the form:

$$\text{Change from baseline } FEV_1 = (E0 + a_1 * baseline) + \frac{(E_{max} + b_1 * baseline) * Dose^{\gamma}}{ED50^{\gamma} + Dose^{\gamma}}$$

The 3-parameter E_{max} dose response model will take the form:

$$\text{Change from baseline } FEV_1 = (E0 + a_1 * baseline) + \frac{(E_{max} + b_1 * baseline) * Dose}{ED50 + Dose}$$

Where: E0 = the response at dose = 0 (placebo)

E_{max} = the maximal response

ED50 = the dose that yields 50% of the maximal response

γ = the slope parameter

a_1, b_1, are covariates for explanatory parameters

Initially, normal non-informative priors will be used for the E0, a_1, a_2, and E_{max} parameters with mean 0 and standard deviation 1E6 L. A functional uniform prior will be used for the ED50 and slope parameters (Bornkamp, 2014), where the prior density for the functional uniform prior is based on all the parameters in the model. An inverse -

gamma prior with shape of 0.001 and scale of 0.001 will be used for the residual variance. However, if a prior distribution appears not to be truly non-informative then alternative prior distributions may be used.

Parameters will be blocked such that the MCMC procedure samples from E0, a_1, b_1, and E_{max}, first, then the ED50 and slope parameters and then finally the residual variance parameter. For the functional uniform priors, the density will be calculated for values of dose from 0.0001 to 750 in steps of 50 (i.e. 0.0001, 50.0001, 100.0001,…, 750.0001). For the continuous covariates, the density will be calculated from the minimum to the maximum in 10 equal steps. For binary covariates the density will be calculated for values 0 and 1. If the model does not converge including covariates, the model may be fitted with covariates removed.

If the log-linear model is fitted an offset of 1 will be used.

The posterior median change from baseline with 95% Highest Posterior Density (HPD) Credible Intervals, will be presented for each dose along with the adjusted median difference from placebo with 95% HPD, calculated at the mean baseline value across the treatment arms. Posterior probabilities that the true improvement is greater than 0 mL and 75 mL will also be presented. Graphical representation of the dose response across the full dose range will also be produced to allow inference to be made for the non-studied doses based upon the model fit.

For the futility analysis:

The predictive probability of success at the end of the study will be calculated (assuming the randomisation ratios remain the same after the interim) for each dose using the formula suggested by Spiegelhalter et al., 2004 as follows:

$$Predictive\ probability = 1 - \Phi\left[\frac{\sqrt{m_1}}{\sqrt{m_1}} z_{0.9} - \sqrt{\frac{n_1 + m_1}{m_1}} \frac{y_n}{\sigma}\right]$$

Where n_1 is the number of subjects with Day 84 data in the active arm of interest, m_1 is the number of subjects yet to be observed in the active arm of interest, y_n is the posterior mean difference from placebo from the fitted model, and σ is the standard deviation of the posterior mean difference from placebo.

For the possible adaptations at Interim Analysis 2:

If the study is not deemed futile, and either the 4 parameter or 3 parameter E_{max} dose response curves has successfully been fitted to the data then adaptation of the randomisation schedule will be considered, to drop, add or amend doses from the randomisation scheme.

The adaptation will be done by comparing the relative information from alternative randomisation schemes with the original randomisation schemes, such to find the design that provides the most information about the dose response relationship. The efficiency ratio (ER) for an alternative scheme comparted to the original, will be calculated as:

$$ER(\theta_i) = \left(\frac{|M(\xi_1,\theta_i)|}{|M(\xi_F,\theta_i)|}\right)^{\frac{1}{p}}, \text{ i=1,…,1000}$$

Where $M(\xi,\theta)$ is the information matrix for the design ξ and model parameters θ = *(e0, emax, ed50, γ, a_1, b_1)*^{T}, ξ_1 is the alternative design one and ξ_F is the fixed original design, and p is the number of parameters (Dette et al 2008). In order to ensure any adaptation is robust to the variability in the parameter estimates at the interim analysis, 1000 samples will be generated from the posterior distribution of the parameters $\theta_1, \ldots, \theta_{1000}$ and the ER calculated for each set of parameter. Adaptation will then only take place if the median ER is >1.05 and the 10th percentile of the ER is >1. The efficiency ratio will be estimated using the mean baseline value across the population.

The alternative designs that will be considered will depend on the dose response model fitted but could include:

1. Add 25mcg dose
2. Add 25mcg dose, drop 500mcg dose
3. Add 25mcg dose, drop 250 mcg and 500 mcg doses
4. Drop 12.5mcg dose
5. Drop 12.5 mcg and 50mcg doses

The potential adaption may also be verified in the moderate and severe subgroups to ensure the adaption is beneficial across both groups.

7.1.2.1. Model Checking & Diagnostics

The following list of convergence diagnostics will be applied for each parameter:

- The Monte Carlo Standard Errors (MCSE) should be compared with the standard deviation of the posterior distribution (SD) to ensure that only a fraction of the posterior variability is due to the simulation. The number of samples generated and/or the thinning may be increased to reduce the ratio of the MCSE/SD as deemed necessary.
- The Geweke diagnostic test will be used to assess whether the mean estimates have converged by comparing means from the early and latter part of the Markov chain using a z-score t-test. Large absolute values of the z-score statistic indicate rejection of the null hypothesis of no difference between the mean estimates obtained from the early and latter parts of the chain.
- Trace plots of samples versus the simulation index will be visually inspected to assess some aspects of convergence. The centre of the chain should appear stable with very small fluctuations, i.e., the distribution of points should not change as the chain progresses and the posterior mean and variance are relatively constant.
- Autocorrelation plots will be visually inspected to assess degree of autocorrelation (should decline rapidly and show no oscillation patterns).

7.1.3. Sensitivity and Supportive Analyses

If there are greater than 20% of participants with an important protocol deviation that results in exclusion from the Per Protocol Population, the primary analysis may be repeated using the Per Protocol Population.

Change from baseline in clinic visit trough FEV_1 at Day 84 will also be compared between treatment groups using a Bayesian Repeated Measures analysis with covariates for baseline-by-Day interaction and treatment-by-Day interaction. Day will be fitted as a repeated effect within each participant. All post-baseline scheduled visits will be included in the analysis using Day. Non-informative priors will be used for all modelling parameters. Wherever possible conjugate priors will be utilised. An unstructured covariance matrix will be used to model the within-subject error.

A further sensitivity analysis may be performed where Baseline FEV_1 is replaced with the FEV_1 measured post-bronchodilator and prior to dosing on day of hospital discharge for participants who were hospitalised for their index exacerbation, i.e. who were randomized with a Severe index exacerbation but kept as Baseline FEV_1 for participants who were randomized with a Moderate index exacerbation.

7.1.4. Subgroup Analyses

A subgroup analysis of change from baseline in clinic visit trough FEV_1 by index exacerbation severity will be performed by fitting separate models to each level of the severity subgroup.

A subgroup analysis of change from baseline in clinic visit trough FEV_1 by index exacerbation severity will also be performed by including a treatment-by-severity-by-Day interaction term in the Bayesian Repeated Measures model.

7.2. Secondary Efficacy Analyses

7.2.1. Rate of exacerbations

Rate of exacerbation is defined as the frequency of exacerbations (subsequent to the index exacerbation) within the specified time period, for example, the 12-Week Treatment Period or the 24-Week Study Period.

The length of time on treatment or in study, depending on the specified time-period, for each participant will be calculated for each endpoint as follows:

Endpoint	Time period	Length of time derivation
Rate of (on-treatment) exacerbations, summarised by: • Moderate/severe exacerbations • Moderate exacerbations • Severe exacerbations • All (mild, moderate and	12-Week Treatment Period	Time from date of randomisation to date of last dose of study treatment

Endpoint	Time period	Length of time derivation
severe) exacerbations		
Rate of (on-or off-treatment) exacerbations, summarised by: • Moderate/severe exacerbations • All exacerbations	12-Week Treatment Period	Time from date of randomisation to Day 84 (Visit 6) Visit Date. For participants who withdraw early from the study: Time from date of randomisation to date of study withdrawal
Rate of (off-treatment) exacerbations, summarised by: • Moderate/severe exacerbations • Moderate exacerbations • Severe exacerbations	12-Week Follow Up Period	Time from date of last dose of study treatment to date of study withdrawal/completion
Rate of (on- and off- treatment) exacerbations, summarised by: • Moderate/severe exacerbations • Moderate exacerbations • Severe exacerbations	Full 24-Week Study Period	Time from date of randomisation to date of study withdrawal/completion

Refer to Section 13.5 for further details regarding the length of time derivation

7.2.1.1. Statistical analyses

The rate of exacerbations will be analysed using a Bayesian generalized linear model assuming a negative binomial distribution for the underlying exacerbation rate with a log link function. An offset to account for the length of time on treatment or in study, depending on the specified time-period, for each participant (as described above) will be included in the model as $\log_e$ (length of time).

Non-informative priors will be used for all modelling parameters. Wherever possible conjugate priors will be utilised.

The median exacerbation rates for each dose arm per 12 weeks, along with the median ratio in exacerbation rates (nemiralisib/placebo) per 12 weeks for each dose, will be estimated and corresponding 95% HPD credible intervals presented. The probability that the true exacerbation rate ratio is less than 1, in addition to other values appropriately selected based on the data, will be presented.

Based on pharmacological predictions, the 500 mcg and 750 mcg doses are expected to result in similar levels of target inhibition and thus potentially translate to similar clinical benefit, therefore estimates of the exacerbation rates for pooled data from 500 mcg plus 750 mcg will also be presented.

7.2.1.2. Subgroup analyses

A subgroup analysis of exacerbation rate by Index exacerbation severity will be performed by including a treatment-by-severity term in the model.

7.2.1.3. Exploratory analyses

A summary of exacerbation rate by the following groups will be presented and, if feasible, a subgroup analyses may be performed:

- Index exacerbation type (New or Relapse)
- Number of exacerbations in previous 12 months (0, 1 or ≥2).

7.2.2. Time to next exacerbation

Time to next (on-treatment) exacerbation following index exacerbation during the 12-Week Treatment Period is defined as time from the date of randomisation until the date of onset of the first exacerbation whilst on study treatment. Participants who did not have an exacerbation whilst on study treatment will be censored at the date of their last dose of study treatment.

Time to next (on-or off-treatment) exacerbation during the 12-Week Treatment Period is defined as time from the date of randomisation until the date of onset of the first exacerbation occurring up to Day 84. Participants who have not had an exacerbation during the 12-Week Treatment Period will be censored at Day 84 or the date of study withdrawal, for participants who withdrew from the study prior to Day 84.

Time to next exacerbation following cessation of study treatment is defined as time from the date of last dose of study treatment until the date of onset of the next exacerbation whilst off study treatment during the 12-Week Follow Up Period. Participants who have not had an exacerbation off-treatment will be censored at the date of their last follow up assessment.

Time to next exacerbation will be analysed by severity, as follows:

Endpoint	Time period
Time to next (on-treatment) exacerbation, summarised by: • Moderate/severe exacerbations • All (mild, moderate and severe) exacerbations	12-Week Treatment Period
Time to next (on-or off-treatment) exacerbation, summarised by: • Moderate/severe exacerbations • All exacerbations	12-Week Treatment Period
Time to next exacerbation following cessation of treatment, summarised by: • Moderate/severe exacerbations	12-Week Follow Up Period

Refer to Section 13.5 for further details regarding the length of time derivation

7.2.2.1. Statistical analyses

Time to next exacerbation will be analysed using a Bayesian Cox proportional hazards model with the "Efron" method for handling ties.

Kaplan-Meier (KM) estimates of the probability of exacerbation will also be presented.

Non-informative priors will be used for all modelling parameters. Wherever possible conjugate priors will be utilised.

The hazard ratio and corresponding 95% HPD credible intervals for each nemiralisib dose versus placebo will be presented. The probability that the true hazard ratio is less than 1, in addition to other values appropriately selected based on the data, will be presented.

Based on pharmacological predictions, the 500 mcg and 750 mcg doses are expected to result in similar levels of target inhibition and thus potentially translate to similar clinical benefit, therefore an estimate of hazard ratio for pooled data from 500 mcg plus 750 mcg nemiralisib doses versus placebo will also be presented.

7.2.2.2. Subgroup analyses

A subgroup analysis of time to exacerbation by Index exacerbation severity will be performed by including a treatment-by-severity term in the model.

7.2.3. Change from baseline in Clinic Visit trough FEV_1

Change from baseline in clinic visit trough FEV_1 at Day 14, 28, 56 measured post-bronchodilator is defined as:

FEV_1 measured prior to dosing and post-bronchodilator on Day X – Post-bronchodilator Baseline FEV_1

Where Day X is Day 14, 28, and 56.

Change from baseline in clinic visit trough FEV_1 at Day 14, 28, 56, 84 measured pre-bronchodilator is defined as:

FEV_1 measured prior to dosing and pre-bronchodilator on Day X – Pre-bronchodilator Baseline FEV_1

Where Day X is Day 14, 28, 56, and 84.

7.2.3.1. Statistical Analyses

Change from baseline in Clinic Visit trough FEV_1 measured post-bronchodilator will be analysed using a dose response model and repeated measures analysis as described for the primary endpoint in Section 7.1.2.

Change from baseline in Clinic Visit trough FEV_1 measured pre-bronchodilator will be analysed using a repeated measures analysis as described in Section 7.1.2

7.2.3.2. Subgroup analyses

A subgroup analysis of change from baseline in clinic visit trough FEV_1 by index exacerbation severity will be performed.

7.2.4. Change from hospital discharge in clinic visit trough FEV_1

Change from hospital discharge in clinic visit trough FEV_1 will be derived only for participants who were hospitalised for their index exacerbation and who have been subsequently discharged.

Change from hospital discharge in clinic visit trough FEV_1 measured post-bronchodilator is defined as:

FEV_1 measured prior to dosing and post-bronchodilator on Day X – FEV_1 measured post-bronchodilator and prior to dosing on day of hospital discharge.

Where Day X is 14, 28, 56 and 84.

Change from hospital discharge in clinic visit trough FEV_1 measured pre-bronchodilator is defined as:

FEV_1 measured prior to dosing and pre-bronchodilator on Day X – FEV_1 measured prior to dosing and post-bronchodilator on day of hospital discharge.

Where Day X is 14, 28, 56 and 84.

Note, as per Section 5.1 of the Protocol, if discharge takes place between Day 11 and Day 17 (inclusive), the assessments planned for Day 14 may be completed on the day of discharge. In these cases, for this endpoint only, the FEV_1 assessment will be assigned the hospital discharge assessment and the Day 14 assessment will be missing. Refer to Section 13.2.1.1 for further details.

In addition, if discharge takes place after Day 14, the Day 14 assessment will be missing for this analysis.

7.2.4.1. Statistical analyses

Change from hospital discharge in clinic visit trough FEV_1 will be analysed using a repeated measures analysis as described in Section 7.1.2 if there are a sufficient number of participants to provide a meaningful analysis, otherwise the data will be summarised.

7.2.5. EXAcerbations of Chronic Pulmonary Disease Tool - Patient Reported Outcome (EXACT)

The EXACT is a 14-item daily diary designed to provide a measure of patient-reported symptoms of COPD exacerbation. An EXACT Total Score, ranging from 0 to 100, where

higher scores indicate a more severe condition, will be derived for each day of diary collection according to the instructions in the EXACT User Manual (Version 8.0, Evidera, 2016).

The electronic EXACT diary does not allow a study patient to skip individual items, therefore no missing data are expected for individual items. However, if missing values occur for individual items, the Total Score that contains the item will be set to missing for that day. Moderate-to-severe COPD patients are expected to experience symptom(s) each day, and a score of zero on all 14 EXACT items is likely to represent a situation where in order to complete the diary quickly, the respondent did not accurately report their daily symptom(s), therefore if the EXACT Total Score is 0, it will be set to missing.

A 3-day Rolling Average EXACT Total Score will be calculated for each day, X, as:

> (EXACT Total Score on Day X-1 + EXACT Total Score on Day X + EXACT Total Score on Day X+1) / (Number of days with non-missing values)

Note, for Day 1, the Rolling Average EXACT Total Score will be calculated as the average of EXACT Total Score on Days 1 (Randomisation) and 2 only, since no EXACT data is collected prior to randomisation. Similarly, the Rolling Average EXACT Total Score for the last study day will be calculated as the average of EXACT Total Score on the last day and on the day before the last day.

The Rolling Average EXACT Total Score will be calculated for each day as long as at least 1 EXACT total score in the sequence is present. Therefore, only in the case where EXACT total scores are missing for 3 consecutive days in a row (or 2 consecutive days in the case of the first and last day rolling average calculation), will the rolling average score be missing.

The Maximum Observed Value (MOV) is defined as the highest Rolling Average EXACT Total Score observed within the first 14 days of randomisation. Note: this definition differs from the definition in the EXACT User Manual of "the highest rolling average EXACT score observed in the context of an EXACT exacerbation within the first 14 days of the exacerbation", since the date of the index exacerbation is likely to be prior to randomisation.

7.2.5.1. Proportion of participants achieving EXACT-defined recovery from index exacerbation

EXACT-defined recovery from the index exacerbation is defined as a decrease in the Rolling Average EXACT Total Score ≥9 points from the Maximum Observed Value, sustained for ≥7 days, with the first of the 7 days defined as the recovery day.

The proportion of participants achieving EXACT-defined recovery from the index exacerbation by Days 14, 28, 56, and 84 will be calculated as:

> (Number of participants who experience an EXACT-defined recovery on or before Day X) / (Total number of participants in the MITT population)

Where Day X is 14, 28, 56, and 84.

7.2.5.2. Time to EXACT-defined recovery from index exacerbation

Time to EXACT-defined recovery from index exacerbation is defined as time from the date of randomisation until date of the first EXACT-defined recovery day during the 12-Week Treatment Period, where EXACT-defined recovery is described in Section 7.2.5.1. Participants who did not experience EXACT-defined recovery during the 12-Week Treatment Period will be censored at the date of their last dose of study treatment.

7.2.5.3. Severity of subsequent HCRU-defined exacerbation(s) defined by EXACT

Severity of subsequent HCRU-defined exacerbation(s) defined by EXACT is defined as the highest EXACT Total Score (not using the 3-day Rolling Average) during the period from date of onset of the subsequent HCRU-exacerbation until date of EXACT-defined recovery of subsequent exacerbation.

Note, in this case, the Maximum Observed Value and EXACT-defined recovery are derived using the date of onset of the subsequent HCRU-exacerbation.

Severity of subsequent HCRU-defined exacerbation(s) defined by EXACT will only be derived for participants who have had a subsequent exacerbation. If a participant has more than one subsequent exacerbation, severity will be calculated for each subsequent exacerbation.

7.2.5.4. Statistical analyses

The proportion of participants achieving EXACT-defined recovery from the index exacerbation will be analysed using a Bayesian logistic regression model. Separate models will be fitted for each time-point.

Non-informative priors will be used for all modelling parameters. Wherever possible conjugate priors will be utilised.

The results of the analysis will be presented in terms of odds ratios together with its associated 95% HPD credible interval. The probability that the true odds ratio is greater than 1, in addition to other values appropriately selected based on the data, will be presented.

Time to EXACT-defined recovery from index exacerbation will be analysed using the same techniques as described in Section 7.2.2.1.

Severity of subsequent HCRU-defined exacerbation(s) defined by EXACT will be summarised for each treatment group and reported by study period. The severity of subsequent HCRU-defined exacerbation(s) occurring whilst a participant is on treatment will be reported as during the 12-Week Treatment Period and the severity of subsequent HCRU-defined exacerbation(s) occurring after the last dose of study treatment will be reported as during the 12-Week Follow-up Period.

7.2.5.5. Subgroup analyses

A subgroup analysis of the proportion of participants achieving EXACT-defined recovery from the index exacerbation by Index Exacerbation Severity will be performed by including a treatment-by-severity term in the model.

7.2.5.6. Sensitivity and supportive analyses

Sensitivity analyses exploring the impact of any missing data, and changes to the definition of EXACT-defined recovery may be conducted and may be performed post-SAC.

7.2.6. COPD Assessment Test (CAT)

The COPD Assessment Test (CAT) is a patient completed questionnaire developed to measure the health status of patients with COPD. The CAT consists of eight items, each on a six-point scale: 0 (no impact) to 5 (high impact). The CAT Score will be calculated for each study day of collection by summing the scores for all questions. The CAT Score ranges from 0 to 40, where higher scores indicate a more severe condition.

7.2.6.1. Proportion of responders using the CAT

The proportion of responders using the CAT will only be derived for participants with a baseline CAT Total Score ≥2.

The Proportion of responders using the CAT is defined as:

> (Number of participants with a decrease from baseline in CAT Total Score ≥2 on or before Day X)/(Total number of participants in the MITT population)

Where Day X is 28, 56, and 84 and the study day following EXACT-defined recovery from the index exacerbation.

Note: due to software limitations of the electronic PRO device, the study day following EXACT-defined recovery is not derived according to the EXACT User Manual, see Section 13.2.1.2 for further details.

Exploratory – Follow-Up Period

The Proportion of responders using the CAT at Day 112 and 168 is defined as:

> (Number of participants with a decrease from baseline in CAT Total Score ≥2 on or before Day X)/(Total number of participants in the MITT population)

Where Day X is Day 112 and Day 168 and the study day following EXACT defined recovery, if it occurs during the Follow-up period.

7.2.6.2. Change from baseline in CAT Total Score

Change from baseline in CAT Total Score is defined as:

CAT Total Score on Day X – Baseline CAT Total Score

Where Day X is 28, 56, 84 and the study day following EXACT defined recovery from the index exacerbation.

Note: due to software limitations of the electronic PRO device, the study day following EXACT-defined recovery is not derived according to the EXACT User Manual, see Section 13.2.1.2 for further details.

Exploratory – Follow-Up Period

The Change from baseline in CAT Total Score at Day 112 and 168 is defined as:

CAT Total Score on Day X – Baseline CAT Total Score

Where Day X is Day 112 and Day 168.

The Change from end of treatment in CAT Total Score at Day 112 and 168 is defined as:

CAT Total Score on Day X – CAT Total Score on Day 84

Where Day X is Day 112 and Day 168.

7.2.6.3. Statistical analyses

The proportion of responders using CAT will be analysed using the same techniques as described in Section 7.2.5.4.

Change from baseline/end of treatment in CAT Total Score will be compared between treatment groups using a Bayesian Repeated Measures analysis with covariates for baseline-by-Day interaction and treatment-by-Day interaction. Day will be fitted as a repeated effect within each participant.

All post-baseline scheduled visits will be included in the analysis using Day.

Non-informative priors will be used for all modelling parameters. Wherever possible conjugate priors will be utilised. An unstructured covariance matrix will be used to model the within-subject error.

Adjusted posterior median change from baseline and corresponding 95% HPD credible intervals will be summarised for each treatment by time-point, together with estimated treatment differences (GSK – Placebo) and corresponding 95% HPD credible intervals. The posterior probability that the true treatment difference is less than 0, in addition to other values appropriately selected based on the data, will also be presented.

7.2.6.4. Subgroup analyses

A subgroup analysis of the proportion of responders using CAT and the change from baseline in CAT Total Score by Index exacerbation severity will be performed by

including a treatment-by-severity term and a treatment-by-severity-by-Day term in the Bayesian logistic regression and Bayesian Repeated Measures models, respectively.

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

St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C) is a 40-item questionnaire designed specifically to focus on COPD patients. SGRQ-C will be scored to be equivalent to the SGRQ Total Score, ranging from 0 to 100, where higher scores reflect worse health-related quality of life. SGRQ Total Scores will be calculated for each day of collection according to the instructions in SGRQ-C Manual (SGRQ, March 2016).

7.2.7.1. Proportion of responders on the SGRQ Total Score

The proportion of responders on the SGRQ Total Score will only be derived for participants with a baseline SGRQ Total Score ≥4.

Proportion of responders on the SGRQ Total Score is defined as:

> (Number of participants with a decrease from baseline in SGRQ Total Score ≥4 on or before Day X)/(Total number of participants in the MITT population)

Where Day X is 28, 56, and 84.

Exploratory – Follow-Up Period

The Proportion of responders on the SGRQ Total Score at Day 112 and 168 is defined as:

> (Number of participants with a decrease from baseline in SGRQ Total Score ≥4 on or before Day X)/(Total number of participants in the MITT population)

Where Day X is Day 112 and Day 168 and the study day following EXACT defined recovery, if it occurs during the Follow-up period.

7.2.7.2. Change from baseline in SGRQ Total Score

Change from baseline in SGRQ Total Score is defined as:

> SGRQ Total Score on Day X – Baseline SGRQ Total Score

Where Day X is Day 28, 56, and 84.

Exploratory – Follow-Up Period

The Change from baseline in SGRQ Total Score at Day 112 and 168 is defined as:

> SGRQ Total Score on Day X – Baseline SGRQ Total Score

Where Day X is Day 112 and Day 168.

The Change from end of treatment in SGRQ Total Score at Day 112 and 168 is defined as:

SGRQ Total Score on Day X – SGRQ Total Score on Day 84

Where Day X is Day 112 and Day 168.

7.2.7.3. Statistical analyses

Change from baseline/end of treatment in SGRQ Total Score and the proportion of responders on the SGRQ Total Score will be analysed using the same techniques as described in Section 7.2.6.3.

7.2.7.4. Subgroup analyses

Subgroup analyses of change from baseline in SGRQ Total Score and the proportion of responders on the SGRQ Total Score by Index exacerbation severity will be conducted as described in Section 7.2.6.4.

7.2.8. Rescue medication use

All participants will record rescue medication use in the eDiary. Rescue medication use will be recorded as the number of occasions of rescue medication use each day.

The Mean Number of Occasions of Rescue Medication Use Per Day is defined as:

(Sum of the number of occasions of rescue medication use each day within the time-period) / (Total number of days with non-missing values within the time-period)

The Percentage of Rescue-Free Days is defined as:

(Sum of the number of days where the number of occasions of rescue medication use is zero within the time-period) / (Total number of days with non-missing values within the time-period)*100

Where the time-period is defined as follows:

Week 1 of the 12-Week Treatment Period: Day 1 to Day 7

Week 2 of the 12-Week Treatment Period: Day 8 to Day 14

Week 3 of the 12-Week Treatment Period: Day 15 to Day 21

Week 4 of the 12-Week Treatment Period: Day 22 to Day 28

Week 5 of the 12-Week Treatment Period: Day 29 to Day 35

Week 6 of the 12-Week Treatment Period: Day 36 to Day 42

Week 7 of the 12-Week Treatment Period: Day 43 to Day 49

Week 8 of the 12-Week Treatment Period: Day 50 to Day 56

Week 9 of the 12-Week Treatment Period: Day 57 to Day 63

Week 10 of the 12-Week Treatment Period: Day 64 to Day 70

Week 11 of the 12-Week Treatment Period: Day 71 to Day 77

Week 12 of the 12-Week Treatment Period: Day 78 to Day of last dose

Over the 12-Week Treatment Period: Day 1 to Day of last dose.

Exploratory – Follow-Up Period

Rescue medication use up to Day 112 will also be summarised by including the time-periods:

Week 13 (Follow-up Period): (Day of last dose + 1) to (Day of last dose + 1) + 6 days

Week 14 (Follow-up Period): (Day of last dose + 7) to (Day of last dose + 1) + 13 days

Week 15 (Follow-up Period): (Day of last dose + 14) to (Day of last dose + 1) + 20 days

Week 16 (Follow-up Period): (Day of last dose + 21) to (Day of last dose + 1) + 27 days

For a subject to be counted in the time periods for rescue medication use, they must have at least one eDiary entry recorded during that time period.

7.2.8.1. Rescue medication use via the clip-on Propeller Sensor for MDI

A subset of participants from countries where the Propeller Sensor for MDI is available will also record rescue medication use via the clip-on Propeller Sensor for MDI. A supportive summary of rescue medication use via the clip-on Propeller Sensor for MDI for these participants will be presented.

Rescue medication use via the clip-on Propeller Sensor for MDI is defined in the same way as rescue medication use via the eDiary, except that the number of actuations will be used instead of the number of occasions in accordance with the way the data is captured.

7.2.8.2. Statistical analyses

The Mean Number of (on-treatment) Occasions of Rescue Medication Use Per Day will be summarised between each treatment group using means, standard deviations, medians, minimum and maximum.

The Percentage of (on-treatment) Rescue-Free Days will be summarised between each treatment group using means, standard deviations, medians, minimum and maximum.

Rescue medication use via the clip-on Propeller Sensor for MDI will be summarised in the same way as rescue medication use via the eDiary.

7.3. Exploratory Efficacy Analyses

7.3.1. Change from Day 84 in Clinic Visit trough FEV_1

Change from Day 84 in clinic visit trough FEV_1 measured post-bronchodilator is defined as:

FEV_1 measured prior to dosing and post-bronchodilator on Day X – Day 84 post-bronchodilator FEV_1

Where Day X is Day112, Day 140 and Day 168.

Change from Day 84 in clinic visit trough FEV_1 measured pre-bronchodilator is defined as:

FEV_1 measured prior to dosing and pre-bronchodilator on Day X – Day 84 pre-bronchodilator FEV_1

Where Day X is Day 112, Day 140 and Day 168.

Participants who discontinue study treatment prior to Day 84 will be excluded from this analysis.

7.3.1.1. Statistical analysis

Change from Day 84 in Clinic Visit trough FEV_1 will be analysed using the same techniques as described for Change from baseline in CAT Total Score in Section 7.2.6.3.

A subgroup analysis of change from Day 84 in FEV_1 will be performed by including a treatment-by-severity-by-Day term in the Bayesian Repeated Measures model.

7.3.2. E-RS:COPD (Evaluating Respiratory Symptoms in COPD)

Change from baseline in E-RS: COPD and subscales will be summarised by treatment group. Exploratory analyses related to E-RS: COPD and subscales may be performed post SAC.

7.3.3. Measures of HCRU related to exacerbations

Unscheduled Healthcare Utilisation will be summarised separately for exacerbation-related, COPD-related or non-COPD related; each summary will be presented by all patients (i.e. moderate and severe index exacerbation combined), and separately by index exacerbation severity.

The number of days of hospital admission for the index and subsequent exacerbations will also be summarised by treatment group.

7.3.3.1. Re-hospitalisation within 30 days of index exacerbation

Re-hospitalisation within 30 days of index exacerbation is defined as 30 days from the date of hospital discharge until the date of next hospital admission (+ 1 day, to account for study day derivation), for participants who were hospitalised for their index exacerbation.

Exacerbation-related, COPD-related and Non-COPD-related hospital admissions are collected in separate eCRFs. The date of hospital admission is not collected in the COPD-related eCRF, therefore the date of next hospital admission will be estimated using the earliest of:

- Date of hospital admission for exacerbation-related hospitalisations
- Date of contact for COPD-related hospitalisations, where the number of inpatient hospitalisation days >0
- Date of hospital admission for non-COPD-related hospitalisations.

The proportion of participants who were re-hospitalised within 30 days of the index exacerbation will be summarised by each treatment arm.

7.3.3.2. Time from resolution of index exacerbation to next exacerbation

Time from resolution of index exacerbation to next exacerbation is defined as time from the date of (Investigator-defined) resolution of index exacerbation until the date of onset of the subsequent exacerbation.

A summary of time from resolution of index exacerbation to next exacerbation will be presented. Participants who did not have a subsequent exacerbation or for whom the index exacerbation was not resolved will be excluded from the summary.

Time from resolution of index exacerbation to next exacerbation will only be derived for the first subsequent exacerbation following the index exacerbation.

7.3.3.3. Subsequent exacerbation treatment type

A summary of the type of treatment for subsequent exacerbations (OCS, antibiotics, or both) may also be presented.

7.3.4. Compliance

Reported compliance for all participants is captured daily in the eDiary from the question "Did you take this morning’s dose of study medication”?

Percentage compliance for each participant is calculated as:

(Sum of the number of days where the question was answered with ‘Y’) / (Number of days from first dose of study treatment to last dose of study treatment) x 100

Overall percentage compliance will be summarised by each treatment group.

7.3.4.1. Number of actuations of double-blind study treatment measured by the clip-on Propeller Sensor

Percentage compliance via the clip-on Propeller Sensor for ELLIPTA in the subset of participants from countries where the Propeller Sensor for ELLIPTA is available is calculated as:

(Sum of the number of days with actuation > 0) / (Number of days from first dose of study treatment to last dose of study treatment) x 100

Overall percentage compliance will be summarised by each treatment group.

7.3.5. Inflammatory/infective markers in blood and sputum in relation to acute exacerbation of COPD

Results of the analysis of blood/spontaneous sputum samples of eosinophil counts and inflammatory/infective mediators/markers will be summarised by treatment group.

Further analyses of inflammatory/infective markers may be performed, for example split by CRP high, CRP low, Procalcitonin high, etc. categories.

7.3.6. Other spirometry measurements

Percent predicted FEV_1, Forced Vital Capacity (FVC), percent predicted FVC and FEV/FVC ratio will be summarised by treatment group.

7.3.7. Other symptoms suggestive of exacerbation

Responses to questions in the eDiary related to symptoms of sputum purulence (colour), fever, sore throat, wheezing and colds collected in the eDiary will be listed by treatment group.

7.3.8. Classification of exacerbating COPD participants and prediction of response to nemiralisib using machine learning techniques

Exploratory analysis of endpoints using machine learning techniques will be performed which will include classification of COPD participants, identification of parameters which describe a responder, and prediction of response to nemiralisib using baseline data. Details of these analyses will be described in a separate RAP and results may be reported separately to the CSR.

8. SAFETY ANALYSES

The safety analyses will be based on the Safety population, unless otherwise specified. The details of the planned displays will be provided in Appendix 11: List of Data Displays.

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs) and Serious (SAEs) will be based on GSK Core Data Standards.

8.1.1. Adverse Events of Special Interest

8.1.1.1. Post-inhalation Cough Immediately Following Dosing

Post-inhalation cough immediately following dosing is an Adverse Event of Special Interest (AESI).

Post-inhalation cough immediately following dosing will be evaluated during study Visits 2-6 in the 12-Week Double-Blind Treatment Period. Investigators (or medically qualified designees) will monitor participants for potential study treatment tolerability issues, including post-inhalation cough, within 5 minutes immediately following dosing.

The percentage of patients experiencing post-inhalation cough following dosing, regardless of whether it was also reported as an AE, overall and by each visit will be summarised for each treatment group. The type of cough, time to onset and duration of cough, and severity will also be summarised.

In addition, any post-inhalation cough immediately following dosing reported as an adverse event during the clinic visit observation or during the course of the study will be summarised by treatment group.

8.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Haematology laboratory tests and liver function tests will be based on GSK Core Data Standards.

8.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified.

8.4. Mortality

A summary of all-cause mortality by treatment will be presented.

9. PHARMACOKINETIC ANALYSES

9.1. Population of Interest

The primary pharmacokinetic analyses will be based on the “Pharmacokinetic” population, unless otherwise specified.

9.2. Drug Concentration Measures

Plasma nemiralisib concentrations of GSK2269557 will be listed and summarised by dose, day and time. Drug levels will be summarised by day (14, 28), dose and time intervals (trough, 0-<1h, 1-6h).

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 13.4.3 Reporting Standards for Pharmacokinetic).

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK Data Standards and statistical principles.

10. POPULATION PK ANALYSIS

A dataset for population PK analysis will be provided by Statistics and Programming based on the NONMEM data specifications in Section 13.8.2.

Conduct of the population PK analyses will be based on the current guidance which contains specific recommendations for working practices, processes and standards for population PK and PK/PD analysis conducted by Clinical Pharmacology Modelling and Simulation (CPMS) [Analysis & Reporting, 2017].

The sparse PK samples will be subjected to a validated population PK model for nemiralisib currently under development.

Details of these analyses will be described in a separate CPMS RAP and results will be reported separately to the CSR. Analyses and reporting of the population PK model will be in accordance with the FDA and EMEA guidance on population PK, PK-PD analyses.

10.1. Derived Pharmacokinetic Parameters

The exposure parameters (e.g. AUC, C_{max}) will be derived from the individual post-hoc estimates from the POP PK model. These will be summarized across dose treatments, subgroups (e.g., gender, race) or as a function of a continuous variable (e.g., age).

11. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

If statistical analyses suggest an effect of nemiralisib on primary and other key clinical endpoints, an integrated longitudinal population dose/exposure versus clinical response on analysis key parameters including FEV_1 and exacerbation rate will be undertaken. Participant characteristics influencing the relationship will be evaluated.

Details of these analyses will be described in a separate CPMS RAP and results will be reported separately to the CSR.

12. REFERENCES

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Dette, H., Bretz, F., Pepelyshev, A. & Pinheiro, J., (2008). Optimal Designs for Dose-Finding Studies. Journal of the American Statistical Association, 103:483, 1255-1237. doi: 10.1198/016214508000000427.

Evidera. (2016). The Exacerbations of Chronic Pulmonary Disease Tool (EXACT®) Patient-Reported Outcome (PRO) USER MANUAL (Version 8.0).

SGRQ-C Manual (2016). St George's Respiratory Questionnaire for COPD Patients (SGRQ-C) Manual (Version 1.3).

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13. APPENDICES

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

13.1.1. Exclusions from Per Protocol Population

Protocol deviations will be reviewed regularly throughout the course of the study, as described in Protocol Deviation Management Plan (PDMP). Deviations which will result in exclusion from the Per Protocol population will be assigned on a case-by-case basis prior to database freeze (DBF).

Decisions on whether or not the subject should be excluded from the PP population because the incorrect treatment was taken, due to the incorrect container being dispensed, will be identified after unblinding (i.e. post DBF). A PD of “incorrect treatment” will be added to the reporting dataset.

13.2. Appendix 2: Assessment Windows

13.2.1. Definitions of Assessment Windows for Analyses

13.2.1.1. Hospital discharge

As per Section 5.1 of the Protocol, if discharge takes place between Day 11 and Day 17 (inclusive), the assessments planned for Day 14 may be completed on the day of discharge. In these cases, for this endpoint only, the FEV_1 assessment will be assigned the hospital discharge FEV_1 assessment and the Day 14 assessment will be missing.

For all other analyses and summaries that include participants who were hospitalised for their index exacerbation, an additional Analysis Timepoint of "HOSPTIAL DISCHARGE" will be derived. However, in the cases where discharge takes place between Day 11 and Day 17 (inclusive), participants will be summarised under DAY 14 and a footnote to say that participants who were discharged at Day 14 are summarised under DAY 14 will be included.

13.2.1.2. EXACT-Defined Recovery for CAT Trigger

Due to software limitations of the electronic PRO device, the study day following EXACT-defined recovery from the index exacerbation is not derived according to the EXACT User Manual. Instead, it has been derived using a 3-day Rolling Average that is calculated as the mean EXACT score [Day X-2, Day X-1, Day X].

13.3. Appendix 3: Study Phases and Treatment Emergent Adverse Events

13.3.1. Study Periods

13.3.1.1. 12-Week Treatment Period

The 12-Week Treatment Period is assigned from Study Day 1 to Study Day 84.

13.3.1.2. 12-Week Follow-Up Period

The 12-Week Follow-up Period is assigned from Study Day 85 to Study Day 168.

13.3.2. Study Phases

Exacerbation events during the 12-Week Treatment Period will be classified according to their occurrence from randomisation until treatment discontinuation/study withdrawal days, as detailed below.

Study Phase	Occurring from randomisation until
On-Treatment during the 12-Week Treatment Period	Treatment Stop Day
On- or Off-Treatment during the 12-Week Treatment Period	Day 84 or Study Withdrawal Day if Treatment Stop Day is < Day 84

13.3.2.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before Randomisation Date
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 6: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

13.3.3. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date & on or before treatment stop date plus 10 days.

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

13.4. Appendix 4: Data Display Standards & Handling Conventions

13.4.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Compound	: \arprod\gsk2269557\mid200879
Analysis Datasets	
• For all interim analyses, except for the End of Treatment Interim Analysis, datasets will be created according to Legacy GSK A&R dataset standards. • For the End of Treatment Interim Analysis and the final reporting effort, datasets will be created according to current CDISC standards	
Generation of RTF Files	
• RTF files will be generated for the final reporting effort.	

13.4.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 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
  • Figures will be produced using PROC SGPLOT in SAS

Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's. • For lab parameters results that contain a character value of '<', or '>', e.g. '<X' or '>X', the parameter value will be imputed with X.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.

Unscheduled Visits	
• Unscheduled visits will be included in summary tables of the worst-case results by potential clinical importance criteria only. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principles 7.01 to 7.13.	

13.4.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PK File	Pop-PK file (CSV format) for the POP-PK analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the data specification detailed in Section 13.8.2 Population Pharmacokinetic (PopPK) Dataset Specification.
NONMEM/PK/PD File	PK/PD file (CSV format) for the PK/PD analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the data specification detailed in the CPMS RAP.

13.5. Appendix 5: Derived and Transformed Data

13.5.1. General

Multiple Measurements at One Analysis Time Point
• Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from Randomisation Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Randomisation Date → Study Day = Ref Date – Randomisation Date
  • Ref Data ≥ Randomisation Date → Study Day = Ref Date – (Randomisation Date) + 1

Time from date of randomisation and time from date of last dose of study treatment

• For endpoints that use the time from the date of randomisation to a reference date, time will be calculated as
  • (Ref Date – Randomisation Date) + 1
• For endpoints that use the time from the date of last dose of study treatment to a reference date, time will be calculated as
  • (Ref Date – (Last Dose Date + 1)) +1

13.5.2. Study Population

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • The cumulative dose will be based on the formula: **Cumulative Dose = Sum of (Number of Days x Total Daily Dose)**

13.5.3. Safety

Adverse Events
AE'S of Special Interest
• Post-inhalation cough is an AE of special interest. The lower level term (LLT) to be included is "coughing after drug inhalation"

13.6. Appendix 6: Reporting Standards for Missing Data

13.6.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) is defined as completing all phases of the study including the last scheduled study visit • A participant is considered to have completed the Treatment Period, if he/she has completed the last on-treatment study visit (Visit 6) • Withdrawn subjects were not replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Withdrawal visits will not be summarised (and will be listed only).

13.6.2. Handling of Missing Data

Element	Reporting Detail

General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument:
	  • These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table.
	  • Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

13.6.2.1. Handling of Missing and Partial Dates

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

Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event:
	  • Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 3: Study Phases and Treatment Emergent Adverse Events.
	  • Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used.
	• Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

Element	Reporting Detail

Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
	  • If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month
	  • If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.
	• The recorded partial date will be displayed in listings.

Age	• The eCRF collects year of birth only. Day and Month will be imputed by Data Management using a PP for the day and PPD for the month • Age will then be derived referenced to the Screening Date • A footnote to say that age has been imputed will be included in any outputs containing age.

13.7. Appendix 7: Values of Potential Clinical Importance

13.7.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Haemoglobin	G/DL	Male 18-64 years	7.1	19.9
		Male 65+ years	7.1	19.9
		Female 18-64 years	7.1	19.9
		Female 65+ years	7.1	19.9
Lymphocytes	GI/L		0.85	4.1
Total Absolute Neutrophil Count	GI/L		1.5	8
Platelet Count	GI/L		31	1499
White Blood Cell count	GI/L	18-64 years	1.1	10.8
		65+ years	1.1	10.8

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	g/L		32	50
Calcium	mmol/L		1.5	3.24
Creatinine		Male 40-49 years	69	160
		Male 50-59 years	67.2	160
		Male 60-69 years	67.2	160
		Male 70+ years	59.2	160
		Female 40-49 years	52.2	160
		Female 50-59 years	53	160
		Female 60-69 years	53	160
		Female 70+ years	55.7	160
Glucose	mmol/L	13-49 years	2.2	27.8
		50+ years	2.2	27.8
Potassium	mmol/L		2.8	6.5
Sodium	mmol/L		120	160
Urea/BUN	mmol/L	13-64 years	2.5	15
		65+ years	2.5	15

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	≥ 2x ULN
AST/SGOT	U/L	High	≥ 2x ULN
AlkPhos	U/L	High	≥ 2x ULN
T Bilirubin	µmol/L	High	≥ 2x ULN
T. Bilirubin + ALT	µmol/L U/L	High	2xULN T.Bilirubin + ≥ 3x ULN ALT
Direct Bilirubin	µmol/L		0 – 6

13.7.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	**Upper**
Absolute			
Absolute QTc Interval	msec		> 530
Absolute PR Interval	msec	< 110	> 240
Absolute QRS Interval	msec	< 75	> 110
Change from Baseline			
Increase from Baseline QTc	msec		> 60

13.7.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	**Upper**
Systolic Blood Pressure	mmHg	< 90	> 140
Diastolic Blood Pressure	mmHg	< 60	> 90
Heart Rate	bpm	< 40	> 110

13.8. Appendix 8: Population Pharmacokinetic (PopPK) Analyses

13.8.1. Population Pharmacokinetic (PopPK) Methodology

All analysis will be performed in the validated Modelling and Analysis Platform (MAP). MAP consists of a Linux desktop containing various modelling applications, including NONMEM, PsN, Pirana, R and RStudio. All software versions used will be documented.

The population PK analysis will be performed in the following sequence of steps:

1. Exploratory data analysis/data check out.
2. Base structural model development.
3. Covariate analysis.
4. Model refinement.
5. Model evaluation.
6. Model application using simulation

The above analysis and reporting steps follow EMEA (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003067.pdf) and FDA population PK guidances (https://www.fda.gov/downloads/drugs/guidances/UCM072137.pdf)

Key components of these regulatory guidelines on population PK are also included in the Global CPMS guidance for pop pk RAP (https://connect.gsk.com/sites/cpms/TandD/Guidances).

13.8.2. Population Pharmacokinetic (PopPK) Dataset Specification

Statistics & Programming, in discussion with CPMS, will provide a NONMEM dataset.

Column headings in NONMEM-ready datasets and specifications should be consistent to minimise the programming process, and facilitate a smooth transfer of projects between users as needed. IDSL standards will be followed where possible.

A list of most common standardised variable names for NONMEM datasets can be found in Table below.

List of Variable Names for NONMEM-Ready Datasets for PopPK Analysis

Variable	Label (Variable description)
C	NONMEM line exclusion identifier
ID	NONMEM subject identifier
STUD	Study ID
SUBJID	Subject identifier for study
SITEID	Unique identifier for a study site
AMT	NONMEM Amount of drug administered then EVID =1- dose event record
UAMT	Unit of AMT (mg)
ADDL	NONMEM Additional dose
CONC	Drug Concentration
UCONC	Unit of CONC (ng/mL)
LNCONC	Natural log of CONC column
ANALYTE	Drug label e.g 557
LLQ	Lower Limit of quantification
LNLLQ	Natural log of LLQ column
DAY	Study day number of record or of dosing
TIME	Plasma sample time after last dose
UTIME	Unit of TIME (h)
DOSE	Dose amount
EVID	NONMEM Event ID If row has dose then EVID=1 else EVID =0 If EVID=1 then this is a dose event record If EVID = 0 then this is an observation record
II	NONMEM Inter-dose interval II=24 – dose every day
SS	Steady state item SS= 1 refers to steady state
MDV	NONMEM Missing data value then MDV=1 else MDV=0
AGE	Subject Age (yrs)
SEX	Subject gender 0 = Male 1 =Female
SEXTEXT	Subject gender text Male or Female
BMI	Baseline Body Mass Index
WT	Baseline Subject weight
CONMED1	Identifier for inhibitor CYP3A4 1 =Yes, 0 = No
CONMED1TXT	Inhibitor Name
CONMED2	Identifier for inducer CYP3A4 1 =Yes, 0 = No
CONMED2TXT	Inducer Name

If observation record e.g CONC has “NA” or “NS” then assign CONC cell as “.”
If observation record e.g CONC has “NQ” or “BQL” then assign CONC cell as “.” and MDV = 1 -this means value can be estimated by model
Missing covariate data should be imputed as “-99.

13.9. Appendix 9: Pharmacokinetic / Pharmacodynamic Analyses

13.9.1. Pharmacokinetic/Pharmacodynamic Methodology

PK-PD analysis of Nemiralisib will be guided by the results of the formal statistical analyses on the key clinical endpoints. The aims of the PK-PD analyses will contribute towards the dose selection in future studies using an integrated longitudinal analysis framework.

The objective is to explore an integrated modelling framework to characterise the longitudinal FEV1 response versus dose (average systemic exposure) during on- & off-treatment phases

$$FEV1_i(t_{ij}) = FEV1_{i,base} \cdot (1 + f(t_{ij}, dose_i, x_i) + \varepsilon_{ij} \text{ with } \varepsilon_{ij} \sim N(0, \sigma 2)$$

A longitudinal nonlinear mixed-effects model will be used to describe the FEV1 response over time measured for each patient (*i*) at each visit (*tij*) with ε denoting the normal distributed residual variability with mean 0 and variance $\sigma 2$. The function *f()* describes the relative change from observed FEV1 at baseline ($FEV1_{,base}$) and any influence of patient characteristics on FEV1 response will be assessed.

Joint relationship between time to first exacerbation and FEV1 change as function of dose/exposure and patient covariates will be assessed.

Details of these analyses will be described in a separate CPMS RAP and results will be reported separately to the CSR.

13.10. Appendix 10: Abbreviations & Trade Marks

13.10.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
QTcF	Fridericia's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SDTM	Study Data Tabulation Model
SGRQ	St. George's Respiratory Questionnaire
SGRQ-C	St. George's Respiratory Questionnaire for COPD Patients
SOP	Standard Operation Procedure

TFL	Tables, Figures & Listings

13.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
COPD Assessment Test (CAT)
ELLIPTA
HARP

Trademarks not owned by the GlaxoSmithKline Group of Companies
E-RS: COPD
EXACT-PRO
NONMEM
Propeller Sensor
SAS
SGRQ

13.11. Appendix 11: List of Data Displays

13.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays for SAC:

Section	Tables	Figures
Study Population	1.1 to 1.28	Not applicable
Efficacy	2.1 to 2.100	2.1 to 2.20
Safety	3.1 to 3.31	3.1 to 3.3
Pharmacokinetic	4.1 to 4.2	Not applicable
Section	**Listings**	
ICH Listings	1 to 27	
Other Listings	28 to 30	

13.11.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 12: Example Mock Shells for Data Displays.

13.11.3. Deliverables

Delivery	Description
IA	Interim Analysis (except the End of treatment Phase Interim Analysis)
EOT	End of Treatment Phase Interim Analysis
SAC	Statistical Analysis Complete

13.11.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	MITT	ES8	Summary of Subject Status and Reason for Study Withdrawal		EOT, SAC
1.2.	MITT	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		EOT, SAC
1.3.	APE	ES6	Summary of Screening Status and Reasons for Screen Failure		SAC
1.4.	APE	NS1	Summary of Number of Participants by Country and Site ID		SAC
Protocol Deviation					
1.5.	MITT	DV1	Summary of Important Protocol Deviations		SAC
1.6.	MITT	IE1	Summary of Inclusion/Exclusion Criteria Deviations		SAC
Population Analysed					
1.7.	MITT	SP1	Summary of Study Populations		SAC
1.8.	MITT	SP2	Summary of Exclusions from the Per Protocol/Safety Population		SAC
Demographic and Baseline Characteristics					
1.9.	MITT	DM1	Summary of Demographic Characteristics	Use the following ranges for the Age Group row: ≤64; 65-74; ≥75	EOT, SAC
1.10.	APE	DM11	Summary of Age Ranges		SAC
1.11.	MITT	DM5	Summary of Race and Racial Combinations		SAC
1.12.	MITT	MH4	Summary of Past Medical Conditions		EOT, SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.13.	MITT	MH4	Summary of Current Medical Conditions		EOT, SAC
1.14.	MITT	FH1	Summary of Family History of Cardiovascular Risk Factors		EOT, SAC
1.15.	MITT	SU1	Summary of Smoking History at Screening		EOT, SAC
1.16.	MITT	SU1	Summary of Smoking Status Over the 12-Week Treatment Period		EOT, SAC
1.17.	MITT	SU1	Summary of Smoking Status Over the 12-Week Follow-Up Period		SAC
1.18.	MITT	Example 7	Summary of COPD Duration at Screening		EOT, SAC
1.19.	MITT	Example 1	Summary of COPD Exacerbation History at Screening	Use categories 0;1;2;3;≥3. Summarise moderate/severe, moderate; severe Include 7-Day History of COPD Exacerbations	EOT, SAC
1.20.	MITT	Example 1	Summary of COPD Exacerbation History at Screening by Country		EOT, SAC
Concomitant Medications					
1.21.	MITT	Example 14	Summary of Baseline COPD Maintenance Therapy		EOT, SAC
1.22.	MITT	Example 15	Summary of On-Treatment COPD Maintenance (Step-up) Therapy		EOT, SAC
1.23.	MITT	CM1	Summary of Concomitant Medications During 12-Week Treatment Period		EOT, SAC
1.24.	MITT	Example 16	Summary of OCS Use		EOT, SAC
1.25.	MITT	CM1	Summary of Concomitant Medications During 12-Week Follow-Up Period		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure and Treatment Compliance					
1.26.	MITT	EX1	Summary of Exposure to Study Treatment		EOT, SAC
1.27.	MITT	Example 2	Summary of Treatment Compliance		EOT, SAC
1.28.	MITT	Example 2	Summary of Actuations of Study Treatment Measured by the Clip-on Propeller Sensor		SAC

13.11.5. Efficacy Tables

13.11.5.1. Efficacy tables for Interim Analysis 1

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in Clinic Visit trough FEV_1					
2.1.	MITT	Example 3	Summary of FEV_1 (L)	Include pre- and post-bronchodilator	IA1
2.2.	MITT	Example 3	Summary of FEV_1 (L) by Index Exacerbation Severity	Include pre- and post-bronchodilator Include additional row for hospital discharge visit for Severe group	IA1
2.3.	MITT	Example 3	Summary of Change from Baseline in FEV_1 (L)	Include pre- and post-bronchodilator	IA1
2.4.	MITT	Example 3	Summary of Change from Baseline in FEV_1 (L) by Index Exacerbation Severity	Include pre- and post-bronchodilator. Include additional row for hospital discharge visit for Severe group	IA1
2.5.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 at Day 14 Measured Post-bronchodilator (Dose Response Model)		IA1

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.6.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 at Day 28 Measured Post-bronchodilator (Dose Response Model)		IA1
2.7.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity (Dose Response Model)		IA1
2.8.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity (Dose Response Model)		IA1
2.9.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) Measured Post-bronchodilator (Repeated Measures Model)		IA1
2.10.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) Measured Pre-bronchodilator (Repeated Measures Model)		IA1
2.11.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) Measured Post-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		IA1
2.12.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) Measured Pre-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		IA1
Rate of Exacerbations					
2.13.	MITT	Example 5	Summary of On-treatment Exacerbations		IA1
2.14.	MITT	Example 5	Summary of On-treatment Exacerbations by Index Exacerbation Severity		IA1
EXAcerbations of Chronic Pulmonary Disease Tool - Patient Reported Outcome (EXACT)					
2.15.	MITT	Example 9	Summary of Proportion of Participants Achieving the EXACT-definition of Recovery by Visit	Exclude statistical analysis information (summary only)	IA1

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.16.	MITT	Example 9	Summary of Proportion of Participants Achieving the EXACT-definition of Recovery by Index Exacerbation Severity	Exclude statistical analysis information (summary only)	IA1
Other Spirometry Measures					
2.17.	MITT	Example 3	Summary of Spirometry Measurements		IA1
2.18.	MITT	Example 3	Summary of Change from Baseline in Spirometry Measurements		IA1

13.11.5.2. Efficacy tables for Interim Analysis 2

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in Clinic Visit trough FEV_1					
2.1.	MITT	Example 3	Summary of FEV_1 (L)	Include pre- and post-bronchodilator	IA2
2.2.	MITT	Example 3	Summary of FEV_1 (L) by Index Exacerbation Severity	Include pre- and post-bronchodilator Include additional row for hospital discharge visit for Severe group	IA2
2.3.	MITT	Example 3	Summary of Change from Baseline in FEV_1 (L)	Include pre- and post-bronchodilator	IA2
2.4.	MITT	Example 3	Summary of Change from Baseline in FEV_1 (L) by Index Exacerbation Severity	Include pre- and post-bronchodilator. Include additional row for hospital discharge visit for Severe group	IA2
2.5.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 14 Measured Post-bronchodilator (Dose Response Model)		IA2
2.6.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 28 Measured Post-bronchodilator (Dose Response Model)		IA2
2.7.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 56 Measured Post-bronchodilator (Dose Response Model)		IA2
2.8.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 84 Measured Post-bronchodilator (Dose Response Model)		IA2
2.9.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate (Dose Response Model)		IA2
2.10.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity: Severe (Dose Response Model)		IA2

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.11.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate (Dose Response Model)		IA2
2.12.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity: Severe (Dose Response Model)		IA2
2.13.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 56 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate (Dose Response Model)		IA2
2.14.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 56 Measured Post-bronchodilator by Index Exacerbation Severity: Severe (Dose Response Model)		IA2
2.15.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 84 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate (Dose Response Model)		IA2
2.16.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 84 Measured Post-bronchodilator by Index Exacerbation Severity: Severe (Dose Response Model)		IA2
2.17.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) Measured Post-bronchodilator (Repeated Measures Model)		IA2
2.18.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) Measured Pre-bronchodilator (Repeated Measures Model)		IA2
2.19.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) Measured Post-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		IA2

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.20.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) Measured Pre-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		IA2
2.21.	MITT	Example 32	Summary of Efficiency Ratio for Possible Adaptions to Randomization Ratio		IA2
Rate of Exacerbations					
2.22.	MITT	Example 5	Summary of On-treatment (Moderate/Severe) Subsequent Exacerbations		IA2
2.23.	MITT	Example 5	Summary of On-treatment (Moderate/Severe) Subsequent Exacerbations by Index Exacerbation Severity		IA2
2.24.	MITT	Example 6	Statistical Analysis of On-treatment (Moderate/Severe) Subsequent Exacerbations		IA2
2.25.	MITT	Example 6	Subgroup Analysis of On-treatment (Moderate/Severe) Subsequent Exacerbations by Index Exacerbation Severity		IA2
EXAcerbations of Chronic Pulmonary Disease Tool - Patient Reported Outcome (EXACT)					
2.26.	MITT	Example 9	Statistical Analysis of Proportion of Participants Achieving the EXACT-definition of Recovery by Visit		IA2
2.27.	MITT	Example 9	Subgroup Analysis of Proportion of Participants Achieving the EXACT-definition of Recovery by Index Exacerbation Severity		IA2
COPD Assessment Test (CAT)					
2.28.	MITT	Example 3	Summary of Change from Baseline in CAT Total Score		IA2
2.29.	MITT	Example 9	Statistical Analysis of Proportion of Responders Using the CAT Total Score by Visit		IA2
2.30.	MITT	Example 11	Statistical Analysis of Change from Baseline in CAT Total Score (Repeated Measures Model)		IA2

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
St. George's Respiratory Questionnaire (SGRQ)					
2.31.	MITT	Example 3	Summary of Change from Baseline in SGRQ Total Score		IA2
2.32.	MITT	Example 9	Statistical Analysis of Proportion of Responders Using the SGRQ Total Score by Visit		IA2
2.33.	MITT	Example 11	Statistical Analysis of Change from Baseline in SGRQ Total Score (Repeated Measures Model)		IA2
Rescue Medication Use					
2.34.	MITT	RM1	Summary of Mean Number of Occasions of Rescue Medication Use Per Day		IA2
2.35.	MITT	RM1	Summary of Percentage of Rescue-Free Days		IA2
Other Spirometry Measures					
2.36.	MITT	Example 3	Summary of Spirometry Measurements		IA2
2.37.	MITT	Example 3	Summary of Change from Baseline in Spirometry Measurements		IA2

13.11.5.3. Efficacy tables for End of Treatment Interim Analysis and SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in Clinic Visit trough FEV_1					
2.1.	MITT	Example 3	Summary of FEV_1 (L)	Include pre- and post-bronchodilator	EOT, SAC
2.2.	MITT	Example 3	Summary of FEV_1 (L) by Index Exacerbation Severity	Include pre- and post-bronchodilator Include additional row for hospital discharge visit for Severe group	EOT, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.3.	MITT	Example 3	Summary of Change from Baseline in FEV_1 (L)	Include pre- and post-bronchodilator	EOT, SAC
2.4.	MITT	Example 3	Summary of Change from Baseline in FEV_1 (L) by Index Exacerbation Severity	Include pre- and post-bronchodilator. Include additional row for hospital discharge visit for Severe group	EOT, SAC
2.5.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 14 Measured Post-bronchodilator (Dose Response Model)		EOT, SAC
2.6.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 28 Measured Post-bronchodilator (Dose Response Model)		EOT, SAC
2.7.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 56 Measured Post-bronchodilator (Dose Response Model)		EOT, SAC
2.8.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 84 Measured Post-bronchodilator (Dose Response Model)		EOT, SAC
2.9.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate (Dose Response Model)		EOT, SAC
2.10.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity: Severe (Dose Response Model)		EOT, SAC
2.11.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate (Dose Response Model)		EOT, SAC
2.12.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity: Severe (Dose Response Model)		EOT, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.13.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 56 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate (Dose Response Model)		EOT, SAC
2.14.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 56 Measured Post-bronchodilator by Index Exacerbation Severity: Severe (Dose Response Model)		EOT, SAC
2.15.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 84 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate (Dose Response Model)		EOT, SAC
2.16.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 84 Measured Post-bronchodilator by Index Exacerbation Severity: Severe (Dose Response Model)		EOT, SAC
2.17.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) Measured Post-bronchodilator (Repeated Measures Model)		EOT, SAC
2.18.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) Measured Post-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		EOT, SAC
Change from Hospital Discharge in Clinic Visit trough FEV_1					
2.19.	MITT	Example 3	Summary of Change from Hospital Discharge in FEV_1 (L)	Include pre- and post-bronchodilator	EOT, SAC
2.20.	MITT	Example 11	Statistical Analysis of Change from Hospital Discharge in FEV_1 (L) Measured Post-bronchodilator (Repeated Measures Model)		EOT, SAC
2.21.	MITT	Example 11	Statistical Analysis of Change from Hospital Discharge in FEV_1 (L) Measured Pre-bronchodilator (Repeated Measures Model)		EOT, SAC
Change from Day 84 in Clinic Visit trough FEV_1					
2.22.	MITT	Example 3	Summary of Change from Day 84 in FEV_1 (L)	Include pre- and post-bronchodilator	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.23.	MITT	Example 11	Statistical Analysis of Change from Day 84 in FEV_1 (L) Measured Post-bronchodilator (Repeated Measures Model)		SAC
2.24.	MITT	Example 11	Statistical Analysis of Change from Day 84 in FEV_1 (L) Measured Pre-bronchodilator (Repeated Measures Model)		SAC
2.25.	MITT	Example 11	Subgroup Analysis of Change from Day 84 in FEV_1 (L) Measured Post-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		SAC
2.26.	MITT	Example 11	Subgroup Analysis of Change from Day 84 in FEV_1 (L) Measured Pre-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		SAC
Rate of Exacerbations					
2.27.	MITT	Example 5	Summary of On-treatment (Moderate/Severe) Subsequent Exacerbations		EOT, SAC
2.28.	MITT	Example 5	Summary of On-treatment (Mild/Moderate/Severe) Subsequent Exacerbations		EOT, SAC
2.29.	MITT	Example 5	Summary of On-treatment (Moderate/Severe) Subsequent Exacerbations by Index Exacerbation Severity		EOT, SAC
2.30.	MITT	Example 6	Statistical Analysis of On-treatment (Moderate/Severe) Subsequent Exacerbations		EOT, SAC
2.31.	MITT	Example 6	Statistical Analysis of On-treatment (Mild/Moderate/Severe) Subsequent Exacerbations		EOT, SAC
2.32.	MITT	Example 6	Subgroup Analysis of On-treatment (Moderate/Severe) Subsequent Exacerbations by Index Exacerbation Severity		EOT, SAC
2.33.	MITT	Example 5	Summary of On-treatment Subsequent Exacerbations by Index Exacerbation Type		EOT, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.34.	MITT	Example 5	Summary of On-treatment Subsequent Exacerbations by Number of Exacerbations in Previous 12 Months		EOT, SAC
2.35.	MITT	Example 5	Summary of On-or Off-treatment (Moderate/Severe) Subsequent Exacerbations During the 12-Week Treatment Period		EOT, SAC
2.36.	MITT	Example 5	Summary of On-or Off-treatment (Mild/Moderate/Severe) Subsequent Exacerbations During the 12-Week Treatment Period		EOT, SAC
2.37.	MITT	Example 5	Summary of On-or Off-treatment (Moderate/Severe) Subsequent Exacerbations During the 12-Week Treatment Period by Index Exacerbation Severity		EOT, SAC
2.38.	MITT	Example 6	Statistical Analysis of On- or Off-treatment (Moderate/Severe) Subsequent Exacerbations During the 12-Week Treatment Period		EOT, SAC
2.39.	MITT	Example 6	Statistical Analysis of On- or Off-treatment (Mild/Moderate/Severe) Subsequent Exacerbations During the 12-Week Treatment Period		EOT, SAC
2.40.	MITT	Example 6	Subgroup Analysis of On- or Off-treatment (Moderate/Severe) Subsequent Exacerbations During the 12-Week Treatment Period by Index Exacerbation Severity		EOT, SAC
2.41.	MITT	Example 5	Summary of Off-treatment (Moderate/Severe) Subsequent Exacerbations		EOT, SAC
2.42.	MITT	Example 5	Summary of Off-treatment (Moderate/Severe) Subsequent Exacerbations by Index Exacerbation Severity		EOT, SAC
2.43.	MITT	Example 6	Statistical Analysis of Off-treatment (Moderate/Severe) Subsequent Exacerbations		EOT, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.44.	MITT	Example 6	Subgroup Analysis of Off-treatment (Moderate/Severe) Subsequent Exacerbations by Index Exacerbation Severity		EOT, SAC
2.45.	MITT	Example 5	Summary of On- and Off-treatment (Moderate/Severe) Subsequent Exacerbations During the 24-Week Study Period		EOT, SAC
2.46.	MITT	Example 5	Summary of On- and Off-treatment (Moderate/Severe) Subsequent Exacerbations During the 24-Week Study Period by Index Exacerbation Severity		EOT, SAC
2.47.	MITT	Example 6	Statistical Analysis of On- and Off-treatment (Moderate/Severe) Subsequent Exacerbations During the 24-Week Study Period		EOT, SAC
2.48.	MITT	Example 6	Subgroup Analysis of On- and Off-treatment (Moderate/Severe) Subsequent Exacerbations During the 24-Week Study Period by Index Exacerbation Severity		EOT, SAC
Time to Next Exacerbation					
2.49.	MITT	Example 8	Statistical Analysis of Time to next On-treatment Exacerbation		EOT, SAC
2.50.	MITT	Example 8	Subgroup Analysis of Time to next On-treatment Exacerbation by Index Exacerbation Severity		EOT, SAC
2.51.	MITT	Example 8	Statistical Analysis of Time to next On- or Off-treatment Exacerbation During the 12-Week Treatment Period		EOT, SAC
2.52.	MITT	Example 8	Statistical Analysis of Time to next On- or Off-treatment Exacerbation During the 12-Week Treatment Period by Index Exacerbation Severity		EOT, SAC
2.53.	MITT	Example 8	Statistical Analysis of Time to Next Exacerbation Following Cessation of Study Treatment		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.54.	MITT	Example 8	Statistical Analysis of Time to Next Exacerbation Following Cessation of Study Treatment by Index Exacerbation Severity		SAC
EXAcerbations of Chronic Pulmonary Disease Tool - Patient Reported Outcome (EXACT)					
2.55.	MITT	Example 9	Statistical Analysis of Proportion of Participants Achieving the EXACT-definition of Recovery by Visit		EOT, SAC
2.56.	MITT	Example 9	Subgroup Analysis of Proportion of Participants Achieving the EXACT-definition of Recovery by Index Exacerbation Severity		EOT, SAC
2.57.	MITT	Example 8	Summary and Statistical Analysis of Time to EXACT-defined Recovery		EOT, SAC
2.58.	MITT	Example 10	Summary of Severity of Subsequent HCRU-defined Exacerbation During 12-Week Treatment Period	Also split by moderate and severe	EOT, SAC
2.59.	MITT	Example 10	Summary of Severity of Subsequent HCRU-Defined Exacerbation During 12-Week Follow-up Period	Also split by moderate and severe	EOT, SAC
COPD Assessment Test (CAT)					
2.60.	MITT	Example 3	Summary of Change from Baseline in CAT Total Score		EOT, SAC
2.61.	MITT	Example 3	Summary of Change from Baseline in CAT Total Score by Index Exacerbation Severity		EOT, SAC
2.62.	MITT	Example 9	Statistical Analysis of Proportion of Responders Using the CAT Total Score by Visit		EOT, SAC
2.63.	MITT	Example 9	Subgroup Analysis of Proportion of Responders Using the CAT Total Score by Visit by Index Exacerbation Severity		EOT, SAC
2.64.	MITT	Example 11	Statistical Analysis of Change from Baseline in CAT Total Score (Repeated Measures Model)		EOT, SAC
2.65.	MITT	Example 11	Subgroup Analysis of Change from Baseline in CAT Total Score (Repeated Measures Model) by Index Exacerbation Severity		EOT, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.66.	MITT	Example 3	Summary of Change from End of Treatment in CAT Total Score		EOT, SAC
2.67.	MITT	Example 3	Summary of Change from End of Treatment in CAT Total Score by Index Exacerbation Severity		EOT, SAC
2.68.	MITT	Example 11	Statistical Analysis of Change from End of Treatment in CAT Total Score (Repeated Measures Model)		EOT, SAC
2.69.	MITT	Example 11	Subgroup Analysis of Change from End of Treatment in CAT Total Score (Repeated Measures Model) by Index Exacerbation Severity		EOT, SAC
St. George's Respiratory Questionnaire (SGRQ)					
2.70.	MITT	Example 3	Summary of Change from Baseline in SGRQ Total Score		EOT, SAC
2.71.	MITT	Example 3	Summary of Change from Baseline in SGRQ Total Score by Index Exacerbation Severity		EOT, SAC
2.72.	MITT	Example 9	Statistical Analysis of Proportion of Responders on the SGRQ Total Score by Visit		EOT, SAC
2.73.	MITT	Example 9	Subgroup Analysis of Proportion of Responders on the SGRQ Total Score by Index Exacerbation Severity		EOT, SAC
2.74.	MITT	Example 11	Statistical Analysis of Change from Baseline SGRQ Total Score (Repeated Measures Model)		EOT, SAC
2.75.	MITT	Example 11	Subgroup Analysis of Change from Baseline SGRQ Total Score (Repeated Measures Model) by Index Exacerbation Severity		EOT, SAC
2.76.	MITT	Example 3	Summary of Change from End of Treatment in SGRQ Total Score		EOT, SAC
2.77.	MITT	Example 3	Summary of Change from End of Treatment in SGRQ Total Score by Index Exacerbation Severity		EOT, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.78.	MITT	Example 11	Statistical Analysis of Change from End of Treatment in SGRQ Total Score (Repeated Measures Model)		EOT, SAC
2.79.	MITT	Example 11	Subgroup Analysis of Change from End of Treatment in SGRQ Total Score (Repeated Measures Model) by Index Exacerbation Severity		EOT, SAC
E-RS: COPD					
2.80.	MITT	Example 3	Summary of Change from Baseline in E-RS: COPD and Subscales		SAC
Rescue Medication Use					
2.81.	MITT	RM1	Summary of Mean Number of Occasions of Rescue Medication Use Per Day		EOT, SAC
2.82.	MITT	RM1	Summary of Percentage of Rescue-Free Days		EOT, SAC
2.83.	MITT	RM1	Summary of Mean Number of Actuations of Rescue Medication Use Per Day Via the Clip-on Propeller Sensor for MDI		EOT, SAC
2.84.	MITT	RM1	Summary of Percentage of Rescue-Free Days Via the Clip-on Propeller Sensor for MDI		EOT, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Compliance					
2.85.	MITT	IP1	Summary of Overall IP Compliance		EOT, SAC
2.86.	MITT	IP1	Summary of Overall IP Compliance Via the Clip-on Propeller Sensor for ELLIPTA		EOT, SAC
Healthcare Resource Utilisation					
2.87.	MITT	Example 19	Summary of Exacerbation Related Unscheduled Healthcare Resource Utilisation		EOT, SA
2.88.	MITT	Example 19	Summary of Exacerbation Related Unscheduled Healthcare Resource Utilization by Index Exacerbation Severity		EOT, SA
2.89.	MITT	Example 21	Summary of Exacerbation Related Hospitalizations		EOT, SAC
2.90.	MITT	Example 19	Summary of COPD Related Unscheduled Healthcare Resource Utilisation		EOT, SAC
2.91.	MITT	Example 19	Summary of COPD Related Unscheduled Healthcare Resource Utilisation by Index Exacerbation Severity		EOT, SAC
2.92.	MITT	Example 20	Summary of Non-COPD Related Unscheduled Healthcare Resource Utilisation		EOT, SAC
2.93.	MITT	Example 20	Summary of Non-COPD Related Unscheduled Healthcare Resource Utilisation by Index Exacerbation Severity		EOT, SAC
2.94.	MITT	Example 22	Summary of Re-hospitalization Within 30 days of Index Exacerbation		EOT, SAC
2.95.	MITT	Example 24	Summary of Time from Resolution of Index Exacerbation to Next Exacerbation		EOT, SAC
2.96.	MITT	Example 23	Summary of Subsequent Exacerbation Treatment		EOT, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Other Spirometry Measures					
2.97.	MITT	Example 3	Summary of Spirometry Measurements		EOT, SAC
2.98.	MITT	Example 3	Summary of Change from Baseline in Spirometry Measurements		EOT, SAC
Inflammatory/infective Markers in Blood and Sputum					
2.99.	MITT	Example 3	Summary of Inflammatory Markers in Blood		SAC
2.100.	MITT	Example 3	Summary of Inflammatory Markers in Sputum		SAC

13.11.6. Efficacy Figures

13.11.6.1. Efficacy Figures for Interim Analysis 1

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in Clinic Visit trough FEV_1					
2.1.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 Measured Post-bronchodilator		IA1
2.2.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 Measured Post-bronchodilator		IA1
2.3.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 56 measured post-bronchodilator		IA1
2.4.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		IA1
2.5.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		IA1
2.6.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		IA1
2.7.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		IA1

13.11.6.2. Efficacy Figures for Interim Analysis 2

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in Clinic Visit trough FEV_1					
2.1.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 Measured Post-bronchodilator		IA2
2.2.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 Measured Post-bronchodilator		IA2
2.3.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 56 Measured Post-bronchodilator		IA2
2.4.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 84 Measured Post-bronchodilator		IA2
2.5.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		IA2
2.6.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		IA2
2.7.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		IA2
2.8.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		IA2
2.9.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 56 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		IA2

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.10.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 56 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		IA2
2.11.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 84 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		IA2
2.12.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 84 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		IA2
2.13.	MITT	Example 31	Plot of Repeated Measures Model of Change from Baseline in FEV_1 Measured Post-bronchodilator		IA2
2.14.	MITT	Example 31	Plot of Repeated Measures Model of Change from Baseline in FEV_1 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		IA2
2.15.	MITT	Example 31	Plot of Repeated Measures Model of Change from Baseline in FEV_1 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		IA2
Time to Next Exacerbation					
2.16.	MITT	Example 30	Kaplan-Meier Plot of Time to Next On-treatment (Moderate/Severe) Exacerbation		IA2
2.17.	MITT	Example 30	Kaplan-Meier Plot of Time to Next On-treatment (Mild/Moderate/Severe) Exacerbation		IA2

13.11.6.3. Efficacy Figures for End of Treatment Interim Analysis and SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in Clinic Visit trough FEV_1					
2.1.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 Measured Post-bronchodilator		EOT, SAC
2.2.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 Measured Post-bronchodilator		EOT, SAC
2.3.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 56 Measured Post-bronchodilator		EOT, SAC
2.4.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 84 Measured Post-bronchodilator		EOT, SAC
2.5.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		EOT, SAC
2.6.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		EOT, SAC
2.7.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		EOT, SAC
2.8.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		EOT, SAC
2.9.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 56 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		EOT, SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.10.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 56 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		EOT, SAC
2.11.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 84 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		EOT, SAC
2.12.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 84 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		EOT, SAC
2.13.	MITT	Example 31	Plot of Repeated Measures Model of Change from Baseline in FEV_1 Measured Post-bronchodilator		EOT, SAC
2.14.	MITT	Example 31	Plot of Repeated Measures Model of Change from Baseline in FEV_1 Measured Post-bronchodilator by Index Exacerbation Severity: Moderate		EOT, SAC
2.15.	MITT	Example 31	Plot of Repeated Measures Model of Change from Baseline in FEV_1 Measured Post-bronchodilator by Index Exacerbation Severity: Severe		EOT, SAC
Time to Next Exacerbation					
2.16.	MITT	Example 30	Kaplan-Meier Plot of Time to Next On-treatment (Moderate/Severe) Exacerbation		EOT, SAC
2.17.	MITT	Example 30	Kaplan-Meier Plot of Time to Next On-treatment (Mild/Moderate/Severe) Exacerbation		EOT, SAC
2.18.	MITT	Example 30	Kaplan-Meier Plot of Time to Next On-or Off-treatment (Moderate/Severe) Exacerbation During the 12-Week Treatment Period		EOT, SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.19.	MITT	Example 30	Kaplan-Meier Plot of Time to Next On-or Off-treatment (Mild/Moderate/Severe) Exacerbation During the 12-Week Treatment Period		EOT, SAC
2.20.	MITT	Example 30	Kaplan-Meier Plot of Time to Next (Moderate/Severe) Exacerbation Following Cessation of Study Treatment		SAC

13.11.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	Safety	AE1	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term		EOT, SAC
3.2.	Safety	AE1	Summary of Post-Treatment Adverse Events by System Organ Class and Preferred Term		SAC
3.3.	Safety	AE3	Summary of Common (>=5%) Treatment Emergent Adverse Events by Overall Frequency		EOT, SAC
3.4.	Safety	AE1	Summary of Drug-Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term		EOT, SAC
3.5.	Safety	AE15	Summary of Common (>=5%) Non-serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.6.	Safety	AE1	Summary of Treatment Emergent Adverse Events for Participants with Absolute Neutrophil Count Below Lower Value of PCI		SAC
Serious and Other Significant Adverse Events					
3.7.	Safety	AE16	Summary of Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)		EOT, SAC
3.8.	Safety	AE16	Summary of Fatal Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	Only with subcategory: Number of Fatal SAEs	EOT, SAC
3.9.	Safety	AE1	Summary of Serious Treatment Emergent Drug-related Adverse Events by System Organ Class and Preferred Term		SAC
3.10.	Safety	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term		EOT, SAC
3.11.	Safety	AE1	Summary of Post-treatment Serious Adverse Events by System Organ Class and Preferred Term		SAC
3.12.	Safety	AE1	Summary of Treatment Emergent Adverse Events of Special Interest by Lower Level Term		EOT, SAC
3.13.	Safety	Example 17	Summary of Post-Inhalation Cough by Visit		EOT, SAC
3.14.	Safety	Example 28	Summary of Post-Inhalation Cough by Visit and Cough Type		EOT, SAC
3.15.	Safety	Example 33	Summary of Post-Inhalation (PI) Cough at Any Visit		EOT, SAC
Laboratory: Chemistry					
3.16.	Safety	LB1	Summary of Chemistry Data		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.17.	Safety	LB17	Summary of Worst Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline		EOT, SAC
Laboratory: Hematology					
3.18.	Safety	LB1	Summary of Hematology Data		SAC
3.19.	Safety	LB1	Summary of Change from Baseline in Hematology	Only for WBC, lymphocytes, neutrophils	SAC
3.20.	Safety	LB17	Summary of Worst Case Hematology Results by PCI Criteria Post-Baseline Relative to Baseline		EOT, SAC
Laboratory: Hepatobiliary (Liver)					
3.21.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting		SAC
3.22.	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities		SAC
ECG					
3.23.	Safety	EG1	Summary of ECG Findings		EOT, SAC
3.24.	Safety	EG2	Summary of ECG Values by Visit	For the following parameters: QTcF, QTcB, PR, Heart rate	EOT, SAC
3.25.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit	For the following parameters: QTcF, QTcB, PR, Heart rate	SAC
3.26.	Safety	Example 27	Summary of QTcF Categories		SAC
3.27.	Safety	Example 27	Summary of QTcB Categories		SAC
3.28.	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category		SAC
3.29.	Safety	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category		SAC
3.30.	Safety	Example 25	Summary of ECG Abnormalities for Participants with Any Abnormal ECG Interpretation		EOT, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
3.31.	Safety	VS1	Summary of Vital Signs		SAC
3.32.	Safety	VS7	Summary of Worst Case Vital Signs Results by PCI Criteria Post-Baseline Relative to Baseline		EOT, SAC

13.11.8. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory					
3.1.	Safety	LB7	LFT Shift from Baseline to Maximum		EOT, SAC
3.2.	Safety	Example 13	Median (range) Absolute Neutrophil Count by Time and Treatment		SAC
ECG					
3.3.	Safety	EG8	Distribution of QTcF Change by Time and Treatment		SAC

13.11.9. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic Concentration-Time Data					
4.1.	PK	PK01	Summary of Plasma GSK2269557 Pharmacokinetic Concentration-Time Data		SAC
4.2.	PK	PK05	Summary of Log-Transformed Plasma GSK2269557 Pharmacokinetic Concentration-Time Data		SAC

13.11.10. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	APE	ES7	Listing of Reasons for Screen Failure		SAC
2.	MITT	ES2	Listing of Reasons for Study Withdrawal		SAC
3.	MITT	SD2	Listing of Reasons for Study Treatment Discontinuation		SAC
4.	MITT	BL1	Listing of Participants for Whom the Treatment Blind was Broken		SAC
5.	MITT	TA1	Listing of Planned and Actual Treatments		SAC
Protocol Deviations					
6.	MITT	DV2	Listing of Important Protocol Deviations		SAC
7.	MITT	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations		SAC
Populations Analysed					
8.	MITT	SP3	Listing of Participants Excluded from Per Protocol Population	For participants excluded from MITT population (i.e. participants in the MITT but not in PP)	SAC
Demographic and Baseline Characteristics					
9.	MITT	DM2	Listing of Demographic Characteristics		SAC
10.	MITT	DM9	Listing of Race		SAC
Prior and Concomitant Medications					
11.	MITT	CP_CM3	Listing of Concomitant Medications		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure and Treatment Compliance					
12.	Safety	EX3	Listing of Exposure Data		SAC
Adverse Events					
13.	Safety	AE8	Listing of All Adverse Events		SAC
14.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		SAC
15.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		SAC
Serious and Other Significant Adverse Events					
16.	Safety	AE8	Listing of Fatal Serious Adverse Events		SAC
17.	Safety	AE8	Listing of Non-Fatal Serious Adverse Events		SAC
18.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event		SAC
19.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment		SAC
Hepatobiliary (Liver)					
20.	Safety	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events		SAC
21.	Safety	SU2	Listing of Substance Use for Participants with Liver Stopping Events		SAC
All Laboratory					
22.	Safety	LB5	Listing of All Chemistry Data for Participants with Any Value of Potential Clinical Importance		SAC
23.	Safety	LB14	Listing of Chemistry Data with Character Results		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
24.	Safety	LB5	Listing of All Hematology Data for Participants with Any Value of Potential Clinical Importance		SAC
25.	Safety	LB14	Listing of all Hematology Data with Character Results		SAC
ECG					
26.	Safety	EG3	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance		SAC
27.	Safety	EG5	Listing of All ECG Findings for Participants with an Abnormal Finding		SAC

13.11.11. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
28.	MITT	Example 29	Listing of Subjects who Received Incorrect Medication		SAC
29.	PK	PK07	Listing of Plasma Pharmacokinetic Concentration-Time Data		SAC
30.	Safety	EG5	Listing of All ECG Findings for Subjects with an Abnormal Finding		SAC

13.12. Appendix 12: Example Mock Shells for Data Displays

13.12.1. Example shell 1

Example Shell X
Protocol: XYZ100001 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of COPD Exacerbation History at Screening

	Treatment A (N=100)	Treatment B (N=100)	Total (N=200)
Moderate COPD exacerbations			
n	X	X	X
0	xx (x%)	xx (x%)	xx (x%)
1	xx (x%)	xx (x%)	xx (x%)
>=2	xx (x%)	xx (x%)	xx (x%)
Severe COPD exacerbations			
n	X	X	X
0	xx (x%)	xx (x%)	xx (x%)
1	xx (x%)	xx (x%)	xx (x%)
>=2	xx (x%)	xx (x%)	xx (x%)
Total number of moderate/severe COPD exacerbations			
n	911	899	1810
0	313 (34%)	317 (35%)	630 (35%)
1	252 (28%)	253 (28%)	505 (28%)
>=2	346 (38%)	329 (37%)	675 (37%)

Note: Number of COPD exacerbations reported in the 12 months prior to the Screening Visit.
PPD

13.12.2. Example Shell 2

Protocol: XYZ100001 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Treatment Compliance

	Treatment A (N=100)	Treatment B (N=100)	Total (N=200)
Overall compliance (%)			
n	xx	xx	xx
Mean	xx	xx	xx
SD	xx	xx	xx
Median	xx	xx	xx
Min.	xx	xx	xx
Max.	xx	xx	xx
Compliance interval			
< 80%	xx (x%)	xx (x%)	xx (x%)
80% - < 100%	xx (x%)	xx (x%)	xx (x%)
100% - < 120%	xx (x%)	xx (x%)	xx (x%)
>=120%	xx (x%)	xx (x%)	xx (x%)

PPD

13.12.3. Example shell 3

Example Shell X
Protocol: ABC123456 Page 1 of n
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Change from Baseline in FEV1 (L)
Measured post-bronchodilator

Visit	N	Treatment Arm	n	Mean	SD	Median	Min.	Max.
Day 1	200	Placebo	200	0.111	0.1111	0.100	-0.11	1.11
	200	GSK2269557 12.5 mcg	190	0.222	0.2222	0.200	-0.22	1.22
	200	GSK2269557 50 mcg	195	0.333	0.3333	0.300	-0.33	1.33
	200	GSK2269557 100 mcg	195	0.444	0.4444	0.400	-0.44	1.44
	200	GSK2269557 250 mcg	190	0.555	0.5555	0.500	-0.55	1.55
	200	GSK2269557 500 mcg	190	0.555	0.5555	0.500	-0.55	1.55
	200	GSK2269557 750 mcg	190	0.555	0.5555	0.500	-0.55	1.55
Day 14	200	Placebo	200	0.111	0.1111	0.100	-0.11	1.11
	200	GSK2269557 12.5 mcg	190	0.222	0.2222	0.200	-0.22	1.22
	200	GSK2269557 50 mcg	195	0.333	0.3333	0.300	-0.33	1.33
	200	GSK2269557 250 mcg	195	0.444	0.4444	0.400	-0.44	1.44
	200	GSK2269557 500 mcg	190	0.555	0.5555	0.500	-0.55	1.55
	200	GSK2269557 750 mcg	190	0.555	0.5555	0.500	-0.55	1.55

PPD

13.12.4. Example Shell 4

Protocol: ABC123456
Population: Intent-to-Treat/Safety/Other study specific

Table X
Statistical Analysis of Change from Baseline in FEV1 (ml)
Measured post-bronchodilator

Visit	N	Treatment Arm	n	Posterior Median	95% Credible Interval
Day 14	x	Placebo	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 12.5 mcg	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 50 mcg	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 100 mcg	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 250 mcg	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 500 mcg	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 750 mcg	x	x.xx	(x.xx, x.xx)
Day 28	x	Placebo	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 12.5 mcg	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 50 mcg	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 100 mcg	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 250 mcg	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 500 mcg	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 750 mcg	x	x.xx	(x.xx, x.xx)

PPD

Protocol: ABC123456
Population: Intent-to-Treat/Safety/Other study specific

Table X
Statistical Analysis of Change from Baseline in FEV1 (ml)
Measured post-bronchodilator

Visit	Treatment Comparison	Adjusted Median Difference	Std Dev	95% Credible Interval	Prob Treat. Diff >0 (%)
Day 14	GSK2269557 12.5 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
	GSK2269557 50 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
	GSK2269557 100 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
	GSK2269557 250 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
	GSK2269557 500 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
	GSK2269557 750 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
Day 28	GSK2269557 12.5 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
	GSK2269557 50 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
	GSK2269557 100 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx

PPD

13.12.5. Example Shell 5

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of On-treatment Exacerbations

	Treatment A (N=100)	Treatment B (N=100)
Number of moderate/severe exacerbations per subject		
0	50 (50%)	98 (98%)
1	6 (6%)	15 (15%)
2	6 (6%)	9 (9%)
3	1 (1%)	1 (1%)
4	0	2 (2%)
5	0	1 (1%)
>5	0	1 (1%)
Subjects with >=1 moderate/severe exacerbation	13 (13%)	28 (28%)
Total Number of moderate/severe exacerbations	21	49
Number of moderate exacerbations per Subject		
0	50 (50%)	98 (98%)
1	6 (6%)	15 (15%)
2	6 (6%)	9 (9%)
3	1 (1%)	1 (1%)

PPD

13.12.6. Example Shell 6

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Statistical Analysis of On-treatment Exacerbations

	Treatment A (N=100)	Treatment B (N=100)
Moderate/severe exacerbations		
Annual exacerbation rate (95% CrI)	0.35 (x.xx, x.xx)	0.30 (x.xx, x.xx)
Active vs. Placebo		
Ratio		0.85 (x.xx, x.xx)
Pr Diff <1		x.xx
Percent reduction in rate (95% CrI)		15% (x.xx, x.xx)
Predictive probability (%) [1]		xx%
[*only when required*]		
Moderate exacerbations		
Annual exacerbation rate (95% CrI)	0.35 (x.xx, x.xx)	0.30 (x.xx, x.xx)
Active vs. Placebo		
Ratio		0.85 (x.xx, x.xx)
Pr Diff <1		x.xx
Percent reduction in rate (95% CrI)		15% (x.xx, x.xx)

[1] Predictive posterior probability of success at end of study, where success is Pr(Reduction>0%)>80%

PPD

13.12.7. Example Shell 7

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of COPD Duration at Screening

	Treatment A (N=100)		Treatment B (N=100)		Total (N=200)	
Duration of COPD:						
n	100		99		199	
<1 year	XX	(x%)	XX	(x%)	XX	(x%)
>=1 to <5 years	XX	(x%)	XX	(x%)	XX	(x%)
>=5 to <10 years	XX	(x%)	XX	(x%)	XX	(x%)
>=10 to <15 years	XX	(x%)	XX	(x%)	XX	(x%)
>=15 to <20 years	XX	(x%)	XX	(x%)	XX	(x%)
>=20 to <25 years	XX	(x%)	XX	(x%)	XX	(x%)
>=25 years	XX	(x%)	XX	(x%)	XX	(x%)

PPD

13.12.8. Example Shell 8

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary and Analysis of Time to Next On-treatment Moderate/Severe Exacerbation (days)
up to Day 84

	Treatment A (N=100)	Treatment B (N=100)
Number of Subjects with Event	10 (10%)	14 (14%)
Number of Subjects Censored	90 (90%)	86 (86%)
Treatment A vs. Placebo		
Hazard Ratio	X.XX	
95% Credible Interval	(x.xx, x.xx)	

Note: Hazard ratio and 95% Credible Interval are from a Bayesian Cox proportional hazards model

PPD

13.12.9. Example Shell 9

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Statistical Analysis of Proportion of Participants Achieving EXACT-definition of Response

	Treatment A (N=100)	Treatment B (N=100)
Day 14		
n	x.xx	x.xx
Responder	x.xx (x%)	x.xx (x%)
Non-responder	x.xx (x%)	x.xx (x%)
Active vs. Placebo		
Odds Ratio (OR) (95% CrI)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Pr OR >1	x.xx	x.xx
Day 28		
n	x.xx	x.xx
Responder	x.xx (x%)	x.xx (x%)
Non-responder	x.xx (x%)	x.xx (x%)
Active vs. Placebo		
Odds Ratio (95% CrI)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Pr Diff >1	x.xx	x.xx

PPD

13.12.10. Example Shell 10

Protocol: XYZ100001 Page 1 of n
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of severity of subsequent HCRU-defined exacerbation during 12-Week Treatment Period

Treatment	N	n	Mean	SD	Median	Min.	Max.
Placebo	30	30	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Trt A	30	30	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Trt B	30	30	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

PPD

13.12.11. Example Shell 11

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Mixed Model Repeated Measures Analysis of CAT Total Score

	Treatment A (N=100)	Treatment B (N=100)
Day 28		
n	x.xx	x.xx
Adjusted mean score change (SE)	x.xx (x)	x.xx (x)
Active - Placebo		
Difference (SE)	x.xx (x.xx)	x.xx (x.xx)
95% (CrI)	x.xx	x.xx
Pr Diff >0	x.xx	x.xx
Day 56		
n	x.xx	x.xx
Adjusted mean score change (SE)	x.xx (x)	x.xx (x)
Active - Placebo		
Difference (SE)	x.xx (x.xx)	x.xx (x.xx)
95% (CrI)	x.xx	x.xx
Pr Diff >0	x.xx	x.xx

PPD

13.12.12. Example Shell 12

Protocol: ABC123456 Page 1 of 3
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of COPD Related Unscheduled Healthcare Resource Utilization

		Treatment A (N=100)	Treatment B (N=100)
Unscheduled Healthcare Utilisation	Yes	97 (97%)	19 (19%)
	No	3 (3%)	81 (81%)
Number of Home Visits (day)	n	100	100
	0	90 (90%)	92 (92%)
	1	4 (4%)	4 (4%)
	2	0	0
	3	0	0
	>3	0	2 (<1%)
	Total [1]	4	4
Number of Home Visits (night)	n	100	100
	0	100 (100%)	100 (100%)
	1	0	0
	2	0	0
	3	0	0
	>3	0	0
	Total [1]	0	0

[1] Total number of contacts across all subjects.
[2] Total number of days across all subjects.

PPD

Protocol: ABC123456
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of COPD Related Unscheduled Healthcare Resource Utilization

		Treatment A (N=100)		Treatment B (N=100)	
Number of Office/Practice Visits	n	911		899	
	0	846	(93%)	808	(90%)
	1	42	(5%)	58	(6%)
	2	13	(1%)	23	(3%)
	3	7	(<1%)	8	(<1%)
	>3	3	(<1%)	2	(<1%)
	Total [1]	103		140	
Number of Urgent Care/Outpatient Visits	n	911		899	
	0	886	(97%)	882	(98%)
	1	15	(2%)	10	(1%)
	2	3	(<1%)	2	(<1%)
	3	3	(<1%)	3	(<1%)
	>3	4	(<1%)	2	(<1%)
	Total [1]	54		37	
Number of Emergency Room Visits	n	911		899	
	0	906	(>99%)	893	(>99%)
	1	5	(<1%)	5	(<1%)
	2	0		1	(<1%)
	3	0		0	
	>3	0		0	
	Total [1]	5		7	

[1] Total number of contacts across all subjects.
[2] Total number of days across all subjects.

PPD

Population: Intent-to-Treat/Safety/Other study specific

Table 2.159
Summary of COPD Related Unscheduled Healthcare Resource Utilization

		Treatment A (N=100)	Treatment B (N=100)
Number of Days in Intensive Care	n	911	899
	0	910 (>99%)	894 (>99%)
	1	0	0
	2	0	1 (<1%)
	3	0	0
	>3	1 (<1%)	4 (<1%)
	Total [2]	12	40
Number of Days in General Ward	n	911	899
	0	896 (98%)	878 (98%)
	1	0	2 (<1%)
	2	1 (<1%)	1 (<1%)
	3	0	0
	>3	14 (2%)	18 (2%)
	Total [2]	119	258

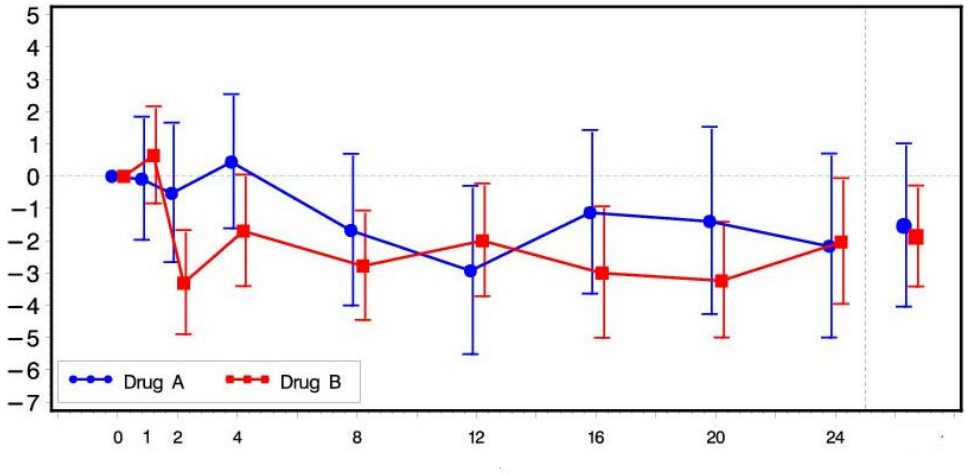
[1] Total number of contacts across all subjects.
[2] Total number of days across all subjects.

PPD

13.12.13. Example shell 13

Protocol: XYZ100001 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Figure X
Median (range) Absolute Neutrophil Count by Time and Treatment



PPD

13.12.14. Example Shell 14

Protocol: XYZ100001
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Baseline COPD Maintenance Therapy

Therapy category	Treatment A (N=81)	Treatment B (N=79)
Any medication at baseline	70 (86%)	50 (63%)
Monotherapy	X (x%)	X (x%)
LAMA only	x (x%)	x (x%)
Dual therapy	x (x%)	x (x%)
ICS/LABA	x (x%)	x (x%)
Dual bronchodilator	xx (xx%)	xx (xx%)
Triple therapy	X (x%)	X (x%)
LAMA/ICS/LABA	x (x%)	0

PPD

13.12.15. Example Shell 15

Protocol: XYZ100001
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of On-Treatment COPD Maintenance (Step-up) Therapy

Therapy category	Treatment A (N=81)	Treatment B (N=79)
Any Step-up Therapy	70 (86%)	50 (63%)

PPD

13.12.16. Example shell 16

Protocol: XYZ100001
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of OCS use

	Treatment A (N=81)	Treatment B (N=79)
OCS use for index exacerbation	81 (100%)	79 (100%)
Total number of Days of OCS use		
Mean	Xx	xx
SD	Xx	xx
Median	Xx	xx
Min.	Xx	xx
Max.	Xx	xx
On-treatment OCS use	xx (xx%)	xx (xx%)
Total number of Days of OCS use		
Mean	Xx	xx
SD	Xx	xx
Median	Xx	xx
Min.	Xx	xx
Max.	Xx	xx

PPD

13.12.17. Example Shell 17

Protocol: ABC123456 Page 1 of x
Population: Safety

Table X
Summary of Post-Inhalation Cough by Visit

Visit: VISIT 2 (RANDOMISATION)

	Placebo (N=43)	GSK2269557 50 mcg (N=14)	GSK2269557 100 mcg (N=15)	GSK2269557 250 mcg (N=16)	GSK2269557 500 mcg (N=14)	GSK2269557 750 mcg (N=42)
Did subject experience PI cough? [1]						
n	20	10	12	15	12	35
Yes	7 (35%)	4 (40%)	6 (50%)	3 (20%)	6 (50%)	12 (34%)
No	13 (65%)	6 (60%)	6 (50%)	12 (80%)	6 (50%)	23 (66%)
Type of cough						
Single cough	4 (57%)	2 (50%)	1 (17%)	1 (33%)	1 (17%)	2 (17%)
Intermittent cough	2 (29%)	2 (50%)	5 (83%)	1 (33%)	4 (67%)	5 (42%)
Continuous cough	1 (14%)	0	0	1 (33%)	1 (17%)	5 (42%)
Severity of cough						
Mild	5 (71%)	3 (75%)	3 (50%)	2 (67%)	1 (17%)	6 (50%)
Moderate	2 (29%)	1 (25%)	2 (33%)	1 (33%)	5 (83%)	4 (33%)
Severe	0	0	1 (17%)	0	0	2 (17%)
Time to onset of PI cough (minutes)						
0-1	6 (86%)	3 (75%)	6 (100%)	3 (100%)	6 (100%)	12 (100%)
>1-2	1 (14%)	1 (25%)	0	0	0	0
>2-3	0	0	0	0	0	0
>3-4	0	0	0	0	0	0
>4-5	0	0	0	0	0	0
>5	0	0	0	0	0	0
Duration of PI cough (minutes)						
<=1	6 (86%)	3 (75%)	5 (83%)	3 (100%)	5 (83%)	11 (92%)
>1-2	1 (14%)	1 (25%)	1 (17%)	0	1 (17%)	1 (8%)
>2-3	0	0	0	0	0	0
>3-4	0	0	0	0	0	0
>4-5	0	0	0	0	0	0

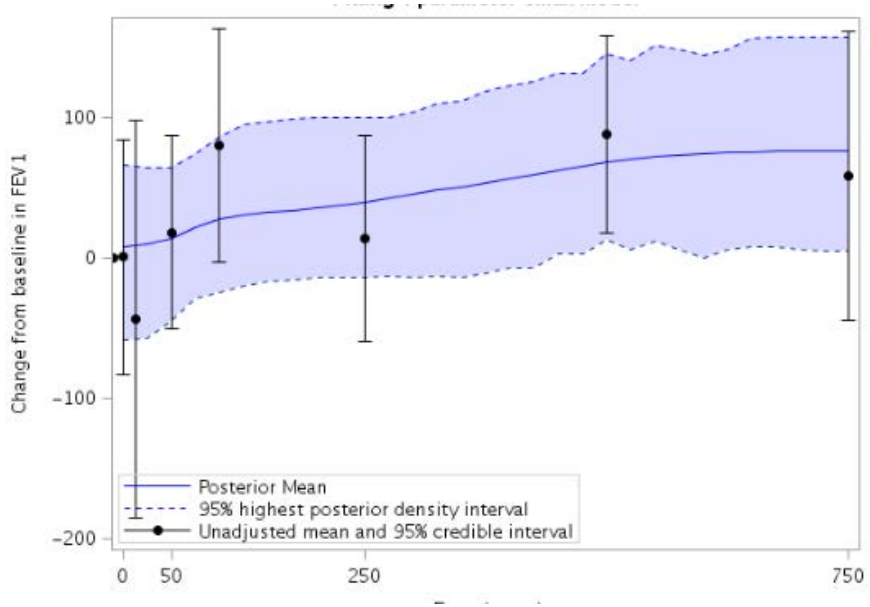
>5-10	x		x								
>10-30	x		x								
>30	x		x								
Number of subjects reporting cough as AE/SAE	2	(29%)	1	(25%)	4	(67%)	0		2	(33%)	3	(25%)
Mild	x	(x%)	x								
Moderate	x	(x%)	x								
Severe	x	(x%)	x								

[1] Percentages are calculated using the number of subjects evaluated at visit as the denominator.
All other percentages are calculated using the number of subjects with a PI cough at visit as the denominator.

13.12.18. Example shell 18

Protocol: ABC123456 Page 1 of x
Population: Intent-to-Treat/Safety/Other study specific

Figure X
Plot of Dose Response Model of Change from Baseline in FEV1



[Footnote to describe the fitted model]

PPD

13.12.19. Example Shell 19

Protocol: ABC123456 Page 1 of 3
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of COPD Related Unscheduled Healthcare Resource Utilization

		Treatment A (N=100)	Treatment B (N=100)
Unscheduled Healthcare Utilisation	Yes	97 (97%)	19 (19%)
	No	3 (3%)	81 (81%)
Number of Home Visits (day)	n	100	100
	0	90 (90%)	92 (92%)
	1	4 (4%)	4 (4%)
	2	0	0
	3	0	0
	>3	0	2 (<1%)
	Total [1]	4	4
Number of Home Visits (night)	n	100	100
	0	100 (100%)	100 (100%)
	1	0	0
	2	0	0
	3	0	0
	>3	0	0
	Total [1]	0	0

[1] Total number of contacts across all subjects.
[2] Total number of days across all subjects.

PPD

Population: Intent-to-Treat/Safety/Other study specific

Table X

Summary of COPD Related Unscheduled Healthcare Resource Utilization

		Treatment A (N=100)		Treatment B (N=100)	
Number of Office/Practice Visits	n	911		899	
	0	846	(93%)	808	(90%)
	1	42	(5%)	58	(6%)
	2	13	(1%)	23	(3%)
	3	7	(<1%)	8	(<1%)
	>3	3	(<1%)	2	(<1%)
	Total [1]	103		140	
Number of Urgent Care/Outpatient Visits	n	911		899	
	0	886	(97%)	882	(98%)
	1	15	(2%)	10	(1%)
	2	3	(<1%)	2	(<1%)
	3	3	(<1%)	3	(<1%)
	>3	4	(<1%)	2	(<1%)
	Total [1]	54		37	
Number of Emergency Room Visits	n	911		899	
	0	906	(>99%)	893	(>99%)
	1	5	(<1%)	5	(<1%)
	2	0		1	(<1%)
	3	0		0	
	>3	0		0	
	Total [1]	5		7	

[1] Total number of contacts across all subjects.
[2] Total number of days across all subjects.
PPD

Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of COPD Related Unscheduled Healthcare Resource Utilization

		Treatment A (N=100)	Treatment B (N=100)
Number of Days in Intensive Care	n	911	899
	0	910 (>99%)	894 (>99%)
	1	0	0
	2	0	1 (<1%)
	3	0	0
	>3	1 (<1%)	4 (<1%)
	Total [2]	12	40
Number of Days in General Ward	n	911	899
	0	896 (98%)	878 (98%)
	1	0	2 (<1%)
	2	1 (<1%)	1 (<1%)
	3	0	0
	>3	14 (2%)	18 (2%)
	Total [2]	119	258

[1] Total number of contacts across all subjects.
[2] Total number of days across all subjects.

PPD

13.12.20. Example Shell 20

Protocol: ABC123456 Page 1 of x
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Non-COPD Related Unscheduled Healthcare Resource Utilization

		Treatment A (N=100)	Treatment B (N=100)
Unscheduled Healthcare Utilisation	Yes	97 (97%)	19 (19%)
	No	3 (3%)	81 (81%)
Number of Days in Accident and emergency	n	100	100
	0	90 (90%)	92 (92%)
	1	4 (4%)	4 (4%)
	2	0	0
	3	0	0
	>3	0	2 (<1%)
	Total	4	4
Number of Days in General Ward	n	100	100
	0	100 (100%)	100 (100%)
	1	0	0
	2	0	0
	3	0	0
	>3	0	0
	Total	0	0

PPD

13.12.21. Example Shell 21

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Exacerbation Related Hospitalizations

	Treatment A (N=100)	Treatment B (N=100)
Index exacerbation		
Participants with hospitalization	x.xx	x.xx
Number of hospitalizations	x.xx	x.xx
Mean duration (days)	x.xx	x.xx
SD	x.xx	x.xx
Median duration (days)	x.xx	x.xx
Minimum duration (days)	x.xx	x.xx
Maximum duration (days)	x.xx	x.xx
Subsequent exacerbations		
Participants with hospitalization	x.xx	x.xx
Number of hospitalizations	x.xx	x.xx
Mean duration (days)	x.xx	x.xx
SD	x.xx	x.xx
Median duration (days)	x.xx	x.xx
Minimum duration (days)	x.xx	x.xx
Maximum duration (days)	x.xx	x.xx

PPD

13.12.22. Example Shell 22

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Re-hospitalization Within 30 days of Index Exacerbation

		Treatment A (N=100)	Treatment B (N=100)
Re-hospitalization Within 30 days	Yes	97 (97%)	19 (19%)
	No	3 (3%)	81 (81%)

PPD

13.12.23. Example Shell 23

Protocol: XYZ100001
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Subsequent Exacerbation Treatment

	Treatment A (N=81)	Treatment B (N=79)
Subsequent exacerbation	70 (86%)	50 (63%)
OCS	X (x%)	X (x%)
Antibiotics	x (x%)	x (x%)
OCS and antibiotics	X (x%)	X (x%)

PPD

13.12.24. Example Shell 24

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Time from Resolution of Index Exacerbation to Next Exacerbation

	Treatment A (N=100)	Treatment B (N=100)
Subsequent exacerbation	x.xx	x.xx
Mean duration (days)	x.xx	x.xx
SD	x.xx	x.xx
Median duration (days)	x.xx	x.xx
Minimum duration (days)	x.xx	x.xx
Maximum duration (days)	x.xx	x.xx

PPD

13.12.25. Example Shell 25

Protocol: ABC123456 Page 1 of x
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of ECG Abnormalities for Participants with Any Abnormal Clinically Significant ECG Interpretation

	Treatment A (N=100)	Treatment B (N=100)
Visit 2 (Day 1)		
Abnormal – Clinically significant	10 (10%)	15 (15%)
Any finding	5 (50%)	5 (33%)
ST depression	5 (50%)	5 (33%)
Short PR Interval	0	5 (33%)
T wave inversion	0	5 (33%)
…….		

Includes Scheduled, unscheduled and Early Withdrawal visits.
Participants may have more than one abnormality at each visit.

PPD

13.12.26. Example Shell 26

Protocol: ABC123456 Page 1 of n
Population: Intent-to-Treat/Safety/Other study specific

Table X
Statistical Analysis of Change from Baseline in FEV1 (mL) (Dose Response Model)
Measured post-bronchodilator

	Placebo (N=xx)	DNX 5mg (N=xx)	DNX 10mg (N=xx)	DNX 25mg (N=xx)	DNX 35mg (N=xx)	DNX 50mg (N=xx)
n [1]	xx	xx	xx	xx	xx	xx
Posterior Adj. Median Change	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
95% HPD Credible Interval	(x.xx,x.xx)	(x.xx,x.xx)	(x.xx,x.xx)	(x.xx,x.xx)	(x.xx,x.xx)	(x.xx,x.xx)
Active - Placebo						
Posterior Adj. Median Difference		x.xx	x.xx	x.xx	x.xx	x.xx
95% HPD Credible Interval		(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)
Prob(Difference>0)		xx%	xx%	xx%	xx%	xx%
Predictive probability (%) [2] *[only if required]*		xx%	xx%	xx%	xx%	xx%

[1] Number of subjects with data contributing to the analysis.
[2] Predictive posterior probability of success at end of study, where success is Pr(Difference>0)>90%.
Note: Model fitted was a…..[insert as appropriate].

PPD

13.12.27. Example Shell 27

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of QTc(F) (msec) Categories

	Treatment A (N=100)		Treatment B (N=100)	
Screening				
n	xx		xx	
<=450	xx	(xx%)	xx	(xx%)
>450 to <=480	xx	(xx%)	xx	(xx%)
>480 to <=500	xx	(xx%)	xx	(xx%)
>500	xx	(xx%)	xx	(xx%)
Day 1 (Baseline)				
n	xx		xx	
<=450	xx	(xx%)	xx	(xx%)
>450 to <=480	xx	(xx%)	xx	(xx%)
>480 to <=500	xx	(xx%)	xx	(xx%)
>500	xx	(xx%)	xx	(xx%)
Day 14				
n	xx		xx	
<=450	xx	(xx%)	xx	(xx%)
>450 to <=480	xx	(xx%)	xx	(xx%)
>480 to <=500	xx	(xx%)	xx	(xx%)
>500	xx	(xx%)	xx	(xx%)

PPD

13.12.28. Example Shell 28

Protocol: ABC123456 Page 1 of x
Population: Safety

Table X
Summary of Post-Inhalation Cough by Visit and Cough Type

Visit 2 (Day 1) Type of cough: Single cough	Treatment A (N=100)
Did subject experience event [1]?	12 (24%)
Cough severity	
Mild	6 (50%)
Moderate	5 (42%)
Severe	1 (8%)
Time to onset of PI cough (minutes)	
0-1	2(17%)
>1-2	3(25%)
>2-3	4(33%)
>3-4	3(25%)
>4-5	0
>5	0
Duration of PI cough (minutes)	
<=1	7(58%)
>1 - 2	2(17%)
>2 - 3	3(25%)
>3 - 4	0
>4 - 5	0
>5 - 10	0
>10 - 30	0
>30	0

[1] Percentages are calculated using the number of subjects evaluated at visit as the denominator.
All other percentages are calculated using the number of subjects with particular cough type at visit as the denominator.

Protocol: ABC123456
Population: Safety

Table X
Summary of Post-Inhalation Cough by Visit and Cough Type

Visit 2 (Day 1) Type of cough: Single cough	Treatment A (N=100)
Number of subjects reporting cough as AE/SAE	4 (33%)
Mild	2 (17%)
Moderate	2 (17%)
Severe	0

Protocol: ABC123456
Population: Safety

Table X
Summary of Post-Inhalation Cough by Visit and Cough Type

Visit 2 (Day 1) Type of cough: Intermittent cough	Treatment A (N=100)
Did subject experience event [1]?	11 (22%)
Cough severity	
Mild	2 (18%)
Moderate	6 (55%)
Severe	3 (27%)
Time to onset of PI cough (minutes)	
0-1	1(9%)
>1-2	4(36%)
>2-3	6(55%)
>3-4	0
>4-5	0
>5	0
Duration of PI cough (minutes)	
<=1	0
>1 - 2	3(27%)
>2 - 3	6(55%)
>3 - 4	1(9%)
>4 - 5	0
>5 - 10	0
>10 - 30	1(9%)
>30	0

Protocol: ABC123456
Population: Safety

Table X
Summary of Post-Inhalation Cough by Visit and Cough Type

Visit 2 (Day 1) Type of cough: Intermittent cough	Treatment A (N=100)
Number of subjects reporting cough as AE/SAE	5 (45%)
Mild	1 (9%)
Moderate	2 (18%)
Severe	2 (18%)

Protocol: ABC123456
Population: Safety

Table X
Summary of Post-Inhalation Cough by Visit and Cough Type

Visit 2 (Day 1) Type of cough: Continuous cough	Treatment A (N=100)
Did subject experience event [1]?	4 (8%)
Cough severity	
Mild	1 (25%)
Moderate	2 (50%)
Severe	1 (25%)
Time to onset of PI cough (minutes)	
0-1	3(75%)
>1-2	1(25%)
>2-3	0
>3-4	0
>4-5	0
>5	0
Duration of PI cough (minutes)	
<=1	0
>1 - 2	0
>2 - 3	0
>3 - 4	1 (25%)
>4 - 5	1 (25%)
>5 - 10	0
>10 - 30	1 (25%)
>30	1 (25%)

Protocol: ABC123456
Population: Safety

Table X
Summary of Post-Inhalation Cough by Visit and Cough Type

Visit 2 (Day 1) Type of cough: Continuous cough	Treatment A (N=100)
Number of subjects reporting cough as AE/SAE	2 (50%)
Mild	1 (25%)
Moderate	1 (25%)
Severe	0

REPEAT FOR EACH VISIT

13.12.29. Example Shell 29

Protocol: MID200879 Page 1 of 1
Population: Intent-to-Treat

Listing X
Listing of Subjects who Received Incorrect Medication

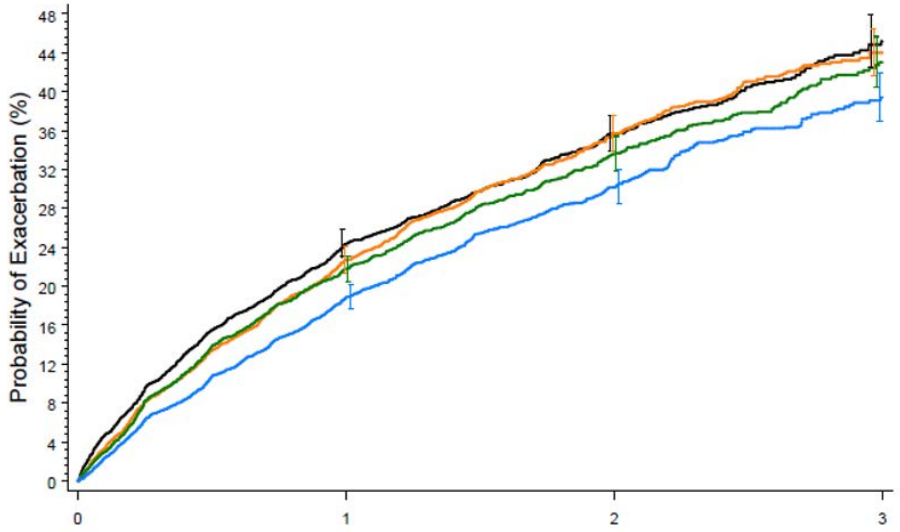
Randomized Treatment	Centre/ Subj	Start Date of Dosing	End Date of Dosing	Duration (Days)	Dispense Visit	Dispense Date	Actual Treatment Dispensed
GSK2269557 500 mcg	PPD	XXXXXXXXX	XXXXXXXXX	XX	Visit 3 (Week 0)	XXFEB2013	GSK2269557 500 mcg
		XXXXXXXXX	XXXXXXXXX	XX	Visit 5 (Week 4)	XXMAR2013	GSK2269557 100 mcg
		XXXXXXXXX	XXXXXXXXX	XX	Visit 6 (Week 8)	XXAPR2013	GSK2269557 500 mcg

PPD

13.12.30. Example Shell 30

Protocol: ABC123456 Page 1 of x
Population: Intent-to-Treat/Safety/Other study specific

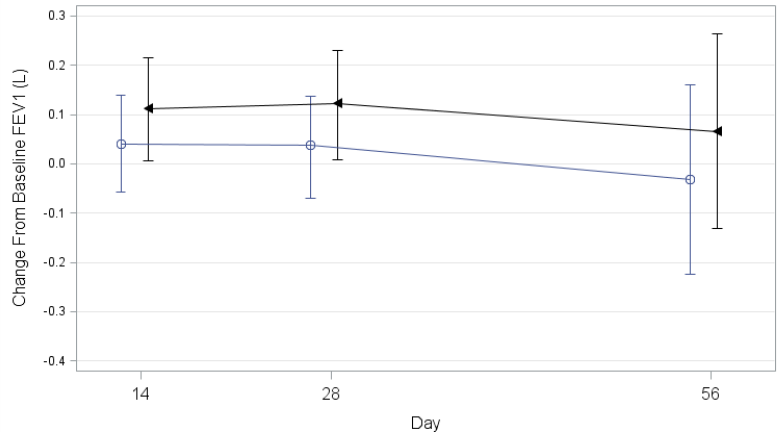
Figure X
Kaplan-Meier Plot of Time to Next On-treatment Exacerbation During the 12-Week Treatment Period



13.12.31. Example Shell 31

Protocol: ABC123456 Page 1 of x
Population: Intent-to-Treat/Safety/Other study specific

Figure X
Plot of Repeated Measures Model of Change from Baseline in FEV1 Measured Post-bronchodilator



13.12.32. Example Shell 32

Protocol: XYZ100001 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Efficiency Ratio for Possible Adaptions to Randomization Ratio

	Median	10th Percentile
Design 1: Add 25mcg dose	xx	xx
Design 2: Add 25mcg dose, drop 500mcg dose	xx	xx
Design 3: Add 25mcg dose, drop 250 mcg and 500 mcg doses	xx	xx
Design 4: Drop 12.5mcg dose	xx	xx
Design 5: Drop 12.5mcg and 50mcg doses	xx	xx

PPD

13.12.33. Example Shell 33

Protocol: ABC123456 Page 1 of x
Population: Safety

Table X
Summary of Post-Inhalation (PI) Cough at Any Visit

	Placebo (N=43)	GSK2269557 50 mcg (N=14)	GSK2269557 100 mcg (N=15)	GSK2269557 250 mcg (N=16)	GSK2269557 500 mcg (N=14)	GSK2269557 750 mcg (N=42)
Did subject experience PI cough at any visit?						
Yes	X (xx%)	X (xx%)	X (xx%)	X (xx%)	X (xx%)	X (xx%)
No	X (xx%)	X (xx%)	X (xx%)	X (xx%)	X (xx%)	X (xx%)
Maximum Severity of cough						
Mild	X (xx%)	X (xx%)	X (xx%)	X (xx%)	X (xx%)	X (xx%)
Moderate	X (xx%)	X (xx%)	X (xx%)	X (xx)	X (xx%)	X (xx%)
Severe	0	0	X (xx%)	0	0	X (xx%)
Maximum Duration of PI cough (minutes)[1]						
Mean	x	x	x	x	x	x
SD	x	x	x	x	x	x
Median	x	x	x	x	x	x
Minimum	x	x	x	x	x	x
Maximum	x	x	x	x	x	x
Number of occurrences of PI cough						
0	x	x	x	x	x	x
1	x	x	x	x	x	x
2	x	x	x	x	x	x
3	x	x	x	x	x	x
4	x	x	x	x	x	x

[1] Duration from the maximum severity cough

PPD

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The GlaxoSmithKline group of companies 200879

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

Title	:	Reporting and Analysis Plan for Phase IIb, Randomized (Stratified), Double-Blind (Sponsor Open), Parallel-Group, Placebo-Controlled, Dose-Finding Study of Nemiralisib (GSK2269557) Added to Standard of Care (SoC) Versus SoC Alone in Participants Diagnosed with an Acute Moderate or Severe Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)
Compound Number	:	GSK2269557
Effective Date	:	08-MAR-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 200879 and at the planned interim analyses.
- This RAP is intended to describe the efficacy, safety and pharmacokinetic analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

RAP Author(s): PPD
Statistics Leader, (Respiratory Clinical Statistics)

Approver	Date	Approval Method
PPD TA Director (Respiratory Clinical Statistics)	07-MAR-2018	Email
PPD Programming Manager (Respiratory Clinical Programming)	08-MAR-2018	Email

RAP Team Approvals:

Approver	Date	Approval Method
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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol 200879.

2. SUMMARY OF KEY PROTOCOL INFORMATION

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To characterise the dose response of nemiralisib administered in addition to SoC compared with placebo and SoC in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Change from baseline in Clinic Visit trough forced expiratory volume in one second (FEV_1) at Day 84 measured post-bronchodilator
Secondary Objectives	**Secondary Endpoints**
• To characterise the dose response and efficacy of nemiralisib administered in addition to SoC compared with placebo and SoC in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Rate of moderate and severe exacerbations over the 12-Week Treatment Period • Time to next moderate/severe exacerbation following index exacerbation • Change from baseline in Clinic Visit trough FEV_1 measured pre- and post-bronchodilator at Days 14, 28, 56, and 84 (Day 84: post-bronchodilator is the primary endpoint; pre-bronchodilator is a secondary endpoint) and at hospital discharge (only for participants who are hospitalized for the index exacerbation) • Change from hospital discharge in clinic visit trough FEV_1 measured pre- and post-bronchodilator at Days, 14, 28, 56, and 84 (in participants hospitalized for index exacerbation only)
• To evaluate the treatment effect of nemiralisib in addition to SoC compared with placebo and SoC on symptoms indicative of an exacerbation and on health status using Patient-Reported Outcomes (PROs) in participants diagnosed with an acute moderate or severe exacerbation of COPD	<u>EXAcerbations of Chronic Pulmonary Disease Tool (EXACT-PRO)</u> • Proportion of participants achieving the EXACT definition of recovery from the index exacerbation by Days 14, 28, 56, and 84 • Time to recovery from index exacerbation • Severity of subsequent HCRU-defined exacerbation(s) defined by EXACT <u>COPD Assessment Test (CAT)</u> • Proportion of responders using the CAT at Treatment Days 28, 56, and 84, and following EXACT defined recovery from the index exacerbation • Change from baseline (Day 1) in CAT total score at Days 28, 56, and 84 and following EXACT defined recovery from the index exacerbation

Objectives	Endpoints
	<u>St. George's Respiratory Questionnaire (SGRQ) Total Score</u> • Proportion of responders on the SGRQ total score as measured by the SGRQ for COPD Patients (SGRQ-C) at Days 28, 56, and 84 • Change from baseline (Day 1) in SGRQ total score at Days 28, 56, and 84
• To evaluate the usage of rescue medication in patients diagnosed with an acute moderate or severe exacerbation of COPD	• Rescue medication use (occasions/day), averaged over each week of treatment and over the 84-day treatment period • The percentage of rescue-free days (24-hour periods) during each week of treatment and over the 84-day treatment period
• To evaluate the population pharmacokinetics of nemiralisib in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Plasma nemiralisib concentrations and derived PK parameters (e.g., area under the curve [AUC (0-24) and AUC(0-t)], maximum concentration [Cmax], time at maximum concentration [Tmax], Ctrough) as appropriate will be collected in a subset of randomized participants (approximately 300) at selected sites as follows: trough (pre-dose) for the study treatment and post-dose for the study treatment from 0-1 hour and >1 to 6 hours on Days 14 and 28 of the 12-Week Treatment Period
• To assess the safety and tolerability of nemiralisib and placebo in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Incidence of adverse events (AEs; including serious AEs and AE of Special Interest [AESI]) • Vital signs (pulse rate, systolic and diastolic blood pressure) (measured at each clinic visit up through Visit 7 [Day 112] or Early Withdrawal Visit) • 12-lead electrocardiogram (ECG) assessments (performed at clinic Visits 1 [Screening], 3 [Day 14], 6 [Day 84], and 7 [Day 112] or Early Withdrawal Visit) • Clinical laboratory tests (hematology and chemistry; performed at each clinic visit up through Visit 7 [Day 112] or Early Withdrawal Visit) • Incidence of COPD exacerbations
Exploratory Objectives	**Exploratory Endpoints**
• To further characterize the dose response, and efficacy, of nemiralisib administered in addition to SoC compared with placebo and SoC in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Rate of mild exacerbations over the 12-Week Treatment Period • Rate of all exacerbations (mild, moderate and severe combined) over the 12-Week Treatment Period • Time to next exacerbation (mild, moderate and severe combined)

Objectives	Endpoints
• To evaluate the treatment effect of nemiralisib in addition to SoC compared with placebo and SoC on symptom stability following an exacerbation using Patient-Reported Outcomes in participants diagnosed with an acute moderate or severe exacerbation of COPD	• Stability of symptoms post recovery measured using E-RS:COPD (Evaluating Respiratory Symptoms in COPD) and subscales from Randomization (Visit 2) to Day 84 (Visit 6)
• To explore the PK/PD relationship for nemiralisib	• Relationship between drug exposure and Pharmacodynamic responses (e.g. efficacy, heart rate, clinical laboratory analytes and blood biomarkers) in the PK subset of participants (approximately 300) at selected sites
• To evaluate the treatment effect of nemiralisib in addition to SoC compared with placebo and SoC on HCRU in participants who experience a severe exacerbation of COPD	• Measures of HCRU related to severe exacerbations (e.g., hospitalizations, length of hospital stay, re-hospitalization within 30 days, number of Emergency Room [ER] visits, etc.)
• To evaluate compliance with study treatment	• Number of actuations of the double-blind study treatment as measured by the clip-on Propeller Sensor (for countries where the Propeller Sensor for ELLIPTA is available)
• To evaluate inflammatory markers in blood in relation to acute exacerbation of COPD	• Blood samples collected at Screening through Visit 7 (as part of the clinical laboratory blood samples) for analysis of blood eosinophil counts and inflammatory mediators • Blood samples for analysis of inflammatory biomarkers (including but not limited to: high sensitivity C-reactive protein [hs-CRP], chemokine interferon-γ inducible protein 10 kDa (CXCL10)], and procalcitonin) collected at Visit 1 (Screening)
• To evaluate inflammatory and infective markers in sputum in relation to acute exacerbation of COPD	• Spontaneous sputum sample for analysis of inflammatory and infective markers collected at Screening/Day 1 (pre-dose) and Day 56 in participants who are willing and able to provide a sample
• To evaluate the potential post-treatment impact of double-blind study treatment during the 12-Week Post-Treatment Follow-Up Period	• Change from baseline (Day 84) in Clinic Visit trough FEV1 measured pre- and postbronchodilator at Day 112, 140 and 168 • Rate of moderate and severe COPD exacerbation(s) during the 12-Week Follow-Up Period • Rate of moderate and severe COPD exacerbation(s) over the 24 week study duration • Time to next exacerbation following cessation of double blind study treatment • Proportion of responders using the CAT at Days 112 and 168 • Change from baseline (Day 1) in CAT Total score at Days 112 and 168 • Proportion of responders on the SGRQ Total Score as measured by the SGRQ-C at Days 112 and 168 • Change from baseline (Day 1) in SGRQ total score at

Objectives	Endpoints
	Days 112 and 168 • Severity of subsequent HCRU exacerbation defined by EXACT • E-RS: COPD and subscales from last dose of double-blind study treatment • Rescue medication use up to Day 112

2.2. Study Design

This is a Phase IIb, multicenter, randomized, stratified (by index COPD exacerbation severity [moderate or severe] and by whether or not the participant is in the PK Subgroup), double-blind (Sponsor Open), placebo-controlled, parallel-group study in participants who present with an acute moderate or severe exacerbation of COPD requiring Standard of Care (SoC).

This study consists of a Screening Period, a 12-Week Treatment Period and a 12-Week Post-Treatment Follow-Up Period. Randomization and the first dose of the double-blind study treatment administration (Visit 2/Day 1) should take place in the morning, as soon as possible following determination of eligibility and completion of the baseline measures, including the EXACT-PRO questionnaire for the day of randomization, and FEV_1 measurement and no later than 48 hours after the start of SoC.

PK Subgroup: Sparse PK sampling will be conducted in a subgroup of participants at selected sites. The PK Subgroup will be identical to the main study in terms of the study population, design, and conduct, with the exception of blood draws (3 per visit on Days 14 and 28) for PK analysis.

3. PLANNED ANALYSES

3.1. Interim Analyses

Ongoing data reviews of unblinded safety data, conducted by an Internal Safety Review Committee (iSRC), will be performed throughout the trial. Details will be documented in the iSRC charter.

Interim analyses of the primary endpoint and key secondary endpoints to inform internal decision making will be conducted periodically throughout the trial. The first analysis (Interim Analysis 1) is planned to occur when approximately 170 participants complete 28 days of treatment, where approximately 50 of the 170 participants have an index exacerbation defined as severe. A change that could arise from this interim analysis is a specification of the stratification proportions by index exacerbation severity status (moderate or severe). This decision will be based on inspection of all available endpoints at the interim analysis.

Further interim analyses will be performed, depending on the observed recruitment rate. At least one interim analysis of the primary endpoint of change from baseline in clinic visit trough FEV_1 at Day 84 measured post-bronchodilator will be performed to

determine whether or not any adjustments to the randomization ratio across doses would help optimize the characterization of the dose response profile for nemiralisib. This analysis (Interim Analysis 2) is planned to occur when approximately 300 participants complete 84 days of treatment or when approximately 400 participants remain to be randomised, whichever occurs first. Adjustments could include ceasing randomization to an existing dose(s) of nemiralisib and/or modification of the allocation ratios for the existing nemiralisib doses and/or addition of a 25mcg dose. Other changes may include specification of the stratification proportions by index exacerbation severity status.

An interim analysis of efficacy data collected during the Double-Blind Treatment Period will be conducted when the last participant in the study has completed the 12-week Double-Blind Treatment Period (End of Treatment Interim Analysis). The aim of this analysis is to provide GSK with timely data to inform internal decision making, prior to the end of study.

The following table describes the endpoints that will be analysed/summarised at each interim:

Interim	Purpose of interim	Endpoints
Interim Analysis 1	To inform internal decision making	• Change from baseline in FEV_1 at Days 14, 28, 56 and 84 measured pre- and post-bronchodilator • Change from hospital discharge in FEV_1 at Day 14, 28, 56 and 84 measured pre- and post-bronchodilator in participants hospitalized for the index exacerbation • Other spirometry measures (percent predicted FEV_1, Forced Vital Capacity (FVC), percent predicted FVC and FEV/FVC ratio • Summary of on-treatment exacerbations • Summary of proportion of participants achieving EXACT-defined recovery by Days 14, 28, 56 and 84

Interim	Purpose of interim	Endpoints
Interim Analysis 2	To determine if any adjustments to the randomization ratio would help characterize the dose response profile for nemiralisib	Endpoints listed for Interim Analysis 1 and also: • Rate of (on-treatment) exacerbations over the 12-Week Treatment Period • Time to next (on-treatment) exacerbation during the 12-Week Treatment Period • Analysis of proportion of participants achieving the EXACT-defined recovery by Days 14, 28, 56, and 84 • Rescue medication use, as measured in eDiary
End of Treatment Interim Analysis	To inform internal decision making	All endpoints to be reported as per Statistical Analysis Complete (SAC) deliverable

The statistical methods of analyses are described in Section 7.

The Respiratory Data Sciences Group will apply machine learning techniques to the interim data to determine if identifiable phenotypic sub-population(s) of COPD participants are present at baseline, and if they result in different responses to Nemiralisib, to predict which participants will respond to Nemiralisib therapy, and to identify/quantify relationship(s) between different endpoints and response measures. Details of these analyses will be described in a separate RAP and results will be reported separately to the Clinical Study Report (CSR).

The following functions will be unblinded to interim analysis data: Clinical Statistics, Clinical Programming and Respiratory Data Sciences Group. Other member of GSK will be unblinded to group level summary data following the interim analyses (as documented internally).

3.1.1. Futility analyses

At least one interim analysis for futility will be performed. The first analysis will occur at Interim Analysis 2, i.e. when 300 participants complete 84 days of treatment, or when approximately 400 participants remain to be randomised, whichever occurs first.

Futility will be assessed in a sequential manner.

1) Futility will first be assessed for the primary endpoint of change from baseline in FEV_1 at Day 84 by fitting a suitable dose response model, as described in Section 7.1.2.
2) If the posterior predictive probability of declaring success for this endpoint is low across all doses, then futility will be assessed for the rate of (on-treatment) exacerbations endpoint.
3) If the posterior predictive probability of declaring success for this endpoint is low, then the study may be stopped.

Any decision to stop will be made after a review of all the data summarised/analysed at the time of the interim, including the proportion of participants achieving the EXACT-defined recovery.

3.1.1.1. Futility rules

The decision rules for futility are defined as follows.

Change from baseline in FEV_1 at Day 84

Stop study for futility if the predictive probability of success at the end of the trial, given the data at the interim is <20%, across all doses, where success at the end of the trial for change from baseline in FEV_1 is defined as demonstrating >90% posterior probability that the true difference from placebo for any dose of nemiralisib is greater than 0.

Rate of on-treatment exacerbations

Stop study for futility if the predictive probability of success at the end of the trial, given the data at the interim is <20%, where success at the end of the trial for rate of exacerbations is defined as demonstrating >80% posterior probability that the true rate reduction on 750 mcg dose versus placebo > 0%.

If a different dose arm appears to be more efficacious than the 750 mcg arm, then futility may be assessed using the rate reduction for this arm versus placebo.

The pre-determined rules will act as guidelines for stopping the study for futility. All of the data summarised/analysed at the time of the interim will be reviewed prior to any decision to stop the study.

3.2. Final Analyses

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

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

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Participants Enrolled (APE) Population	• All participants who are screened for eligibility.	• Study Population
Modified Intent To treat (MITT) Population	• All randomized participants who receive at least one dose of study treatment. • Participants will be analyzed according to the treatment that they were randomised to.	• Study Population • Efficacy
Per Protocol (PP) Population	• All randomized participants who receive at least one dose of study treatment, excluding any participants with an important protocol deviation. • Participants will be analyzed according to the treatment that they were randomised to.	• Sensitivity analyses of efficacy
Safety Population	• All randomized participants who received at least one dose of study treatment. • Participants will be summarised according to the treatment that they actually received. o If participants receive >1 treatment, then they will be summarised according to the most frequently dosed treatment. In cases where the frequency is equal, the participant will be assigned the lowest dose strength of nemiralisib	• Safety
Pharmacokinetic (PK) Population	• All participants in the Safety population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). • Participants will be summarised according to the treatment that they actually received	• PK

Refer to Appendix 11: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

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

Important deviations which result in exclusion from the analysis population will also be summarised and listed. (Please refer to Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).

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

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

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

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG Randomization System		Data Displays for Reporting	
Code	Description	Description	Order in TLF
A	Placebo	Placebo	1
B	GSK2269557 12.5 mcg	NEMI 12.5 mcg	2
C	GSK2269557 25 mcg*	NEMI 25 mcg	3
D	GSK2269557 50 mcg	NEMI 50 mcg	4
E	GSK2269557 100 mcg	NEMI 100 mcg	5
F	GSK2269557 250 mcg	NEMI 250 mcg	6
G	GSK2269557 500 mcg	NEMI 500 mcg	7
H	GSK2269557 750 mcg	NEMI 750 mcg	8

* The nemiralisib dose of 25 mcg may be added following the results of an un-blinded interim analysis if further characterization of the lower end of the dose response curve is required.

Treatment comparisons will be displayed as follows using the descriptors as specified:

1. NEMI 12.5 mcg vs Placebo
2. NEMI 25 mcg vs Placebo
3. NEMI 50 mcg vs Placebo
4. NEMI 100 mcg vs Placebo
5. NEMI 250 mcg vs Placebo
6. NEMI 500 mcg vs Placebo
7. NEMI 750 mcg vs Placebo

5.2. Baseline Definitions

For all endpoints, the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Baseline FEV_1 is defined as FEV_1 measured prior to the first dose of study treatment and post-bronchodilator on Day 1.

Baseline CAT Total Score is defined as CAT Total Score measured prior to the first dose of study treatment on Day 1.

Baseline SGRQ Total Score is defined as SGRQ Total Score measured prior to the first dose of study treatment on Day 1.

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

Prior to use in any statistical model, Baseline will be 'centred'. A centred baseline will be derived for each participant by subtracting the mean baseline across all participants from each participant's baseline value.

5.3. Multicentre Studies

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

5.4. Examination of Covariates and Subgroups

5.4.1. Covariates

The list of covariates may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses. Additional covariates of clinical interest may also be considered. The decision to include covariates in the model will be based on their impact on the model fit and will be detailed in the CSR.

Any continuous covariates will be 'centred' prior to use in statistical models. A centred covariate will be derived for each participant by subtracting the mean covariate across all participants from each participant's covariate value.

Covariate	Details
Index exacerbation severity	Categorical variable (Moderate or Severe), collected in eCRF. The stratification variable from the randomisation system may be used at the interim analyses if data in eCRF is sparse.
Age (at screening)	Continuous variable derived as described in Section 13.6.2.1
BMI	Continuous variable derived using Height and Weight variables collected in eCRF: BMI = Weight (kg) / (Height (m))^2
Gender	Categorical variable (Male or Female), collected in eCRF
Country	Categorical variable
Smoking status	Categorical variable (Current or Former), collected in eCRF
Baseline COPD maintenance therapy type	Categorical variable derived depending on data observed
Index exacerbation type	Categorical variable: New or Relapse, derived using the question: "Other than the current prescription, for the index exacerbation, has the subject received oral/systemic corticosteroids and/or antibiotics for a COPD exacerbation within the last 7 days?" in the eCRF: New = No Relapse = Yes
Number of exacerbations in the previous 12 months	Categorical variable derived from "Total number of COPD exacerbations in the last 12 months" in the eCRF

5.4.2. Examination of Subgroups

The list of subgroups may be used in descriptive summaries and statistical analyses. Additional subgroups of clinical interest may also be considered.

- If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined.
- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup.

Subgroup	Categories
Index exacerbation severity	Moderate vs. Severe
Baseline COPD maintenance therapy type	Possible categories of interest are: Monotherapy vs. Dual therapy vs. Triple therapy
Index exacerbation type	New vs. Relapse
Number of exacerbations in the previous 12 months	Possible categories of interest are: 0 vs. 1 vs. ≥2
Gender	Male vs. Female
Smoking status	Current vs. Former

5.5. Other Considerations for Data Analyses and Data Handling Conventions

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

Section	Component
Section 13.2	Appendix 2: Assessment Windows
Section 13.3	Appendix 3: Study Phases and Treatment Emergent Adverse Events
Section 13.4	Appendix 4: Data Display Standards & Handling Conventions
Section 13.5	Appendix 5: Derived and Transformed Data
Section 13.6	Appendix 6: Reporting Standards for Missing Data
Section 13.7	Appendix 7: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the "APE" and/or "MITT" populations, unless otherwise specified.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, and exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 11: List of Data Displays.

6.1.1. Concomitant medications

Concomitant medications will be summarised by treatment group. Separate summaries of Baseline and On-treatment (Step-up) COPD Maintenance Therapy, and duration of OCS use will also be presented.

Additional summaries or sensitivity analyses of on-treatment COPD maintenance therapy (step-up therapy) may be performed if the data indicate that further investigation is warranted.

7. EFFICACY ANALYSES

Details of the outputs are provided in Appendix 11: List of Data Displays and will be based on GSK data standards and statistical principles.

Details of Study Day calculations, including protocol-defined time windows, for use in the endpoint derivations below can be found in Section 13.2.

7.1. Primary Efficacy Analyses

7.1.1. Primary Endpoint

The primary endpoint of change from baseline in clinic visit trough FEV_1 at Day 84 measured post-bronchodilator is defined as:

FEV_1 measured prior to dosing and post-bronchodilator on Day 84 – Baseline FEV_1

7.1.2. Primary Statistical Analyses

The primary endpoint will be analysed, by first intent, using a Bayesian 4-parameter E_{max} dose response model. Should the data not allow for a suitable model fit, then the following Bayesian models will be attempted in this sequential order: a 3-parameter E_{max} model and a Log-linear model.

The 4-parameter E_{max} dose response model will take the form:

$$\text{Change from baseline } FEV_1 = (E0 + a_1 * baseline) + \frac{(E_{max} + b_1 * baseline) * Dose^{\gamma}}{ED50^{\gamma} + Dose^{\gamma}}$$

Where: E0 = the response at dose = 0 (placebo)

E_{max} = the maximal response

ED50 = the dose that yields 50% of the maximal response

γ = the slope parameter

a_1, b_1, are covariates for explanatory parameters

Initially, normal non-informative priors will be used for the E0, a_1, a_2, and E_{max} parameters with mean 0 and standard deviation 1E6 L. A functional uniform prior will be used for the ED50 and slope parameters (Bornkamp, 2014), where the prior density for the functional uniform prior is based on all the parameters in the model. An inverse - gamma prior with shape of 0.001 and scale of 0.001 will be used for the residual variance. However, if a prior distribution appears not to be truly non-informative then alternative prior distributions may be used.

Parameters will be blocked such that the MCMC procedure samples from E0, a_1, b_1, and E_{max}, first, then the ED50 and slope parameters and then finally the residual variance

parameter. For the functional uniform priors, the density will be calculated for values of dose from 0.0001 to 750 in steps of 50 (i.e. 0.0001, 50.0001, 100.0001,…, 750.0001). For the continuous covariates, the density will be calculated from the minimum to the maximum in 10 equal steps. For binary covariates the density will be calculated for values 0 and 1. If the model does not converge including covariates, the model may be fitted with covariates removed.

If the log-linear model is fitted an offset of 1 will be used.

The posterior median change from baseline with 95% Highest Posterior Density (HPD) Credible Intervals, will be presented for each dose along with the adjusted median difference from placebo with 95% HPD. Posterior probabilities that the true improvement is greater than 0 mL, 50 mL and 100 mL will also be presented. Graphical representation of the dose response across the full dose range will also be produced to allow inference to be made for the non-studied doses based upon the model fit.

For the futility analysis:

The predictive probability of success at the end of the study will be calculated for each dose using the formula suggested by Spiegelhalter et al., 2004 as follows:

$$Predictive\ probability\ (\%) = \Phi\left[\frac{\sqrt{(m+n)}}{\sqrt{mn}}\frac{(my_m)}{\sigma} + \sqrt{\frac{m}{n}}z_{0.9}\right]$$

Where m is the average number of subjects with Day 84 data in the placebo and dose arm of interest, n is the average number of subjects yet to be observed, y_m is the posterior mean difference from placebo from the fitted model, σ is the standard deviation of the posterior mean difference from placebo.

For the possible adaptations at Interim Analysis 2:

If the study is not deemed futile, and either the 4 parameter or 3 parameter E_{max} dose response curves has successfully been fitted to the data then adaptation of the randomisation schedule will be considered, to drop, add or amend doses from the randomisation scheme.

The adaptation will be done by comparing the relative information from alternative randomisation schemes with the original randomisation schemes, such to find the design that provides the most information about the dose response relationship. The efficiency ratio (ER) for an alternative scheme comparted to the original, will be calculated as:

$$ER(\theta_i) = \left(\frac{|M(\xi_1,\theta_i)|}{|M(\xi_F,\theta_i)|}\right)^{\frac{1}{p}},\ i=1,\ldots,1000$$

Where $M(\xi,\theta)$ is the information matrix for the design ξ and model parameters $\theta = (e0, emax, ed50, \gamma)^T$, ξ_1 is the alternative design one and $\xi_F$is the fixed original design. In order to ensure any adaptation is robust to the variability in the parameter estimates at the interim analysis, 1000 samples will be generated from the posterior distribution of the parameters $\theta_1, \ldots, \theta_{1000}$ and the ER calculated for each set of

parameter. Adaptation will then only take place if the median ER is >1.05 and the 10th percentile of the ER is >1.

7.1.2.1. Model Checking & Diagnostics

The following list of convergence diagnostics will be applied for each parameter:

- The Monte Carlo Standard Errors (MCSE) should be compared with the standard deviation of the posterior distribution (SD) to ensure that only a fraction of the posterior variability is due to the simulation. The number of samples generated and/or the thinning may be increased to reduce the ratio of the MCSE/SD as deemed necessary.
- The Geweke diagnostic test will be used to assess whether the mean estimates have converged by comparing means from the early and latter part of the Markov chain using a z-score t-test. Large absolute values of the z-score statistic indicate rejection of the null hypothesis of no difference between the mean estimates obtained from the early and latter parts of the chain.
- Trace plots of samples versus the simulation index will be visually inspected to assess some aspects of convergence. The centre of the chain should appear stable with very small fluctuations, i.e., the distribution of points should not change as the chain progresses and the posterior mean and variance are relatively constant.
- Autocorrelation plots will be visually inspected to assess degree of autocorrelation (should decline rapidly and show no oscillation patterns).

7.1.3. Sensitivity and Supportive Analyses

If there are greater than 20% of participants with an important protocol deviation that results in exclusion from the Per Protocol Population, the primary analysis may be repeated using the Per Protocol Population.

Change from baseline in clinic visit trough FEV_1 at Day 84 will also be compared between treatment groups using a Bayesian Repeated Measures analysis with covariates for baseline-by-Day interaction and treatment-by-Day interaction. Day will be fitted as a repeated effect within each participant. All post-baseline scheduled visits will be included in the analysis using Day. Non-informative priors will be used for all modelling parameters. Wherever possible conjugate priors will be utilised. An unstructured covariance matrix will be used to model the within-subject error.

A further sensitivity analysis may be performed where Baseline FEV_1 is replaced with the FEV_1 measured post-bronchodilator and prior to dosing on day of hospital discharge for participants who were hospitalised for their index exacerbation, i.e. who were randomised with a Severe index exacerbation but kept as Baseline FEV_1 for participants who were randomised with a Moderate index exacerbation.

7.1.4. Subgroup Analyses

A subgroup analysis of change from baseline in clinic visit trough FEV_1 by index exacerbation severity will be performed by including the severity covariate term in the

model, if possible. For the Bayesian 4-parameter E_{max} dose response model this would take the form:

Change from baseline FEV_1 =

$$(E0 + a_1 * baseline + a_2 severity) + \frac{(E_{max} + b_1 * baseline + b_2 * severity) * Dose^{\gamma}}{ED50^{\gamma} + Dose^{\gamma}}$$

Where a_1, a_2, b_1, b_2 are covariates for explanatory parameters.

If there are convergence issues, then the model for the primary endpoint may be fitted separately to each level of the subgroup.

A subgroup analysis of change from baseline in clinic visit trough FEV_1 by index exacerbation severity will also be performed by including a treatment-by-severity-by-Day interaction term in the Bayesian Repeated Measures model.

7.2. Secondary Efficacy Analyses

7.2.1. Rate of exacerbations

Rate of exacerbation is defined as the frequency of exacerbations (subsequent to the index exacerbation) within the specified time period, for example, the 12-Week Treatment Period or the 24-Week Study Period.

The length of time on treatment or in study, depending on the specified time-period, for each participant will be calculated for each endpoint as follows:

Endpoint	Time period	Length of time derivation
Rate of (on-treatment) exacerbations, summarised by: • Moderate and severe exacerbations • Moderate exacerbations • Severe exacerbations • All (mild, moderate and severe) exacerbations	12-Week Treatment Period	Time from date of randomisation to date of last dose of study treatment
Rate of (on-or off-treatment) exacerbations, summarised by: • Moderate and severe exacerbations • All exacerbations	12-Week Treatment Period	Time from date of randomisation to Day 84. For participants who withdraw early from the study: Time from date of randomisation to date of study withdrawal
Rate of (off-treatment) exacerbations, summarised by: • Moderate and severe exacerbations • Moderate exacerbations	12-Week Follow Up Period	Time from date of last dose of study treatment to date of last follow up assessment

Endpoint	Time period	Length of time derivation
• Severe exacerbations		
Rate of (on- and off- treatment) exacerbations, summarised by: • Moderate and severe exacerbations • Moderate exacerbations • Severe exacerbations	Full 24-Week Study Period	Time from date of randomisation to date of last follow up assessment

Refer to Section 13.5 for further details regarding the length of time derivation

7.2.1.1. Statistical analyses

The rate of exacerbations will be analysed using a Bayesian generalized linear model assuming a negative binomial distribution for the underlying exacerbation rate with a log link function. An offset to account for the length of time on treatment or in study, depending on the specified time-period, for each participant (as described above) will be included in the model as $\log_e$ (length of time).

Non-informative priors will be used for all modelling parameters. Wherever possible conjugate priors will be utilised.

The median exacerbation rates for each dose arm per 12 weeks, along with the median ratio in exacerbation rates (nemiralisib/placebo) per 12 weeks for each dose, will be estimated and corresponding 95% HPD credible intervals presented. The probability that the true exacerbation rate ratio is less than 1, in addition to other values appropriately selected based on the data, will be presented.

Based on pharmacological predictions, the 500 mcg and 750 mcg doses are expected to result in similar levels of target inhibition and thus potentially translate to similar clinical benefit, therefore estimates of the exacerbation rates for pooled data from 500 mcg plus 750 mcg will also be presented.

7.2.1.2. Subgroup analyses

A subgroup analysis of exacerbation rate by Index exacerbation severity will be performed by including a treatment-by-severity term in the model.

7.2.1.3. Exploratory analyses

A summary of exacerbation rate by the following groups will be presented and, if feasible, a subgroup analyses may be performed:

- Index exacerbation type (New or Relapse)
- Number of exacerbations in previous 12 months (0, 1 or ≥2).

7.2.2. Time to next exacerbation

Time to next (on-treatment) exacerbation following index exacerbation during the 12-Week Treatment Period is defined as time from the date of randomisation until the date of onset of the first exacerbation whilst on study treatment. Participants who did not have an exacerbation whilst on study treatment will be censored at the date of their last dose of study treatment.

Time to next (on-or off-treatment) exacerbation during the 12-Week Treatment Period is defined as time from the date of randomisation until the date of onset of the first exacerbation occurring up to Day 84. Participants who have not had an exacerbation during the 12-Week Treatment Period will be censored at Day 84 or the date of study withdrawal, for participants who withdrew from the study prior to Day 84.

Time to next exacerbation following cessation of study treatment is defined as time from the date of last dose of study treatment until the date of onset of the next exacerbation whilst off study treatment during the 12-Week Follow Up Period. Participants who have not had an exacerbation off-treatment will be censored at the date of their last follow up assessment.

Time to next exacerbation will be analysed by severity, as follows:

Endpoint	Time period
Time to next (on-treatment) exacerbation, summarised by: • Moderate and severe exacerbations • Moderate exacerbations • Severe exacerbations • All (mild, moderate and severe) exacerbations	12-Week Treatment Period
Time to next (on-or off-treatment) exacerbation, summarised by: • Moderate and severe exacerbations • All exacerbations	12-Week Treatment Period
Time to next exacerbation following cessation of treatment, summarised by: • Moderate and severe exacerbations • Moderate exacerbations • Severe exacerbations	12-Week Follow Up Period

Refer to Section 13.5 for further details regarding the length of time derivation

7.2.2.1. Statistical analyses

Time to next exacerbation will be analysed using a Bayesian Cox proportional hazards model with the “Efron” method for handling ties. Kaplan-Meier (KM) estimates of the probability of exacerbation will also be presented.

Non-informative priors will be used for all modelling parameters. Wherever possible conjugate priors will be utilised.

The hazard ratio and corresponding 95% HPD credible intervals for each nemiralisib dose versus placebo will be presented. The probability that the true hazard ratio is less than 1, in addition to other values appropriately selected based on the data, will be presented.

Based on pharmacological predictions, the 500 mcg and 750 mcg doses are expected to result in similar levels of target inhibition and thus potentially translate to similar clinical benefit, therefore an estimate of hazard ratio for pooled data from 500 mcg plus 750 mcg nemiralisib doses versus placebo will also be presented.

7.2.2.2. Subgroup analyses

A subgroup analysis of time to exacerbation by Index exacerbation severity will be performed by including a treatment-by-severity term in the model.

7.2.3. Change from baseline in Clinic Visit trough FEV_1

Change from baseline in clinic visit trough FEV_1 at Day 14, 28, 56 measured post-bronchodilator is defined as:

FEV_1 measured prior to dosing and post-bronchodilator on Day X – Baseline FEV_1

Where Day X is Day 14, 28, and 56.

Change from baseline in clinic visit trough FEV_1 at Day 14, 28, 56, 84 measured pre-bronchodilator is defined as:

FEV_1 measured prior to dosing and pre-bronchodilator on Day X – Baseline FEV_1

Where Day X is Day 14, 28, 56, and 84.

7.2.3.1. Statistical Analyses

Change from baseline in Clinic Visit trough FEV_1 will be analysed using a dose response model and repeated measures analysis as described for the primary endpoint in Section 7.1.2.

7.2.3.2. Subgroup analyses

A subgroup analysis of change from baseline in clinic visit trough FEV_1 by index exacerbation severity will be performed.

7.2.4. Change from hospital discharge in clinic visit trough FEV_1

Change from hospital discharge in clinic visit trough FEV_1 will be derived only for participants who were hospitalised for their index exacerbation and who have been subsequently discharged.

Change from hospital discharge in clinic visit trough FEV_1 measured post-bronchodilator is defined as:

FEV_1 measured prior to dosing and post-bronchodilator on Day X – FEV_1 measured post-bronchodilator and prior to dosing on day of hospital discharge.

Where Day X is 14, 28, 56 and 84.

Change from hospital discharge in clinic visit trough FEV_1 measured pre-bronchodilator is defined as:

FEV_1 measured prior to dosing and pre-bronchodilator on Day X – FEV_1 measured prior to dosing and post-bronchodilator on day of hospital discharge.

Where Day X is 14, 28, 56 and 84.

Note, as per Section 5.1 of the Protocol, if discharge takes place between Day 11 and Day 17 (inclusive), the assessments planned for Day 14 may be completed on the day of discharge. In these cases, for this endpoint only, the FEV_1 assessment will be assigned the hospital discharge assessment and the Day 14 assessment will be missing. Refer to Section 13.2.1.1 for further details.

In addition, if discharge takes place after Day 14, the Day 14 assessment will be missing for this analysis.

7.2.4.1. Statistical analyses

Change from hospital discharge in clinic visit trough FEV_1 will be analysed using a dose response model and repeated measures analysis as described for the primary endpoint in Section 7.1.2 if there are a sufficient number of participants to provide a meaningful analysis, otherwise the data will be summarised.

7.2.5. EXAcerbations of Chronic Pulmonary Disease Tool - Patient Reported Outcome (EXACT)

The EXACT is a 14-item daily diary designed to provide a measure of patient-reported symptoms of COPD exacerbation. An EXACT Total Score, ranging from 0 to 100, where higher scores indicate a more severe condition, will be derived for each day of diary collection according to the instructions in the EXACT User Manual (Version 8.0, Evidera, 2016).

The electronic EXACT diary does not allow a study patient to skip individual items, therefore no missing data are expected for individual items. However, if missing values occur for individual items, the Total Score that contains the item will be set to missing for that day. Moderate-to-severe COPD patients are expected to experience symptom(s) each day, and a score of zero on all 14 EXACT items is likely to represent a situation where in order to complete the diary quickly, the respondent did not accurately report their daily symptom(s), therefore if the EXACT Total Score is 0, it will be set to missing.

A 3-day Rolling Average EXACT Total Score will be calculated for each day, X, as:

(EXACT Total Score on Day X-1 + EXACT Total Score on Day X + EXACT Total Score on Day X+1) / (Number of days with non-missing values)

Note, for Day 1, the Rolling Average EXACT Total Score will be calculated as the average of EXACT Total Score on Days 1 (Randomisation) and 2 only, since no EXACT data is collected prior to randomisation. Similarly, the Rolling Average EXACT Total Score for the last study day will be calculated as the average of EXACT Total Score on the last day and on the day before the last day.

The Rolling Average EXACT Total Score will be calculated for each day as long as at least 1 EXACT total score in the sequence is present. Therefore, only in the case where EXACT total scores are missing for 3 consecutive days in a row (or 2 consecutive days in the case of the first and last day rolling average calculation), will the rolling average score be missing.

The Maximum Observed Value (MOV) is defined as the highest Rolling Average EXACT Total Score observed within the first 14 days of randomisation. Note: this definition differs from the definition in the EXACT User Manual of "the highest rolling average EXACT score observed in the context of an EXACT exacerbation within the first 14 days of the exacerbation", since the date of the index exacerbation is likely to be prior to randomisation.

7.2.5.1. Proportion of participants achieving EXACT-defined recovery from index exacerbation

EXACT-defined recovery from the index exacerbation is defined as a decrease in the Rolling Average EXACT Total Score ≥9 points from the Maximum Observed Value, sustained for ≥7 days, with the first of the 7 days defined as the recovery day.

The proportion of participants achieving EXACT-defined recovery from the index exacerbation by Days 14, 28, 56, and 84 will be calculated as:

(Number of participants who experience an EXACT-defined recovery on or before Day X) / (Total number of participants in the MITT population)

Where Day X is 14, 28, 56, and 84.

7.2.5.2. Time to EXACT-defined recovery from index exacerbation

Time to EXACT-defined recovery from index exacerbation is defined as time from the date of randomisation until date of the first EXACT-defined recovery day during the 12-Week Treatment Period, where EXACT-defined recovery is described in Section 7.2.5.1. Participants who did not experience EXACT-defined recovery during the 12-Week Treatment Period will be censored at the date of their last dose of study treatment.

7.2.5.3. Severity of subsequent HCRU-defined exacerbation(s) defined by EXACT

Severity of subsequent HCRU-defined exacerbation(s) defined by EXACT is defined as the highest EXACT Total Score (not using the 3-day Rolling Average) during the period

from date of onset of the subsequent HCRU-exacerbation until date of EXACT-defined recovery of subsequent exacerbation.

Note, in this case, the Maximum Observed Value and EXACT-defined recovery are derived using the date of onset of the subsequent HCRU-exacerbation.

Severity of subsequent HCRU-defined exacerbation(s) defined by EXACT will only be derived for participants who have had a subsequent exacerbation. If a participant has more than one subsequent exacerbation, severity will be calculated for each subsequent exacerbation.

7.2.5.4. Statistical analyses

The proportion of participants achieving EXACT-defined recovery from the index exacerbation will be analysed using a Bayesian logistic regression model. Separate models will be fitted for each time-point.

Non-informative priors will be used for all modelling parameters. Wherever possible conjugate priors will be utilised.

The results of the analysis will be presented in terms of odds ratios together with its associated 95% HPD credible interval. The probability that the true odds ratio is greater than 1, in addition to other values appropriately selected based on the data, will be presented.

Time to EXACT-defined recovery from index exacerbation will be analysed using the same techniques as described in Section 7.2.2.1.

Severity of subsequent HCRU-defined exacerbation(s) defined by EXACT will be summarised for each treatment group and reported by study period. The severity of subsequent HCRU-defined exacerbation(s) occurring whilst a participant is on treatment will be reported as during the 12-Week Treatment Period and the severity of subsequent HCRU-defined exacerbation(s) occurring after the last dose of study treatment will be reported as during the 12-Week Follow-up Period.

7.2.5.5. Subgroup analyses

A subgroup analysis of the proportion of participants achieving EXACT-defined recovery from the index exacerbation by Index Exacerbation Severity will be performed by including a treatment-by-severity term in the model.

7.2.5.6. Sensitivity and supportive analyses

Sensitivity analyses exploring the impact of any missing data, and changes to the definition of EXACT-defined recovery may be conducted and may be performed post-SAC.

7.2.6. COPD Assessment Test (CAT)

The COPD Assessment Test (CAT) is a patient completed questionnaire developed to measure the health status of patients with COPD. The CAT consists of eight items, each on a six-point scale: 0 (no impact) to 5 (high impact). The CAT Score will be calculated for each study day of collection by summing the scores for all questions. The CAT Score ranges from 0 to 40, where higher scores indicate a more severe condition.

7.2.6.1. Proportion of responders using the CAT

The proportion of responders using the CAT will only be derived for participants with a baseline CAT Total Score ≥2.

The Proportion of responders using the CAT is defined as:

> (Number of participants with a decrease from baseline in CAT Total Score ≥2 on or before Day X)/(Total number of participants in the MITT population)

Where Day X is 28, 56, and 84, and the study day following EXACT-defined recovery from the index exacerbation.

Note: due to software limitations of the electronic PRO device, the study day following EXACT-defined recovery is not derived according to the EXACT User Manual, see Section 13.2.1.2 for further details.

Exploratory – Follow-Up Period

The Proportion of responders using the CAT at Day 112 and 168 is defined as:

> (Number of participants with a decrease from baseline in CAT Total Score ≥2 on or before Day X)/(Total number of participants in the MITT population)

Where Day X is FU Day 28 and FU Day 56, as defined in Section 13.2.1, and the study day following EXACT defined recovery, if it occurs during the Follow-up period.

7.2.6.2. Change from baseline in CAT Total Score

Change from baseline in CAT Total Score is defined as:

> CAT Total Score on Day X – Baseline CAT Total Score

Where Day X is 28, 56, 84, and the study day following EXACT defined recovery from the index exacerbation.

Note: due to software limitations of the electronic PRO device, the study day following EXACT-defined recovery is not derived according to the EXACT User Manual, see Section 13.2.1.2 for further details.

Exploratory – Follow-Up Period

The Change from baseline in CAT Total Score at Day 112 and 168 is defined as:

CAT Total Score on Day X – Baseline CAT Total Score

Where Day X is FU Day 28 and FU Day 84, as defined in Section 13.2.1.

The Change from end of treatment in CAT Total Score at Day 112 and 168 is defined as:

CAT Total Score on Day X – CAT Total Score on Day 84

Where Day X is FU Day 28 and FU Day 84, as defined in Section 13.2.1.

7.2.6.3. Statistical analyses

The proportion of responders using CAT will be analysed using the same techniques as described in Section 7.2.5.4.

Change from baseline in CAT Total Score will be compared between treatment groups using a Bayesian Repeated Measures analysis with covariates for baseline-by-Day interaction and treatment-by-Day interaction. Day will be fitted as a repeated effect within each participant.

All post-baseline scheduled visits will be included in the analysis using Day.

Non-informative priors will be used for all modelling parameters. Wherever possible conjugate priors will be utilised. An unstructured covariance matrix will be used to model the within-subject error.

Adjusted posterior median change from baseline and corresponding 95% HPD credible intervals will be summarised for each treatment by time-point, together with estimated treatment differences (GSK – Placebo) and corresponding 95% HPD credible intervals. The posterior probability that the true treatment difference is less than 0, in addition to other values appropriately selected based on the data, will also be presented.

7.2.6.4. Subgroup analyses

A subgroup analysis of the proportion of responders using CAT and the change from baseline in CAT Total Score by Index exacerbation severity will be performed by including a treatment-by-severity term and a treatment-by-severity-by-Day term in the Bayesian logistic regression and Bayesian Repeated Measures models, respectively.

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

St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C) is a 40-item questionnaire designed specifically to focus on COPD patients. SGRQ-C will be scored to be equivalent to the SGRQ Total Score, ranging from 0 to 100, where higher scores reflect worse health-related quality of life. SGRQ Total Scores will be calculated for each

day of collection according to the instructions in SGRQ-C Manual (Version 1.3, March 2016).

7.2.7.1. Proportion of responders on the SGRQ Total Score

The proportion of responders on the SGRQ Total Score will only be derived for participants with a baseline SGRQ Total Score ≥4.

Proportion of responders on the SGRQ Total Score is defined as:

> (Number of participants with a decrease from baseline in SGRQ Total Score ≥4 on or before Day X)/(Total number of participants in the MITT population)

Where Day X is 28, 56, and 84.

Exploratory – Follow-Up Period

The Proportion of responders on the SGRQ Total Score at Day 112 and 168 is defined as:

> (Number of participants with a decrease from baseline in SGRQ Total Score ≥4 on or before Day X)/(Total number of participants in the MITT population)

Where Day X is FU Day 28 and FU Day 84, as defined in Section 13.2.1 and the study day following EXACT defined recovery, if it occurs during the Follow-up period.

7.2.7.2. Change from baseline in SGRQ Total Score

Change from baseline in SGRQ Total Score is defined as:

> SGRQ Total Score on Day X – Baseline SGRQ Total Score

Where Day X is Day 28, 56, and 84.

Exploratory – Follow-Up Period

The Change from baseline in SGRQ Total Score at Day 112 and 168 is defined as:

> SGRQ Total Score on Day X – Baseline SGRQ Total Score

Where Day X is FU Day 28 and FU Day 84, as defined in Section 13.2.1.

The Change from end of treatment in SGRQ Total Score at Day 112 and 168 is defined as:

> SGRQ Total Score on Day X – SGRQ Total Score on Day 84

Where Day X is FU Day 28 and FU Day 84, as defined in Section 13.2.1.

7.2.7.3. Statistical analyses

Change from baseline in SGRQ Total Score and the proportion of responders on the SGRQ Total Score will be analysed using the same techniques as described in Section 7.2.6.3.

7.2.7.4. Subgroup analyses

Subgroup analyses of change from baseline in SGRQ Total Score and the proportion of responders on the SGRQ Total Score by Index exacerbation severity will be conducted as described in Section 7.2.6.4.

7.2.8. Rescue medication use

All participants will record rescue medication use in the eDiary. Rescue medication use will be recorded as the number of occasions of rescue medication use each day.

The Mean Number of (on-treatment) Occasions of Rescue Medication Use Per Day is defined as:

> (Sum of the number of occasions of rescue medication use each day within the time-period) / (Total number of days with non-missing values within the time-period)

The Percentage of (on-treatment) Rescue-Free Days is defined as:

> (Sum of the number of days where the number of occasions of rescue medication use is zero within the time-period) / (Total number of days with non-missing values within the time-period)*100

Where the time-period is defined as follows:

Week 1 of the 12-Week Treatment Period: Day 1 to Day 7

Week 2 of the 12-Week Treatment Period: Day 8 to Day 14

Week 3 of the 12-Week Treatment Period: Day 15 to Day 21

Week 4 of the 12-Week Treatment Period: Day 22 to Day 28

Week 5 of the 12-Week Treatment Period: Day 29 to Day 35

Week 6 of the 12-Week Treatment Period: Day 36 to Day 42

Week 7 of the 12-Week Treatment Period: Day 43 to Day 49

Week 8 of the 12-Week Treatment Period: Day 50 to Day 56

Week 9 of the 12-Week Treatment Period: Day 57 to Day 63

Week 10 of the 12-Week Treatment Period: Day 64 to Day 70

Week 11 of the 12-Week Treatment Period: Day 71 to Day 77

Week 12 of the 12-Week Treatment Period: Day 78 to Day of last dose

Over the 12-Week Treatment Period: Day 1 to Day of last dose.

Exploratory – Follow-Up Period

Rescue medication use up to Day 112 will also be summarised by including the time-periods:

Week 13 (Follow-up Period): (Day of last dose + 1) to (Day of last dose + 1) + 6 days

Week 14 (Follow-up Period): (Day of last dose + 7) to (Day of last dose + 1) + 13 days

Week 15 (Follow-up Period): (Day of last dose + 14) to (Day of last dose + 1) + 20 days

Week 16 (Follow-up Period): (Day of last dose + 21) to (Day of last dose + 1) + 27 days

For a subject to be counted in the time periods for rescue medication use, they must have at least one eDiary entry recorded during that time period.

7.2.8.1. Rescue medication use via the clip-on Propeller Sensor for MDI

A subset of participants from countries where the Propeller Sensor for MDI is available will also record rescue medication use via the clip-on Propeller Sensor for MDI. A supportive summary of rescue medication use via the clip-on Propeller Sensor for MDI for these participants will be presented.

Rescue medication use via the clip-on Propeller Sensor for MDI is defined in the same way as rescue medication use via the eDiary, except that the number of actuations will be used instead of the number of occasions in accordance with the way the data is captured.

7.2.8.2. Statistical analyses

The Mean Number of (on-treatment) Occasions of Rescue Medication Use Per Day will be summarised between each treatment group using means, standard deviations, medians, minimum and maximum.

The Percentage of (on-treatment) Rescue-Free Days will be summarised between each treatment group using means, standard deviations, medians, minimum and maximum.

The Percentage of Participants Taking (on-treatment) Rescue Medication By Day for each treatment group will also be presented.

Rescue medication use via the clip-on Propeller Sensor for MDI will be summarised in the same way as rescue medication use via the eDiary.

7.3. Exploratory Efficacy Analyses

7.3.1. Change from Day 84 in Clinic Visit trough FEV_1

Change from Day 84 in clinic visit trough FEV_1 measured post-bronchodilator is defined as:

FEV_1 measured prior to dosing and post-bronchodilator on Day X – Day 84 post-bronchodilator FEV_1

Where Day X is FU Day 28, FU Day 56 and FU Day 84, as defined in Section 13.2.1.

Change from Day 84 in clinic visit trough FEV_1 measured pre-bronchodilator is defined as:

FEV_1 measured prior to dosing and pre-bronchodilator on Day X – Day 84 post-bronchodilator FEV_1

Where Day X is FU Day 28, FU Day 56 and FU Day 84, as defined in Section 13.2.1.

Participants who discontinue study treatment prior to Day 84 will be excluded from this analysis.

7.3.1.1. Statistical analysis

Change from Day 84 in Clinic Visit trough FEV_1 will be analysed using the same techniques as described for Change from baseline in CAT Total Score in Section 7.2.6.3.

A subgroup analysis of change from Day 84 in FEV_1 will be performed by including a treatment-by-severity-by-Day term in the Bayesian Repeated Measures model.

7.3.2. E-RS:COPD (Evaluating Respiratory Symptoms in COPD)

Change from baseline in E-RS: COPD and subscales will be summarised by treatment group. Exploratory analyses related to E-RS: COPD and subscales may be performed post SAC.

7.3.3. Measures of HCRU related to exacerbations

Unscheduled Healthcare Utilisation will be summarised separately for exacerbation-related, COPD-related or non-COPD related; each summary will be presented by all patients (i.e. moderate and severe index exacerbation combined), and separately by index exacerbation severity.

The number of days of hospital admission for the index and subsequent exacerbations will also be summarised by treatment group.

7.3.3.1. Re-hospitalisation within 30 days of index exacerbation

Re-hospitalisation within 30 days of index exacerbation is defined as 30 days from the date of hospital discharge until the date of next hospital admission (+ 1 day, to account for study day derivation), for participants who were hospitalised for their index exacerbation.

Exacerbation-related, COPD-related and Non-COPD-related hospital admissions are collected in separate eCRFs. The date of hospital admission is not collected in the COPD-related eCRF, therefore the date of next hospital admission will be estimated using the earliest of:

- Date of hospital admission for exacerbation-related hospitalisations
- Date of contact for COPD-related hospitalisations, where the number of inpatient hospitalisation days >0
- Date of hospital admission for non-COPD-related hospitalisations.

The proportion of participants who were re-hospitalised within 30 days of the index exacerbation will be summarised by each treatment arm.

7.3.3.2. Time from resolution of index exacerbation to next exacerbation

Time from resolution of index exacerbation to next exacerbation is defined as time from the date of (Investigator-defined) resolution of index exacerbation until the date of onset of the subsequent exacerbation.

A summary of time from resolution of index exacerbation to next exacerbation will be presented. Participants who did not have a subsequent exacerbation or for whom the index exacerbation was not resolved will be excluded from the summary.

Time from resolution of index exacerbation to next exacerbation will only be derived for the first subsequent exacerbation following the index exacerbation.

7.3.3.3. Subsequent exacerbation treatment type

A summary of the type of treatment for subsequent exacerbations (OCS, antibiotics, or both) may also be presented.

7.3.4. Compliance

Reported compliance for all participants is captured daily in the eDiary from the question "Did you take this morning’s dose of study medication”?

Percentage compliance for each participant is calculated as:

(Sum of the number of days where the question was answered with ‘Y’) / (Number of days from first dose of study treatment to last dose of study treatment) x 100

Overall percentage compliance will be summarised by each treatment group.

7.3.4.1. Number of actuations of double-blind study treatment measured by the clip-on Propeller Sensor

Percentage compliance via the clip-on Propeller Sensor for ELLIPTA in the subset of participants from countries where the Propeller Sensor for ELLIPTA is available is calculated as:

(Sum of the total number of actuations) / (Number of days from first dose of study treatment to last dose of study treatment) x 100

Overall percentage compliance will be summarised by each treatment group.

7.3.5. Inflammatory/infective markers in blood and sputum in relation to acute exacerbation of COPD

Results of the analysis of blood/spontaneous sputum samples of eosinophil counts and inflammatory/infective mediators/markers will be summarised by treatment group.

Further analyses of inflammatory/infective markers may be performed, for example split by CRP high, CRP low, Procalcitonin high, etc. categories.

7.3.6. Other spirometry measurements

Percent predicted FEV_1, Forced Vital Capacity (FVC), percent predicted FVC and FEV/FVC ratio will be summarised by treatment group.

7.3.7. Other PRO symptoms suggestive of exacerbation

Responses to questions related to PRO symptoms of sputum purulence (colour), fever, sore throat, wheezing and colds collected in the eDiary will be listed by treatment group.

8. SAFETY ANALYSES

The safety analyses will be based on the Safety population, unless otherwise specified. The details of the planned displays will be provided in Appendix 11: List of Data Displays.

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs) and Serious (SAEs) will be based on GSK Core Data Standards.

8.1.1. Adverse Events of Special Interest

8.1.1.1. Post-inhalation Cough Immediately Following Dosing

Post-inhalation cough immediately following dosing is an Adverse Event of Special Interest (AESI).

Post-inhalation cough immediately following dosing will be evaluated during study Visits 2-6 in the 12-Week Double-Blind Treatment Period. Investigators (or medically qualified designees) will monitor participants for potential study treatment tolerability issues, including post-inhalation cough, within 5 minutes immediately following dosing.

The percentage of patients experiencing post-inhalation cough following dosing, regardless of whether it was also reported as an AE, overall and by each visit will be summarised for each treatment group. The type of cough, time to onset and duration of cough, and severity will also be summarised.

In addition, any post-inhalation cough immediately following dosing reported as an adverse event during the clinic visit observation or during the course of the study will be summarised by treatment group.

8.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Haematology laboratory tests and liver function tests will be based on GSK Core Data Standards.

8.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified.

8.4. Mortality

A summary of all-cause mortality by treatment will be presented.

9. PHARMACOKINETIC ANALYSES

9.1. Population of Interest

The primary pharmacokinetic analyses will be based on the “Pharmacokinetic” population, unless otherwise specified.

9.2. Drug Concentration Measures

Plasma nemiralisib concentrations of GSK2269557 will be listed and summarised by dose, day and time. Drug levels will be summarised by day (14, 28), dose and time intervals (trough, 0-<1h, 1-6h).

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 13.4.3 Reporting Standards for Pharmacokinetic).

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK Data Standards and statistical principles.

10. POPULATION PK ANALYSIS

A dataset for population PK analysis will be provided by Statistics and Programming based on the NONMEM data specifications in Section 13.8.2.

Conduct of the population PK analyses will be based on the current guidance which contains specific recommendations for working practices, processes and standards for population PK and PK/PD analysis conducted by Clinical Pharmacology Modelling and Simulation (CPMS) [Analysis & Reporting, 2017].

The sparse PK samples will be subjected to a validated population PK model for nemiralisib currently under development.

Details of these analyses will be described in a separate CPMS RAP and results will be reported separately to the CSR. Analyses and reporting of the population PK model will be in accordance with the FDA and EMEA guidance on population PK, PK-PD analyses.

10.1. Derived Pharmacokinetic Parameters

The exposure parameters (e.g. AUC, C_{max}) will be derived from the individual post-hoc estimates from the POP PK model. These will be summarized across dose treatments, subgroups (e.g., gender, race) or as a function of a continuous variable (e.g., age).

11. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

If statistical analyses suggest an effect of nemiralisib on primary and other key clinical endpoints, an integrated longitudinal population dose/exposure versus clinical response on analysis key parameters including FEV_1 and exacerbation rate will be undertaken. Participant characteristics influencing the relationship will be evaluated.

Details of these analyses will be described in a separate CPMS RAP and results will be reported separately to the CSR.

12. REFERENCES

Bornkamp, B. (2014). Practical considerations for using functional uniform prior distributions for dose-response estimation in clinical trials. Biometrical Journal, 56(6), 947-962. doi: 10.1002/bimj.201300138

Evidera. (2016). The Exacerbations of Chronic Pulmonary Disease Tool (EXACT®) Patient-Reported Outcome (PRO) USER MANUAL (Version 8.0).

Spiegelhalter, D.J., Abrams, K.R. & Myles, J.P., (2004). Bayesian Approaches to Clinical Trials and Health-Care Evaluation. John Wiley & Sons, Ltd.

13. APPENDICES

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

13.1.1. Exclusions from Per Protocol Population

Protocol deviations will be reviewed regularly throughout the course of the study, as described in Protocol Deviation Management Plan (PDMP). Deviations which will result in exclusion from the Per Protocol population will be assigned on a case-by-case basis prior to database freeze (DBF).

Decisions on whether or not the subject should be excluded from the PP population because the incorrect treatment was taken, due to the incorrect container being dispensed, will be identified after unblinding (i.e. post DBF). A PD of “incorrect treatment” will be added to the reporting dataset.

13.2. Appendix 2: Assessment Windows

13.2.1. Definitions of Assessment Windows for Analyses

The target Study Day and Analysis Timepoint for summaries and analyses for participants who do not discontinue treatment prior to the Day 84 (+window) is shown in the table below:

Target	Analysis Window		Analysis Timepoint
	Beginning Timepoint	Ending Timepoint	
Study Day 1	Day 1	Day 1	DAY 1
Study Day 14	Day 11	Day 17	DAY 14
Study Day 28	Day 25	Day 31	DAY 28
Study Day 56	Day 52	Day 59	DAY 56
Study Day 84	Day 80	Day 87	DAY 84
Study Day 112	Day 108	Day 115	FU DAY 28
Study Day 140	Day 136	Day 143	FU DAY 56
Study Day 168	Day 164	Day 171	FU DAY 84

FU = Follow Up

For participants who discontinue treatment prior to Day 84 (+window), a follow-up (FU) Study Day will be derived as:

FU Study Day = (Date of follow-up assessment – Date of last dose of study treatment) +1

The FU Study Day will then be used to assign Study Days and Analysis Timepoints for summaries and analyses as shown in the table below:

Derived follow-up (FU) Study day	Analysis Window		Analysis Timepoint
	Beginning Timepoint	Ending Timepoint	
FU Study Day 28	FU Study Day 24	FU Study Day 31	FU DAY 28
FU Study Day 56	FU Study Day 52	FU Study Day 59	FU DAY 56
FU Study Day 84	FU Study Day 80	FU Study Day 87	FU DAY 84

13.2.1.1. Hospital discharge

For the change from hospital discharge in clinic visit trough FEV_1 endpoint, the assessment on the day of hospital discharge can be derived using the date of hospital discharge for the index exacerbation from the eCRF. As per Section 5.1 of the Protocol, if discharge takes place between Day 11 and Day 17 (inclusive), the assessments planned for Day 14 may be completed on the day of discharge. In these cases, for this endpoint only, the FEV_1 assessment will be assigned the hospital discharge FEV_1 assessment and the Day 14 assessment will be missing.

For all other analyses and summaries that include participants who were hospitalised for their index exacerbation, an additional Analysis Timepoint of "HOSPTIAL DISCHARGE" will be derived. However, in the cases where discharge takes place between Day 11 and Day 17 (inclusive), participants will be summarised under DAY 14 and a footnote to say that participants who were discharged at Day 14 are summarised under DAY 14 will be included.

13.2.1.2. EXACT-Defined Recovery for CAT Trigger

Due to software limitations of the electronic PRO device, the study day following EXACT-defined recovery from the index exacerbation is not derived according to the EXACT User Manual. Instead, it has been derived using a 3-day Rolling Average that is calculated as the mean EXACT score [Day $_{X-2}$, Day $_{X-1}$, Day $_{X}$] .

13.3. Appendix 3: Study Phases and Treatment Emergent Adverse Events

13.3.1. Study Periods

13.3.1.1. 12-Week Treatment Period

The 12-Week Treatment Period is assigned from Study Day 1 to Study Day 84.

13.3.1.2. 12-Week Follow-Up Period

The 12-Week Follow-up Period is assigned from Study Day 85 to Study Day 168.

Refer to Section 13.2.1 for details on how Study Days and Analysis Timepoints will be derived for participants who discontinue treatment prior to Day 84.

13.3.2. Study Phases

Exacerbation events during the 12-Week Treatment Period will be classified according to their occurrence from randomisation until treatment discontinuation/study withdrawal days, as detailed below.

Study Phase	Occurring from randomisation until
On-Treatment during the 12-Week Treatment Period	Treatment Stop Day
On- or Off-Treatment during the 12-Week Treatment Period	Day 84 or Study Withdrawal Day if Treatment Stop Day is < Day 84

13.3.2.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before Randomisation Date
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 6: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

13.3.3. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date & on or before treatment stop date plus 10 days.

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

13.4. Appendix 4: Data Display Standards & Handling Conventions

13.4.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Compound	: \arprod\gsk2269557\mid200879
Analysis Datasets	
• For all interim analyses, except for the End of Treatment Interim Analysis, datasets will be created according to Legacy GSK A&R dataset standards. • For the End of Treatment Interim Analysis and the final reporting effort, datasets will be created according to current CDISC standards	
Generation of RTF Files	
• RTF files will be generated for the final reporting effort.	

13.4.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 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
  • Figures will be produced using PROC SGPLOT in SAS

Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.

Unscheduled Visits	
• Unscheduled visits will be included in summary tables of the worst-case results by potential clinical importance criteria only. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principles 7.01 to 7.13.	

13.4.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PK File	Pop-PK file (CSV format) for the POP-PK analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the data specification detailed in Section 13.8.2 Population Pharmacokinetic (PopPK) Dataset Specification.
NONMEM/PK/PD File	PK/PD file (CSV format) for the PK/PD analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the data specification detailed in the CPMS RAP.

13.5. Appendix 5: Derived and Transformed Data

13.5.1. General

Multiple Measurements at One Analysis Time Point
• If there are two values within a time window (as per Section 13.2.1) the value closest to the target day for that window will be used. If values are the same distance from the target, then the mean will be taken. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from Randomisation Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Randomisation Date → Study Day = Ref Date – Randomisation Date
  • Ref Data ≥ Randomisation Date → Study Day = Ref Date – (Randomisation Date) + 1

Time from date of randomisation and time from date of last dose of study treatment

• For endpoints that use the time from the date of randomisation to a reference date, time will be calculated as
  • (Ref Date – Randomisation Date) + 1
• For endpoints that use the time from the date of last dose of study treatment to a reference date, time will be calculated as
  • (Ref Date – (Last Dose Date + 1)) +1

13.5.2. Study Population

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • The cumulative dose will be based on the formula: **Cumulative Dose = Sum of (Number of Days x Total Daily Dose)** • If there are any treatment breaks during the study, exposure data will be adjusted accordingly.

13.5.3. Safety

Adverse Events
AE'S of Special Interest
• Post-inhalation cough is an AE of special interest. The lower level term (LLT) to be included is "coughing after drug inhalation"

13.6. Appendix 6: Reporting Standards for Missing Data

13.6.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) is defined as completing all phases of the study including the last scheduled study visit • A participant is considered to have completed the Treatment Period, if he/she has completed the last on-treatment study visit (Visit 6) • Withdrawn subjects were not replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Withdrawal visits will be slotted as per Appendix 2: Assessment Windows otherwise they will not be summarised (and will be listed only).

13.6.2. Handling of Missing Data

Element	Reporting Detail

General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument:
	  • These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table.
	  • Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

13.6.2.1. Handling of Missing and Partial Dates

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

Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event:
	  • Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 3: Study Phases and Treatment Emergent Adverse Events.
	  • Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used.
	• Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

Element	Reporting Detail

Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
	  • If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month
	  • If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.
	• The recorded partial date will be displayed in listings.

Age	• The eCRF collects year of birth only. Day and Month will be imputed by Data Management using a PP for the day and PPD for the month • Age will then be derived referenced to the Screening Date • A footnote to say that age has been imputed will be included in any outputs containing age.

13.7. Appendix 7: Values of Potential Clinical Importance

13.7.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Haemoglobin	G/DL	Male 18-64 years	7.1	19.9
		Male 65+ years	7.1	19.9
		Female 18-64 years	7.1	19.9
		Female 65+ years	7.1	19.9
Lymphocytes	GI/L		0.85	4.1
Total Absolute Neutrophil Count	GI/L		1.5	8
Platelet Count	GI/L		31	1499
White Blood Cell count	GI/L	18-64 years	1.1	10.8
		65+ years	1.1	10.8

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	g/L		32	50
Calcium	mmol/L		1.5	3.24
Creatinine		Male 40-49 years	69	160
		Male 50-59 years	67.2	160
		Male 60-69 years	67.2	160
		Male 70+ years	59.2	160
		Female 40-49 years	52.2	160
		Female 50-59 years	53	160
		Female 60-69 years	53	160
		Female 70+ years	55.7	160
Glucose	mmol/L	13-49 years	2.2	27.8
		50+ years	2.2	27.8
Potassium	mmol/L		2.8	6.5
Sodium	mmol/L		120	160
Urea/BUN	mmol/L	13-64 years	2.5	15
		65+ years	2.5	15

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	≥ 2x ULN
AST/SGOT	U/L	High	≥ 2x ULN
AlkPhos	U/L	High	≥ 2x ULN
T Bilirubin	µmol/L	High	≥ 2x ULN
T. Bilirubin + ALT	µmol/L U/L	High	2xULN T.Bilirubin + ≥ 3x ULN ALT
Direct Bilirubin	µmol/L		0 – 6

13.7.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	**Upper**
Absolute			
Absolute QTc Interval	msec		> 530
Absolute PR Interval	msec	< 110	> 240
Absolute QRS Interval	msec	< 75	> 110
Change from Baseline			
Increase from Baseline QTc	msec		> 60

13.7.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	**Upper**
Systolic Blood Pressure	mmHg	< 90	> 140
Diastolic Blood Pressure	mmHg	< 60	> 90
Heart Rate	bpm	< 40	> 110

13.8. Appendix 8: Population Pharmacokinetic (PopPK) Analyses

13.8.1. Population Pharmacokinetic (PopPK) Methodology

All analysis will be performed in the validated Modelling and Analysis Platform (MAP). MAP consists of a Linux desktop containing various modelling applications, including NONMEM, PsN, Pirana, R and RStudio. All software versions used will be documented.

The population PK analysis will be performed in the following sequence of steps:

1. Exploratory data analysis/data check out.
2. Base structural model development.
3. Covariate analysis.
4. Model refinement.
5. Model evaluation.
6. Model application using simulation

The above analysis and reporting steps follow EMEA (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003067.pdf) and FDA population PK guidances (https://www.fda.gov/downloads/drugs/guidances/UCM072137.pdf)

Key components of these regulatory guidelines on population PK are also included in the Global CPMS guidance for pop pk RAP (https://connect.gsk.com/sites/cpms/TandD/Guidances).

13.8.2. Population Pharmacokinetic (PopPK) Dataset Specification

Statistics & Programming, in discussion with CPMS, will provide a NONMEM dataset.

Column headings in NONMEM-ready datasets and specifications should be consistent to minimise the programming process, and facilitate a smooth transfer of projects between users as needed. IDSL standards will be followed where possible.

A list of most common standardised variable names for NONMEM datasets can be found in Table below.

List of Variable Names for NONMEM-Ready Datasets for PopPK Analysis

Variable	Label (Variable description)
C	NONMEM line exclusion identifier
ID	NONMEM subject identifier
STUD	Study ID
SUBJID	Subject identifier for study
SITEID	Unique identifier for a study site
AMT	NONMEM Amount of drug administered then EVID =1- dose event record
UAMT	Unit of AMT (mg)
ADDL	NONMEM Additional dose
CONC	Drug Concentration
UCONC	Unit of CONC (ng/mL)
LNCONC	Natural log of CONC column
ANALYTE	Drug label e.g 557
LLQ	Lower Limit of quantification
LNLLQ	Natural log of LLQ column
DAY	Study day number of record or of dosing
TIME	Plasma sample time after last dose
UTIME	Unit of TIME (h)
DOSE	Dose amount
EVID	NONMEM Event ID If row has dose then EVID=1 else EVID =0 If EVID=1 then this is a dose event record If EVID = 0 then this is an observation record
II	NONMEM Inter-dose interval II=24 – dose every day
SS	Steady state item SS= 1 refers to steady state
MDV	NONMEM Missing data value then MDV=1 else MDV=0
AGE	Subject Age (yrs)
SEX	Subject gender 0 = Male 1 =Female
SEXTEXT	Subject gender text Male or Female
BMI	Baseline Body Mass Index
WT	Baseline Subject weight
CONMED1	Identifier for inhibitor CYP3A4 1 =Yes, 0 = No
CONMED1TXT	Inhibitor Name
CONMED2	Identifier for inducer CYP3A4 1 =Yes, 0 = No
CONMED2TXT	Inducer Name

If observation record e.g CONC has “NA” or “NS” then assign CONC cell as “.”
If observation record e.g CONC has “NQ” or “BQL” then assign CONC cell as “.” and MDV = 1 -this means value can be estimated by model
Missing covariate data should be imputed as “-99.

13.9. Appendix 9: Pharmacokinetic / Pharmacodynamic Analyses

13.9.1. Pharmacokinetic/Pharmacodynamic Methodology

PK-PD analysis of Nemiralisib will be guided by the results of the formal statistical analyses on the key clinical endpoints. The aims of the PK-PD analyses will contribute towards the dose selection in future studies using an integrated longitudinal analysis framework.

The objective is to explore an integrated modelling framework to characterise the longitudinal FEV1 response versus dose (average systemic exposure) during on- & off-treatment phases

$$FEV1_i(t_{ij}) = FEV1_{i,base} \cdot (1 + f(t_{ij}, dose_i, x_i) + \varepsilon_{ij} \text{ with } \varepsilon_{ij} \sim N(0, \sigma 2)$$

A longitudinal nonlinear mixed-effects model will be used to describe the FEV1 response over time measured for each patient (i) at each visit (tij) with ε denoting the normal distributed residual variability with mean 0 and variance $\sigma 2$. The function $f()$ describes the relative change from observed FEV1 at baseline ($FEV1_{,base}$) and any influence of patient characteristics on FEV1 response will be assessed.

Joint relationship between time to first exacerbation and FEV1 change as function of dose/exposure and patient covariates will be assessed.

Details of these analyses will be described in a separate CPMS RAP and results will be reported separately to the CSR.

13.10. Appendix 10: Abbreviations & Trade Marks

13.10.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
QTcF	Fridericia's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TFL	Tables, Figures & Listings

13.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
COPD Assessment Test (CAT)
ELLIPTA
HARP

Trademarks not owned by the GlaxoSmithKline Group of Companies
E-RS: COPD
EXACT-PRO
NONMEM
Propeller Sensor
SAS
SGRQ

13.11. Appendix 11: List of Data Displays

13.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays for SAC:

Section	Tables	Figures
Study Population	1.1 to 1.28	Not applicable
Efficacy	2.1 to 2.121	2.1 to 2.12
Safety	3.1 to 3.31	3.1 to 3.3
Pharmacokinetic	4.1 to 4.2	Not applicable
Section	**Listings**	
ICH Listings	1 to 27	
Other Listings	28 to 30	

13.11.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 12: Example Mock Shells for Data Displays.

13.11.3. Deliverables

Delivery	Description
IA	Interim Analyses (except the End of treatment Phase Interim Analysis)
EOT	End of Treatment Phase Interim Analysis
SAC	Statistical Analysis Complete

13.11.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	MITT	ES8	Summary of Subject Status and Reason for Study Withdrawal		EOT, SAC
1.2.	MITT	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		EOT, SAC
1.3.	APE	ES6	Summary of Screening Status and Reasons for Screen Failure		SAC
1.4.	APE	NS1	Summary of Number of Participants by Country and Site ID		SAC
Protocol Deviation					
1.5.	MITT	DV1	Summary of Important Protocol Deviations		EOT, SAC
1.6.	MITT	IE1	Summary of Inclusion/Exclusion Criteria Deviations		EOT, SAC
Population Analysed					
1.7.	MITT	SP1	Summary of Study Populations		SAC
1.8.	MITT	SP2	Summary of Exclusions from the Per Protocol/Safety Population		SAC
Demographic and Baseline Characteristics					
1.9.	MITT	DM1	Summary of Demographic Characteristics		EOT, SAC
1.10.	APE	DM11	Summary of Age Ranges		SAC
1.11.	MITT	DM5	Summary of Race and Racial Combinations		SAC
1.12.	MITT	MH4	Summary of Past Medical Conditions		EOT, SAC
1.13.	MITT	MH4	Summary of Current Medical Conditions		EOT, SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.14.	MITT	FH1	Summary of Family History of Cardiovascular Risk Factors		EOT, SAC
1.15.	MITT	SU1	Summary of Smoking History at Screening		EOT, SAC
1.16.	MITT	SU1	Summary of Smoking Status over the 12-Week Treatment Period		EOT, SAC
1.17.	MITT	SU1	Summary of Smoking Status over the 12-Week Follow-Up Period		EOT, SAC
1.18.	MITT	Example 7	Summary of COPD Duration at Screening		EOT, SAC
1.19.	MITT	Example 1	Summary of COPD Exacerbation History at Screening	Use categories 0;1;2;3;≥3. Summarise moderate/severe, moderate; severe Include 7-Day History of COPD Exacerbations	EOT, SAC
1.20.	MITT	Example 1	Summary of COPD Exacerbation History at Screening by Country		EOT, SAC
Concomitant Medications					
1.21.	MITT	Example 14	Summary of Baseline COPD Maintenance Therapy		EOT, SAC
1.22.	MITT	Example 15	Summary of On-Treatment COPD Maintenance (Step-up) Therapy		EOT, SAC
1.23.	MITT	CM1	Summary of Concomitant Medications during 12-Week Treatment Period		EOT, SAC
1.24.	MITT	Example 16	Summary of OCS Use		EOT, SAC
1.25.	MITT	CM1	Summary of Concomitant Medications during 12-Week Follow-Up Period		EOT, SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure and Treatment Compliance					
1.26.	MITT	EX1	Summary of Exposure to Study Treatment		EOT, SAC
1.27.	MITT	Example 2	Summary of Treatment Compliance		EOT, SAC
1.28.	MITT	Example 2	Summary of actuations of study treatment measured by the clip-on Propeller Sensor		EOT, SAC

13.11.5. Efficacy Tables

13.11.5.1. Efficacy tables for Interim Analysis 1

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in Clinic Visit trough FEV_1					
2.1.	MITT	Example 3	Summary of FEV_1 (L)	Include pre- and post-bronchodilator	IA1
2.2.	MITT	Example 3	Summary of FEV_1 (L) by Index Exacerbation Severity	Include pre- and post-bronchodilator Include additional row for hospital discharge visit for Severe group	IA1
2.3.	MITT	Example 3	Summary of Change from Baseline in FEV_1 (L)	Include pre- and post-bronchodilator	IA1
2.4.	MITT	Example 3	Summary of Change from Baseline in FEV_1 (L) by Index Exacerbation Severity	Include pre- and post-bronchodilator. Include additional row for hospital discharge visit for Severe group	IA1
2.5.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 at Day 14 measured post-bronchodilator (Dose Response Model)		IA1

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.6.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 at Day 28 measured post-bronchodilator (Dose Response Model)		IA1
2.7.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 14 measured post-bronchodilator by Index Exacerbation Severity (Dose Response Model)		IA1
2.8.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 28 measured post-bronchodilator by Index Exacerbation Severity (Dose Response Model)		IA1
2.9.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) measured post- bronchodilator (Repeated Measures Model)		IA1
2.10.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) measured pre- bronchodilator (Repeated Measures Model)		IA1
2.11.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) measured post- bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		IA1
2.12.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) measured pre- bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		IA1
Change from Hospital Discharge in Clinic Visit trough FEV_1					
2.13.	MITT	Example 3	Summary of Change from Hospital Discharge in FEV_1 (L)	Include pre- and post-bronchodilator	IA1
2.14.	MITT	Example 11	Sensitivity Analysis of Change from Hospital Discharge in FEV_1 (L) measured post- bronchodilator (Repeated Measures Model)		IA1
2.15.	MITT	Example 11	Sensitivity Analysis of Change from Hospital Discharge in FEV_1 (L) measured pre- bronchodilator (Repeated Measures Model)		IA1

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.16.	MITT	Example 11	Sensitivity Analysis of Change from Hospital Discharge in FEV_1 (L) measured post- bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		IA1
2.17.	MITT	Example 11	Sensitivity Analysis of Change from Hospital Discharge in FEV_1 (L) measured pre- bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		IA1
Rate of Exacerbations					
2.18.	MITT	Example 5	Summary of On-treatment Exacerbations		IA1
2.19.	MITT	Example 5	Summary of On-treatment Exacerbations by Index Exacerbation Severity		IA1
EXAcerbations of Chronic Pulmonary Disease Tool - Patient Reported Outcome (EXACT)					
2.20.	MITT	Example 9	Statistical Analysis of Proportion of Participants Achieving the EXACT-definition of Recovery by Visit	Exclude statistical analysis information (summary only)	IA1
2.21.	MITT	Example 9	Subgroup Analysis of Proportion of Participants Achieving the EXACT-definition of Recovery by Index Exacerbation Severity	Exclude statistical analysis information (summary only)	IA1
Other Spirometry Measures					
2.22.	MITT	Example 3	Summary of Spirometry Measurements		IA1
2.23.	MITT	Example 3	Summary of Change from Baseline in Spirometry Measurements		IA1

13.11.5.2. Efficacy tables for Interim Analysis 2

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in Clinic Visit trough FEV_1					
2.1.	MITT	Example 3	Summary of FEV_1 (L)	Include pre- and post-bronchodilator	IA2
2.2.	MITT	Example 3	Summary of FEV_1 (L) by Index Exacerbation Severity	Include pre- and post-bronchodilator Include additional row for hospital discharge visit for Severe group	IA2
2.3.	MITT	Example 3	Summary of Change from Baseline in FEV_1 (L)	Include pre- and post-bronchodilator	IA2
2.4.	MITT	Example 3	Summary of Change from Baseline in FEV_1 (L) by Index Exacerbation Severity	Include pre- and post-bronchodilator. Include additional row for hospital discharge visit for Severe group	IA2
2.5.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 14 measured post-bronchodilator (Dose Response Model)		IA2
2.6.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 28 measured post-bronchodilator (Dose Response Model)		IA2
2.7.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 56 measured post-bronchodilator (Dose Response Model)		IA2
2.8.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 84 measured post-bronchodilator (Dose Response Model)		IA2
2.9.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 14 measured post-bronchodilator by Index Exacerbation Severity (Dose Response Model)		IA2
2.10.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 28 measured post-bronchodilator by Index Exacerbation Severity (Dose Response Model)		IA2

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.11.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 56 measured post-bronchodilator by Index Exacerbation Severity (Dose Response Model)		IA2
2.12.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 84 measured post-bronchodilator by Index Exacerbation Severity (Dose Response Model)		IA2
2.13.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) measured post-bronchodilator (Repeated Measures Model)		IA2
2.14.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) measured pre-bronchodilator (Repeated Measures Model)		IA2
2.15.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) measured post-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		IA2
2.16.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) measured pre-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		IA2
Change from Hospital Discharge in Clinic Visit trough FEV_1					
2.17.	MITT	Example 3	Summary of Change from Hospital Discharge in FEV_1 (L)	Include pre- and post-bronchodilator	IA2
2.18.	MITT	Example 26	Statistical Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 28 measured post-bronchodilator (Dose Response Model)		IA2
2.19.	MITT	Example 26	Statistical Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 56 measured post-bronchodilator (Dose Response Model)		IA2

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.20.	MITT	Example 26	Statistical Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 84 measured post-bronchodilator (Dose Response Model)		IA2
2.21.	MITT	Example 26	Subgroup Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 28 measured post-bronchodilator by Index Exacerbation Severity (Dose Response Model)		IA2
2.22.	MITT	Example 26	Subgroup Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 56 measured post-bronchodilator by Index Exacerbation Severity (Dose Response Model)		IA2
2.23.	MITT	Example 26	Subgroup Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 84 measured post-bronchodilator by Index Exacerbation Severity (Dose Response Model)		IA2
2.24.	MITT	Example 11	Sensitivity Analysis of Change from Hospital Discharge in FEV_1 (L) measured post-bronchodilator (Repeated Measures Model)		IA2
2.25.	MITT	Example 11	Sensitivity Analysis of Change from Hospital Discharge in FEV_1 (L) measured pre-bronchodilator (Repeated Measures Model)		IA2
2.26.	MITT	Example 11	Sensitivity Analysis of Change from Hospital Discharge in FEV_1 (L) measured post-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		IA2
2.27.	MITT	Example 11	Sensitivity Analysis of Change from Hospital Discharge in FEV_1 (L) measured pre-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		IA2
Rate of Exacerbations					
2.28.	MITT	Example 5	Summary of On-treatment Exacerbations		IA2
2.29.	MITT	Example 5	Summary of On-treatment Exacerbations by Index Exacerbation Severity		IA2

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.30.	MITT	Example 6	Statistical Analysis of On-treatment Exacerbations		IA2
2.31.	MITT	Example 6	Subgroup Analysis of On-treatment Exacerbations by Index Exacerbation Severity		IA2
Time to Next Exacerbation					
2.32.	MITT	Example 8	Summary and Statistical Analysis of Time to next On-treatment Exacerbation During the 12-Week Treatment Period		IA2
2.33.	MITT	Example 8	Subgroup Analysis of Time to next On-treatment Exacerbation During the 12-Week Treatment Period by Index Exacerbation Severity		IA2
EXAcerbations of Chronic Pulmonary Disease Tool - Patient Reported Outcome (EXACT)					
2.34.	MITT	Example 9	Statistical Analysis of Proportion of Participants Achieving the EXACT-definition of Recovery by Visit		IA2
2.35.	MITT	Example 9	Subgroup Analysis of Proportion of Participants Achieving the EXACT-definition of Recovery by Index Exacerbation Severity		IA2
Rescue Medication Use					
2.36.	MITT	RM1	Summary of Mean Number of Occasions of Rescue Medication Use Per Day		IA2
2.37.	MITT	RM1	Summary of Percentage of Rescue-Free Days		IA2
Other Spirometry Measures					
2.38.	MITT	Example 3	Summary of Spirometry Measurements		IA2
2.39.	MITT	Example 3	Summary of Change from Baseline in Spirometry Measurements		IA2

13.11.5.3. Efficacy tables for End of Treatment Interim Analysis and SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in Clinic Visit trough FEV_1					
2.1.	MITT	Example 3	Summary of FEV_1 (L)	Include pre- and post-bronchodilator	EOT, SAC
2.2.	MITT	Example 3	Summary of FEV_1 (L) by Index Exacerbation Severity	Include pre- and post-bronchodilator Include additional row for hospital discharge visit for Severe group	EOT, SAC
2.3.	MITT	Example 3	Summary of Change from Baseline in FEV_1 (L)	Include pre- and post-bronchodilator	EOT, SAC
2.4.	MITT	Example 3	Summary of Change from Baseline in FEV_1 (L) by Index Exacerbation Severity	Include pre- and post-bronchodilator. Include additional row for hospital discharge visit for Severe group	EOT, SAC
2.5.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 14 measured post-bronchodilator (Dose Response Model)		EOT, SAC
2.6.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 14 measured pre-bronchodilator (Dose Response Model)		EOT, SAC
2.7.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 28 measured post-bronchodilator (Dose Response Model)		EOT, SAC
2.8.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 28 measured pre-bronchodilator (Dose Response Model)		EOT, SAC
2.9.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 56 measured post-bronchodilator (Dose Response Model)		EOT, SAC
2.10.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 56 measured pre-bronchodilator (Dose Response Model)		EOT, SAC
2.11.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 84 measured post-bronchodilator (Dose Response Model)		EOT, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.12.	MITT	Example 26	Statistical Analysis of Change from Baseline in FEV_1 (L) at Day 84 measured pre-bronchodilator (Dose Response Model)		EOT, SAC
2.13.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 14 measured post-bronchodilator by Index Exacerbation Severity (Dose Response Model)		EOT, SAC
2.14.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 14 measured pre-bronchodilator by Index Exacerbation Severity (Dose Response Model)		EOT, SAC
2.15.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 28 measured post-bronchodilator by Index Exacerbation Severity (Dose Response Model)		EOT, SAC
2.16.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 28 measured pre-bronchodilator by Index Exacerbation Severity (Dose Response Model)		EOT, SAC
2.17.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 56 measured post-bronchodilator by Index Exacerbation Severity (Dose Response Model)		EOT, SAC
2.18.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 56 measured pre-bronchodilator by Index Exacerbation Severity (Dose Response Model)		EOT, SAC
2.19.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 84 measured post-bronchodilator by Index Exacerbation Severity (Dose Response Model)		EOT, SAC
2.20.	MITT	Example 26	Subgroup Analysis of Change from Baseline in FEV_1 (L) at Day 84 measured pre-bronchodilator by Index Exacerbation Severity (Dose Response Model)		EOT, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.21.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) measured post-bronchodilator (Repeated Measures Model)		EOT, SAC
2.22.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) measured pre-bronchodilator (Repeated Measures Model)		EOT, SAC
2.23.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) measured post-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		EOT, SAC
2.24.	MITT	Example 11	Sensitivity Analysis of Change from Baseline in FEV_1 (L) measured pre-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		EOT, SAC
Change from Hospital Discharge in Clinic Visit trough FEV_1					
2.25.	MITT	Example 3	Summary of Change from Hospital Discharge in FEV_1 (L)	Include pre- and post-bronchodilator	EOT, SAC
2.26.	MITT	Example 26	Statistical Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 14 measured post-bronchodilator (Dose Response Model)		EOT, SAC
2.27.	MITT	Example 26	Statistical Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 14 measured pre-bronchodilator (Dose Response Model)		EOT, SAC
2.28.	MITT	Example 26	Statistical Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 28 measured post-bronchodilator (Dose Response Model)		EOT, SAC
2.29.	MITT	Example 26	Statistical Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 28 measured pre-bronchodilator (Dose Response Model)		EOT, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.30.	MITT	Example 26	Statistical Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 56 measured post-bronchodilator (Dose Response Model)		EOT, SAC
2.31.	MITT	Example 26	Statistical Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 56 measured pre-bronchodilator (Dose Response Model)		EOT, SAC
2.32.	MITT	Example 26	Statistical Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 84 measured post-bronchodilator (Dose Response Model)		EOT, SAC
2.33.	MITT	Example 26	Statistical Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 84 measured pre-bronchodilator (Dose Response Model)		EOT, SAC
2.34.	MITT	Example 26	Subgroup Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 14 measured post-bronchodilator by Index Exacerbation Severity (Dose Response Model)		EOT, SAC
2.35.	MITT	Example 26	Subgroup Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 14 measured pre-bronchodilator by Index Exacerbation Severity (Dose Response Model)		EOT, SAC
2.36.	MITT	Example 26	Subgroup Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 28 measured post-bronchodilator by Index Exacerbation Severity (Dose Response Model)		EOT, SAC
2.37.	MITT	Example 26	Subgroup Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 28 measured pre-bronchodilator by Index Exacerbation Severity (Dose Response Model)		EOT, SAC
2.38.	MITT	Example 26	Subgroup Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 56 measured post-bronchodilator by Index Exacerbation Severity (Dose Response Model)		EOT, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.39.	MITT	Example 26	Subgroup Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 56 measured pre-bronchodilator by Index Exacerbation Severity (Dose Response Model)		EOT, SAC
2.40.	MITT	Example 26	Subgroup Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 84 measured post-bronchodilator by Index Exacerbation Severity (Dose Response Model)		EOT, SAC
2.41.	MITT	Example 26	Subgroup Analysis of Change from Hospital Discharge in FEV_1 (L) at Day 84 measured pre-bronchodilator by Index Exacerbation Severity (Dose Response Model)		EOT, SAC
2.42.	MITT	Example 11	Sensitivity Analysis of Change from Hospital Discharge in FEV_1 (L) measured post-bronchodilator (Repeated Measures Model)		EOT, SAC
2.43.	MITT	Example 11	Sensitivity Analysis of Change from Hospital Discharge in FEV_1 (L) measured pre-bronchodilator (Repeated Measures Model)		EOT, SAC
2.44.	MITT	Example 11	Sensitivity Analysis of Change from Hospital Discharge in FEV_1 (L) measured post-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		EOT, SAC
2.45.	MITT	Example 11	Sensitivity Analysis of Change from Hospital Discharge in FEV_1 (L) measured pre-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		EOT, SAC
Change from Day 84 in Clinic Visit trough FEV_1					
2.46.	MITT	Example 3	Summary of Change from Day 84 in FEV_1 (L)	Include pre- and post-bronchodilator	EOT, SAC
2.47.	MITT	Example 11	Statistical Analysis of Change from Day 84 in FEV_1 (L) measured post-bronchodilator (Repeated Measures Model)		EOT, SAC
2.48.	MITT	Example 11	Statistical Analysis of Change from Day 84 in FEV_1 (L) measured pre-bronchodilator (Repeated Measures Model)		EOT, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.49.	MITT	Example 11	Subgroup Analysis of Change from Day 84 in FEV_1 (L) measured post-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		EOT, SAC
2.50.	MITT	Example 11	Subgroup Analysis of Change from Day 84 in FEV_1 (L) measured pre-bronchodilator by Index Exacerbation Severity (Repeated Measures Model)		EOT, SAC
Rate of Exacerbations					
2.51.	MITT	Example 5	Summary of On-treatment Exacerbations		EOT, SAC
2.52.	MITT	Example 5	Summary of On-treatment Exacerbations by Index Exacerbation Severity		EOT, SAC
2.53.	MITT	Example 6	Statistical Analysis of On-treatment Exacerbations		EOT, SAC
2.54.	MITT	Example 6	Subgroup Analysis of On-treatment Exacerbations by Index Exacerbation Severity		EOT, SAC
2.55.	MITT	Example 5	Summary of On-treatment Exacerbations by Index Exacerbation Type		EOT, SAC
2.56.	MITT	Example 5	Summary of On-treatment Exacerbations by Number of Exacerbations in Previous 12 Months		EOT, SAC
2.57.	MITT	Example 5	Summary of On-or Off-treatment Exacerbations During the 12-Week Treatment Period		EOT, SAC
2.58.	MITT	Example 5	Summary of On-or Off-treatment Exacerbations During the 12-Week Treatment Period by Index Exacerbation Severity		EOT, SAC
2.59.	MITT	Example 6	Statistical Analysis of On- or Off-treatment Exacerbations During the 12-Week Treatment Period		EOT, SAC
2.60.	MITT	Example 6	Subgroup Analysis of On- or Off-treatment Exacerbations During the 12-Week Treatment Period by Index Exacerbation Severity		EOT, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.61.	MITT	Example 5	Summary of Off-treatment Exacerbations		EOT, SAC
2.62.	MITT	Example 5	Summary of Off-treatment Exacerbations by Index Exacerbation Severity		EOT, SAC
2.63.	MITT	Example 6	Statistical Analysis of Off-treatment Exacerbations		EOT, SAC
2.64.	MITT	Example 6	Subgroup Analysis of Off-treatment Exacerbations by Index Exacerbation Severity		EOT, SAC
2.65.	MITT	Example 5	Summary of On- and Off-treatment Exacerbations During the 24-Week Study Period		EOT, SAC
2.66.	MITT	Example 5	Summary of On- and Off-treatment Exacerbations During the 24-Week Study Period by Index Exacerbation Severity		EOT, SAC
2.67.	MITT	Example 6	Statistical Analysis of On- and Off-treatment Exacerbations During the 24-Week Study Period		EOT, SAC
2.68.	MITT	Example 6	Subgroup Analysis of On- and Off-treatment Exacerbations During the 24-Week Study Period by Index Exacerbation Severity		EOT, SAC
Time to Next Exacerbation					
2.69.	MITT	Example 8	Summary and Statistical Analysis of Time to next On-treatment Exacerbation During the 12-Week Treatment Period		EOT, SAC
2.70.	MITT	Example 8	Subgroup Analysis of Time to next On-treatment Exacerbation During the 12-Week Treatment Period by Index Exacerbation Severity		EOT, SAC
2.71.	MITT	Example 8	Summary and Statistical Analysis of Time to next On- or Off-treatment Exacerbation During the 12-Week Treatment Period		EOT, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.72.	MITT	Example 8	Statistical Analysis of Time to next On- or Off-treatment Exacerbation During the 12-Week Treatment Period by Index Exacerbation Severity		EOT, SAC
2.73.	MITT	Example 8	Summary and Statistical Analysis of Time to Next Exacerbation Following Cessation of Study Treatment		EOT, SAC
2.74.	MITT	Example 8	Statistical Analysis of Time to Next Exacerbation Following Cessation of Study Treatment by Index Exacerbation Severity		EOT, SAC
EXAcerbations of Chronic Pulmonary Disease Tool - Patient Reported Outcome (EXACT)					
2.75.	MITT	Example 9	Statistical Analysis of Proportion of Participants Achieving the EXACT-definition of Recovery by Visit		EOT, SAC
2.76.	MITT	Example 9	Subgroup Analysis of Proportion of Participants Achieving the EXACT-definition of Recovery by Index Exacerbation Severity		EOT, SAC
2.77.	MITT	Example 8	Summary and Statistical Analysis of Time to EXACT-defined Recovery		EOT, SAC
2.78.	MITT	Example 8	Subgroup Analysis of Time to EXACT-defined Recovery by Index Exacerbation Severity		EOT, SAC
2.79.	MITT	Example 10	Summary of severity of subsequent HCRU-defined exacerbation during 12-Week Treatment Period	Also split by moderate and severe	EOT, SAC
2.80.	MITT	Example 10	Summary of severity of subsequent HCRU-defined exacerbation during 12-Week Follow-up Period	Also split by moderate and severe	EOT, SAC
COPD Assessment Test (CAT)					
2.81.	MITT	Example 3	Summary of Change from Baseline in CAT Total Score		EOT, SAC
2.82.	MITT	Example 3	Summary of Change from Baseline in CAT Total Score by Index Exacerbation Severity		EOT, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.83.	MITT	Example 9	Statistical Analysis of Proportion of Responders Using the CAT Total Score by Visit		EOT, SAC
2.84.	MITT	Example 9	Subgroup Analysis of Proportion of Responders Using the CAT Total Score by Visit by Index Exacerbation Severity		EOT, SAC
2.85.	MITT	Example 11	Statistical Analysis of Change from Baseline in CAT Total Score (Repeated Measures Model)		EOT, SAC
2.86.	MITT	Example 11	Subgroup Analysis of Change from Baseline in CAT Total Score (Repeated Measures Model) by Index Exacerbation Severity		EOT, SAC
2.87.	MITT	Example 3	Summary of Change from End of Treatment in CAT Total Score		EOT, SAC
2.88.	MITT	Example 3	Summary of Change from End of Treatment in CAT Total Score by Index Exacerbation Severity		EOT, SAC
2.89.	MITT	Example 11	Statistical Analysis of Change from End of Treatment in CAT Total Score (Repeated Measures Model)		EOT, SAC
2.90.	MITT	Example 11	Subgroup Analysis of Change from End of Treatment in CAT Total Score (Repeated Measures Model) by Index Exacerbation Severity		EOT, SAC
St. George's Respiratory Questionnaire (SGRQ)					
2.91.	MITT	Example 3	Summary of Change from Baseline in SGRQ Total Score		EOT, SAC
2.92.	MITT	Example 3	Summary of Change from Baseline in SGRQ Total Score by Index Exacerbation Severity		EOT, SAC
2.93.	MITT	Example 9	Statistical Analysis of Proportion of Responders on the SGRQ Total Score by Visit		EOT, SAC
2.94.	MITT	Example 9	Subgroup Analysis of Proportion of Responders on the SGRQ Total Score by Index Exacerbation Severity		EOT, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.95.	MITT	Example 11	Statistical Analysis of Change from Baseline SGRQ Total Score (Repeated Measures Model)		EOT, SAC
2.96.	MITT	Example 11	Subgroup Analysis of Change from Baseline SGRQ Total Score (Repeated Measures Model) by Index Exacerbation Severity		EOT, SAC
2.97.	MITT	Example 3	Summary of Change from End of Treatment in SGRQ Total Score		EOT, SAC
2.98.	MITT	Example 3	Summary of Change from End of Treatment in SGRQ Total Score by Index Exacerbation Severity		EOT, SAC
2.99.	MITT	Example 11	Statistical Analysis of Change from End of Treatment in SGRQ Total Score (Repeated Measures Model)		EOT, SAC
2.100.	MITT	Example 11	Subgroup Analysis of Change from End of Treatment in SGRQ Total Score (Repeated Measures Model) by Index Exacerbation Severity		EOT, SAC
E-RS: COPD					
2.101.	MITT	Example 3	Summary of Change from Baseline in E-RS: COPD and subscales		SAC
Rescue Medication Use					
2.102.	MITT	RM1	Summary of Mean Number of Occasions of Rescue Medication Use Per Day		EOT, SAC
2.103.	MITT	RM1	Summary of Percentage of Rescue-Free Days		EOT, SAC
2.104.	MITT	RM1	Summary of Mean Number of Actuations of Rescue Medication Use Per Day via the clip-on Propeller Sensor for MDI		EOT, SAC
2.105.	MITT	RM1	Summary of Percentage of Rescue-Free Days via the clip-on Propeller Sensor for MDI		EOT, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Compliance					
2.106.	MITT	IP1	Summary of Overall IP Compliance		EOT, SAC
2.107.	MITT	IP1	Summary of Overall IP Compliance via the clip-on Propeller Sensor for ELLIPTA		EOT, SAC
Healthcare Resource Utilisation					
2.108.	MITT	Example 19	Summary of Exacerbation Related Unscheduled Healthcare Resource Utilisation		EOT, SA
2.109.	MITT	Example 19	Summary of Exacerbation Related Unscheduled Healthcare Resource Utilization by Index Exacerbation Severity		EOT, SA
2.110.	MITT	Example 21	Summary of Exacerbation Related Hospitalizations		EOT, SAC
2.111.	MITT	Example 19	Summary of COPD Related Unscheduled Healthcare Resource Utilisation		EOT, SAC
2.112.	MITT	Example 19	Summary of COPD Related Unscheduled Healthcare Resource Utilisation by Index Exacerbation Severity		EOT, SAC
2.113.	MITT	Example 20	Summary of Non-COPD Related Unscheduled Healthcare Resource Utilisation		EOT, SAC
2.114.	MITT	Example 20	Summary of Non-COPD Related Unscheduled Healthcare Resource Utilisation by Index Exacerbation Severity		EOT, SAC
2.115.	MITT	Example 22	Summary of Re-hospitalization Within 30 days of Index Exacerbation		EOT, SAC
2.116.	MITT	Example 24	Summary of Time from Resolution of Index Exacerbation to Next Exacerbation		EOT, SAC
2.117.	MITT	Example 23	Summary of Subsequent Exacerbation Treatment		EOT, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Other Spirometry Measures					
2.118.	MITT	Example 3	Summary of Spirometry Measurements		EOT, SAC
2.119.	MITT	Example 3	Summary of Change from Baseline in Spirometry Measurements		EOT, SAC
Inflammatory/infective Markers in Blood and Sputum					
2.120.	MITT	Example 3	Summary of Inflammatory Markers in Blood		SAC
2.121.	MITT	Example 3	Summary of Inflammatory Markers in Sputum		SAC

13.11.6. Efficacy Figures

13.11.6.1. Efficacy Figures for Interim Analysis 1

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in Clinic Visit trough FEV_1					
2.1.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 measured post-bronchodilator		IA1
2.2.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 measured post-bronchodilator		IA1
2.3.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 measured post-bronchodilator by Index Exacerbation Severity: Moderate		IA1
2.4.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 measured post-bronchodilator by Index Exacerbation Severity: Severe		IA1
2.5.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 measured post-bronchodilator by Index Exacerbation Severity: Moderate		IA1
2.6.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 measured post-bronchodilator by Index Exacerbation Severity: Severe		IA1

13.11.6.2. Efficacy Figures for Interim Analysis 2

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in Clinic Visit trough FEV_1					
2.1.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 measured post-bronchodilator		IA2
2.2.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 measured post-bronchodilator		IA2
2.3.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 56 measured post-bronchodilator		IA2
2.4.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 84 measured post-bronchodilator		IA2
2.5.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 measured post-bronchodilator by Index Exacerbation Severity: Moderate		IA2
2.6.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 14 measured post-bronchodilator by Index Exacerbation Severity: Severe		IA2
2.7.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 measured post-bronchodilator by Index Exacerbation Severity: Moderate		IA2
2.8.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 28 measured post-bronchodilator by Index Exacerbation Severity: Severe		IA2
2.9.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 56 measured post-bronchodilator by Index Exacerbation Severity: Moderate		IA2

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.10.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 56 measured post-bronchodilator by Index Exacerbation Severity: Severe		IA2
2.11.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 84 measured post-bronchodilator by Index Exacerbation Severity: Moderate		IA2
2.12.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 at Day 84 measured post-bronchodilator by Index Exacerbation Severity: Severe		IA2
Change from Hospital Discharge in Clinic Visit trough FEV_1					
2.13.	MITT	Example 18	Plot of Dose Response Model of Change from Hospital Discharge in FEV_1 at Day 28 measured post-bronchodilator		IA2
2.14.	MITT	Example 18	Plot of Dose Response Model of Change from Hospital Discharge in FEV_1 at Day 56 measured post-bronchodilator		IA2
2.15.	MITT	Example 18	Plot of Dose Response Model of Change from Hospital Discharge in FEV_1 at Day 84 measured post-bronchodilator		IA2
2.16.	MITT	Example 18	Plot of Dose Response Model of Change from Hospital Discharge in FEV_1 at Day 28 measured post-bronchodilator by Index Exacerbation Severity: Moderate		IA2
2.17.	MITT	Example 18	Plot of Dose Response Model of Change from Hospital Discharge in FEV_1 at Day 28 measured post-bronchodilator by Index Exacerbation Severity: Severe		IA2
2.18.	MITT	Example 18	Plot of Dose Response Model of Change from Hospital Discharge in FEV_1 at Day 56 measured post-bronchodilator by Index Exacerbation Severity: Moderate		IA2

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.19.	MITT	Example 18	Plot of Dose Response Model of Change from Hospital Discharge in FEV_1 at Day 56 measured post-bronchodilator by Index Exacerbation Severity: Severe		IA2
2.20.	MITT	Example 18	Plot of Dose Response Model of Change from Hospital Discharge in FEV_1 at Day 84 measured post-bronchodilator by Index Exacerbation Severity: Moderate		IA2
2.21.	MITT	Example 18	Plot of Dose Response Model of Change from Hospital Discharge in FEV_1 at Day 84 measured post-bronchodilator by Index Exacerbation Severity: Severe		IA2

13.11.6.3. Efficacy Figures for End of Treatment Interim Analysis and SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Change from Baseline in Clinic Visit trough FEV_1					
2.1.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 measured post-bronchodilator		EOT, SAC
2.2.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 measured pre-bronchodilator		EOT, SAC
2.3.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 measured post-bronchodilator by Index Exacerbation Severity: Moderate		EOT, SAC
2.4.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 measured post-bronchodilator by Index Exacerbation Severity: Severe		EOT, SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.5.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 measured pre-bronchodilator by Index Exacerbation Severity: Moderate		EOT, SAC
2.6.	MITT	Example 18	Plot of Dose Response Model of Change from Baseline in FEV_1 measured pre-bronchodilator by Index Exacerbation Severity: Severe		EOT, SAC
Change from Hospital Discharge in Clinic Visit trough FEV_1					
2.7.	MITT	Example 18	Plot of Dose Response Model of Change from Hospital Discharge in FEV_1 measured post-bronchodilator		EOT, SAC
2.8.	MITT	Example 18	Plot of Dose Response Model of Change from Hospital Discharge in FEV_1 measured pre-bronchodilator		EOT, SAC
2.9.	MITT	Example 18	Plot of Dose Response Model of Change from Hospital Discharge in FEV_1 measured post-bronchodilator by Index Exacerbation Severity: Moderate		EOT, SAC
2.10.	MITT	Example 18	Plot of Dose Response Model of Change from Hospital Discharge in FEV_1 measured post-bronchodilator by Index Exacerbation Severity: Severe		EOT, SAC
2.11.	MITT	Example 18	Plot of Dose Response Model of Change from Hospital Discharge in FEV_1 measured pre-bronchodilator by Index Exacerbation Severity: Moderate		EOT, SAC
2.12.	MITT	Example 18	Plot of Dose Response Model of Change from Hospital Discharge in FEV_1 measured pre-bronchodilator by Index Exacerbation Severity: Severe		EOT, SAC

13.11.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	Safety	AE1	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term		SAC
3.2.	Safety	AE1	Summary of Post-Treatment Adverse Events by System Organ Class and Preferred Term		SAC
3.3.	Safety	AE3	Summary of Common (>=5%) Treatment Emergent Adverse Events by Overall Frequency		SAC
3.4.	Safety	AE1	Summary of Treatment Emergent Drug-Related Adverse Events by System Organ Class and Preferred Term		SAC
3.5.	Safety	AE15	Summary of Common (>=5%) Non-serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)		SAC
3.6.	Safety	AE1	Summary of Treatment Emergent Adverse Events for Participants with Absolute Neutrophil Count Below Lower Value of PCI		SAC
Serious and Other Significant Adverse Events					
3.7.	Safety	AE16	Summary of Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)		SAC
3.8.	Safety	AE16	Summary of Fatal Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	Only with subcategory: Number of Fatal SAEs	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.9.	Safety	AE1	Summary of Serious Treatment Emergent Drug-related Adverse Events by System Organ Class and Preferred Term		SAC
3.10.	Safety	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term		SAC
3.11.	Safety	AE1	Summary of Post-treatment Serious Adverse Events by System Organ Class and Preferred Term		SAC
3.12.	Safety	AE1	Summary of Treatment Emergent Adverse Events of Special Interest by Lower Level Term		SAC
3.13.	Safety	Example 17	Summary of Post-Inhalation Cough by Visit		SAC
3.14.	Safety	Example 28	Summary of Post-Inhalation Cough by Visit and Cough Type		SAC
Laboratory: Chemistry					
3.15.	Safety	LB1	Summary of Chemistry Data		SAC
3.16.	Safety	LB17	Summary of Worst Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline		SAC
Laboratory: Hematology					
3.17.	Safety	LB1	Summary of Hematology Data		SAC
3.18.	Safety	LB1	Summary of Change from Baseline in Hematology	Only for WBC, lymphocytes, neutrophils	SAC
3.19.	Safety	LB17	Summary of Worst Case Hematology Results by PCI Criteria Post-Baseline Relative to Baseline		SAC
Laboratory: Hepatobiliary (Liver)					
3.20.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting		SAC
3.21.	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
ECG					
3.22.	Safety	EG1	Summary of ECG Findings		SAC
3.23.	Safety	EG2	Summary of ECG Values by Visit	For the following parameters: QTcF, QTcB, PR, Heart rate	SAC
3.24.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit	For the following parameters: QTcF, QTcB, PR, Heart rate	SAC
3.25.	Safety	Example 27	Summary of QTcF Categories		SAC
3.26.	Safety	Example 27	Summary of QTcB Categories		SAC
3.27.	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category		SAC
3.28.	Safety	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category		SAC
3.29.	Safety	Example 25	Summary of ECG Abnormalities for Participants with Any Abnormal Clinically Significant ECG Interpretation		SAC
Vital Signs					
3.30.	Safety	VS1	Summary of Vital Signs		SAC
3.31.	Safety	VS7	Summary of Worst Case Vital Signs Results by PCI Criteria Post-Baseline Relative to Baseline		SAC

13.11.8. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory					
3.1.	Safety	LB7	LFT Shift from Baseline to Maximum		SAC
3.2.	Safety	Example 13	Median (range) Absolute Neutrophil Count by Time and Treatment		SAC
ECG					
3.3.	Safety	EG8	Distribution of QTcF Change by Time and Treatment		SAC

13.11.9. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic Concentration-Time Data					
4.1.	PK	PK01	Summary of Plasma GSK2269557 Pharmacokinetic Concentration-Time Data		SAC
4.2.	PK	PK05	Summary of Log-Transformed Plasma GSK2269557 Pharmacokinetic Concentration-Time Data		SAC

13.11.10. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	APE	ES7	Listing of Reasons for Screen Failure		SAC
2.	MITT	ES2	Listing of Reasons for Study Withdrawal		SAC
3.	MITT	SD2	Listing of Reasons for Study Treatment Discontinuation		SAC
4.	MITT	BL1	Listing of Participants for Whom the Treatment Blind was Broken		SAC
5.	MITT	TA1	Listing of Planned and Actual Treatments		SAC
Protocol Deviations					
6.	MITT	DV2	Listing of Important Protocol Deviations		SAC
7.	MITT	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations		SAC
Populations Analysed					
8.	MITT	SP3	Listing of Participants Excluded from Any Population	For participants excluded from MITT population (i.e. participants in the MITT but not in PP)	SAC
Demographic and Baseline Characteristics					
9.	MITT	DM2	Listing of Demographic Characteristics		SAC
10.	MITT	DM9	Listing of Race		SAC
Prior and Concomitant Medications					
11.	MITT	CP_CM3	Listing of Concomitant Medications		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure and Treatment Compliance					
12.	Safety	EX3	Listing of Exposure Data		SAC
Adverse Events					
13.	Safety	AE8	Listing of All Adverse Events		SAC
14.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		SAC
15.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		SAC
Serious and Other Significant Adverse Events					
16.	Safety	AE8	Listing of Fatal Serious Adverse Events		SAC
17.	Safety	AE8	Listing of Non-Fatal Serious Adverse Events		SAC
18.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event		SAC
19.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment		SAC
Hepatobiliary (Liver)					
20.	Safety	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events		SAC
21.	Safety	SU2	Listing of Substance Use for Participants with Liver Stopping Events		SAC
All Laboratory					
22.	Safety	LB5	Listing of All Chemistry Data for Participants with Any Value of Potential Clinical Importance		SAC
23.	Safety	LB14	Listing of Chemistry Data with Character Results		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
24.	Safety	LB5	Listing of All Hematology Data for Participants with Any Value of Potential Clinical Importance		SAC
25.	Safety	LB14	Listing of all Hematology Data with Character Results		SAC
ECG					
26.	Safety	EG3	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance		SAC
27.	Safety	EG5	Listing of All ECG Findings for Participants with an Abnormal Finding		SAC

13.11.11. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
28.	MITT	Example 29	Listing of Subjects who Received Incorrect Medication		SAC
29.	PK	PK07	Listing of Plasma Pharmacokinetic Concentration-Time Data		SAC
30.	Safety	EG5	Listing of All ECG Findings for Subjects with an Abnormal Finding		SAC

13.12. Appendix 12: Example Mock Shells for Data Displays

13.12.1. Example shell 1

Example Shell X
Protocol: XYZ100001 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of COPD Exacerbation History at Screening

	Treatment A (N=100)	Treatment B (N=100)	Total (N=200)
Moderate COPD exacerbations			
n	X	X	X
0	xx (x%)	xx (x%)	xx (x%)
1	xx (x%)	xx (x%)	xx (x%)
>=2	xx (x%)	xx (x%)	xx (x%)
Severe COPD exacerbations			
n	X	X	X
0	xx (x%)	xx (x%)	xx (x%)
1	xx (x%)	xx (x%)	xx (x%)
>=2	xx (x%)	xx (x%)	xx (x%)
Total number of moderate/severe COPD exacerbations			
n	911	899	1810
0	313 (34%)	317 (35%)	630 (35%)
1	252 (28%)	253 (28%)	505 (28%)
>=2	346 (38%)	329 (37%)	675 (37%)

Note: Number of COPD exacerbations reported in the 12 months prior to the Screening Visit.

PPD

13.12.2. Example Shell 2

Protocol: XYZ100001 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Treatment Compliance

	Treatment A (N=100)	Treatment B (N=100)	Total (N=200)
Overall compliance (%)			
n	xx	xx	xx
Mean	xx	xx	xx
SD	xx	xx	xx
Median	xx	xx	xx
Min.	xx	xx	xx
Max.	xx	xx	xx
Compliance interval			
< 80%	xx (x%)	xx (x%)	xx (x%)
80% - < 100%	xx (x%)	xx (x%)	xx (x%)
100% - < 120%	xx (x%)	xx (x%)	xx (x%)
>=120%	xx (x%)	xx (x%)	xx (x%)

PPD

13.12.3. Example shell 3

Example Shell X
Protocol: ABC123456 Page 1 of n
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Change from Baseline in FEV1 (L)
Measured post-bronchodilator

Visit	N	Treatment Arm	n	Mean	SD	Median	Min.	Max.
Day 1	200	Placebo	200	0.111	0.1111	0.100	-0.11	1.11
	200	GSK2269557 12.5 mcg	190	0.222	0.2222	0.200	-0.22	1.22
	200	GSK2269557 50 mcg	195	0.333	0.3333	0.300	-0.33	1.33
	200	GSK2269557 100 mcg	195	0.444	0.4444	0.400	-0.44	1.44
	200	GSK2269557 250 mcg	190	0.555	0.5555	0.500	-0.55	1.55
	200	GSK2269557 500 mcg	190	0.555	0.5555	0.500	-0.55	1.55
	200	GSK2269557 750 mcg	190	0.555	0.5555	0.500	-0.55	1.55
Day 14	200	Placebo	200	0.111	0.1111	0.100	-0.11	1.11
	200	GSK2269557 12.5 mcg	190	0.222	0.2222	0.200	-0.22	1.22
	200	GSK2269557 50 mcg	195	0.333	0.3333	0.300	-0.33	1.33
	200	GSK2269557 250 mcg	195	0.444	0.4444	0.400	-0.44	1.44
	200	GSK2269557 500 mcg	190	0.555	0.5555	0.500	-0.55	1.55
	200	GSK2269557 750 mcg	190	0.555	0.5555	0.500	-0.55	1.55

PPD

13.12.4. Example Shell 4

Protocol: ABC123456
Population: Intent-to-Treat/Safety/Other study specific

Table X
Statistical Analysis of Change from Baseline in FEV1 (ml)
Measured post-bronchodilator

Visit	N	Treatment Arm	n	Posterior Median	95% Credible Interval
Day 14	x	Placebo	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 12.5 mcg	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 50 mcg	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 100 mcg	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 250 mcg	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 500 mcg	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 750 mcg	x	x.xx	(x.xx, x.xx)
Day 28	x	Placebo	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 12.5 mcg	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 50 mcg	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 100 mcg	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 250 mcg	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 500 mcg	x	x.xx	(x.xx, x.xx)
	x	GSK2269557 750 mcg	x	x.xx	(x.xx, x.xx)

PPD

Population: Intent-to-Treat/Safety/Other study specific

Table X
Statistical Analysis of Change from Baseline in FEV1 (ml)
Measured post-bronchodilator

Visit	Treatment Comparison	Adjusted Median Difference	Std Dev	95% Credible Interval	Prob Treat. Diff >0 (%)
Day 14	GSK2269557 12.5 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
	GSK2269557 50 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
	GSK2269557 100 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
	GSK2269557 250 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
	GSK2269557 500 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
	GSK2269557 750 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
Day 28	GSK2269557 12.5 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
	GSK2269557 50 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx
	GSK2269557 100 mg vs Placebo	x.xx	x.xx	(x.xx, x.xx)	x.xx

PPD

13.12.5. Example Shell 5

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of On-treatment Exacerbations

	Treatment A (N=100)	Treatment B (N=100)
Number of moderate & severe exacerbations per subject		
0	50 (50%)	98 (98%)
1	6 (6%)	15 (15%)
2	6 (6%)	9 (9%)
3	1 (1%)	1 (1%)
4	0	2 (2%)
5	0	1 (1%)
>5	0	1 (1%)
Subjects with >=1 moderate & severe exacerbation	13 (13%)	28 (28%)
Total Number of moderate & severe exacerbations	21	49
Number of moderate exacerbations per Subject		
0	50 (50%)	98 (98%)
1	6 (6%)	15 (15%)
2	6 (6%)	9 (9%)
3	1 (1%)	1 (1%)

PPD

13.12.6. Example Shell 6

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Statistical Analysis of On-treatment Exacerbations

	Treatment A (N=100)	Treatment B (N=100)
Moderate and severe exacerbations		
Annual exacerbation rate (95% CrI)	0.35 (x.xx, x.xx)	0.30 (x.xx, x.xx)
Active vs. Placebo		
Ratio		0.85 (x.xx, x.xx)
Pr Diff <1		x.xx
Percent reduction in rate (95% CrI)		15% (x.xx, x.xx)
Moderate exacerbations		
Annual exacerbation rate (95% CrI)	0.35 (x.xx, x.xx)	0.30 (x.xx, x.xx)
Active vs. Placebo		
Ratio		0.85 (x.xx, x.xx)
Pr Diff <1		x.xx
Percent reduction in rate (95% CrI)		15% (x.xx, x.xx)

PPD

13.12.7. Example Shell 7

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of COPD Duration at Screening

	Treatment A (N=100)		Treatment B (N=100)		Total (N=200)	
Duration of COPD:						
n	100		99		199	
<1 year	XX	(x%)	XX	(x%)	XX	(x%)
>=1 to <5 years	XX	(x%)	XX	(x%)	XX	(x%)
>=5 to <10 years	XX	(x%)	XX	(x%)	XX	(x%)
>=10 to <15 years	XX	(x%)	XX	(x%)	XX	(x%)
>=15 to <20 years	XX	(x%)	XX	(x%)	XX	(x%)
>=20 to <25 years	XX	(x%)	XX	(x%)	XX	(x%)
>=25 years	XX	(x%)	XX	(x%)	XX	(x%)

PPD

13.12.8. Example Shell 8

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary and Analysis of Time to Next On-treatment Moderate or Severe Exacerbation (days)
up to Day 84

	Treatment A (N=100)	Treatment B (N=100)
Number of Subjects with Event	10 (10%)	14 (14%)
Number of Subjects Censored	90 (90%)	86 (86%)
Probability of Having Event (%)	X.X	XX
95% C.I.	(x.x, x.x)	(x.x, x.x)
Treatment A vs. Placebo		
Hazard Ratio	X.XX	
95% Credible Interval	(x.xx, x.xx)	

Note: Probability of having event, 95% C.I. are taken from the Kaplan-Meier analysis.
Note: Hazard ratio and 95% Credible Interval are from a Bayesian Cox proportional hazards model

PPD

13.12.9. Example Shell 9

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Statistical Analysis of Proportion of Participants Achieving EXACT-definition of Response

	Treatment A (N=100)	Treatment B (N=100)
Day 14		
n	x.xx	x.xx
Responder	x.xx (x%)	x.xx (x%)
Non-responder	x.xx (x%)	x.xx (x%)
Active vs. Placebo		
Odds Ratio (95% CrI)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Pr Diff >1	x.xx	x.xx
Day 28		
n	x.xx	x.xx
Responder	x.xx (x%)	x.xx (x%)
Non-responder	x.xx (x%)	x.xx (x%)
Active vs. Placebo		
Odds Ratio (95% CrI)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)
Pr Diff >1	x.xx	x.xx

PPD

13.12.10. Example Shell 10

Protocol: XYZ100001 Page 1 of n
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of severity of subsequent HCRU-defined exacerbation during 12-Week Treatment Period

Treatment	N	n	Mean	SD	Median	Min.	Max.
Placebo	30	30	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Trt A	30	30	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Trt B	30	30	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx

PPD

13.12.11. Example Shell 11

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Mixed Model Repeated Measures Analysis of CAT Total Score

	Treatment A (N=100)	Treatment B (N=100)
Day 28		
n	x.xx	x.xx
Adjusted mean score change (SE)	x.xx (x)	x.xx (x)
Active - Placebo		
Difference (SE)	x.xx (x.xx)	x.xx (x.xx)
95% (CrI)	x.xx	x.xx
Pr Diff >0	x.xx	x.xx
Day 56		
n	x.xx	x.xx
Adjusted mean score change (SE)	x.xx (x)	x.xx (x)
Active - Placebo		
Difference (SE)	x.xx (x.xx)	x.xx (x.xx)
95% (CrI)	x.xx	x.xx
Pr Diff >0	x.xx	x.xx

PPD

13.12.12. Example Shell 12

Protocol: ABC123456 Page 1 of 3
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of COPD Related Unscheduled Healthcare Resource Utilization

		Treatment A (N=100)	Treatment B (N=100)
Unscheduled Healthcare Utilisation	Yes	97 (97%)	19 (19%)
	No	3 (3%)	81 (81%)
Number of Home Visits (day)	n	100	100
	0	90 (90%)	92 (92%)
	1	4 (4%)	4 (4%)
	2	0	0
	3	0	0
	>3	0	2 (<1%)
	Total [1]	4	4
Number of Home Visits (night)	n	100	100
	0	100 (100%)	100 (100%)
	1	0	0
	2	0	0
	3	0	0
	>3	0	0
	Total [1]	0	0

[1] Total number of contacts across all subjects.
[2] Total number of days across all subjects.

PPD

Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of COPD Related Unscheduled Healthcare Resource Utilization

		Treatment A (N=100)		Treatment B (N=100)	
Number of Office/Practice Visits	n	911		899	
	0	846	(93%)	808	(90%)
	1	42	(5%)	58	(6%)
	2	13	(1%)	23	(3%)
	3	7	(<1%)	8	(<1%)
	>3	3	(<1%)	2	(<1%)
	Total [1]	103		140	
Number of Urgent Care/Outpatient Visits	n	911		899	
	0	886	(97%)	882	(98%)
	1	15	(2%)	10	(1%)
	2	3	(<1%)	2	(<1%)
	3	3	(<1%)	3	(<1%)
	>3	4	(<1%)	2	(<1%)
	Total [1]	54		37	
Number of Emergency Room Visits	n	911		899	
	0	906	(>99%)	893	(>99%)
	1	5	(<1%)	5	(<1%)
	2	0		1	(<1%)
	3	0		0	
	>3	0		0	
	Total [1]	5		7	

[1] Total number of contacts across all subjects.
[2] Total number of days across all subjects.
PPD

Population: Intent-to-Treat/Safety/Other study specific

Table 2.159
Summary of COPD Related Unscheduled Healthcare Resource Utilization

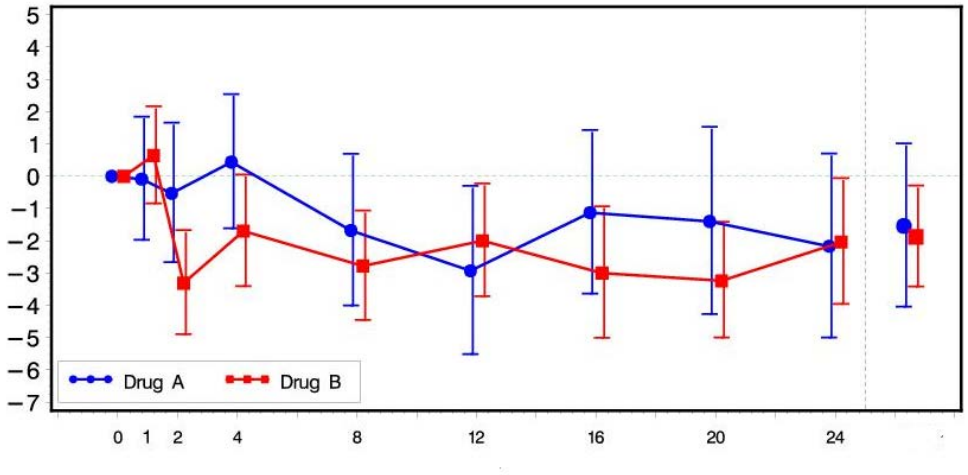
		Treatment A (N=100)	Treatment B (N=100)
Number of Days in Intensive Care	n	911	899
	0	910 (>99%)	894 (>99%)
	1	0	0
	2	0	1 (<1%)
	3	0	0
	>3	1 (<1%)	4 (<1%)
	Total [2]	12	40
Number of Days in General Ward	n	911	899
	0	896 (98%)	878 (98%)
	1	0	2 (<1%)
	2	1 (<1%)	1 (<1%)
	3	0	0
	>3	14 (2%)	18 (2%)
	Total [2]	119	258

[1] Total number of contacts across all subjects.
[2] Total number of days across all subjects.
PPD

13.12.13. Example shell 13

Protocol: XYZ100001
Population: Intent-to-Treat/Safety/Other study specific

Figure X
Median (range) Absolute Neutrophil Count by Time and Treatment



PPD

13.12.14. Example Shell 14

Protocol: XYZ100001 Page 1 of n
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Baseline COPD Maintenance Therapy

Therapy category	Treatment A (N=81)	Treatment B (N=79)
Any medication at baseline	70 (86%)	50 (63%)
Monotherapy	X (x%)	X (x%)
LAMA only	x (x%)	x (x%)
Dual therapy	x (x%)	x (x%)
ICS/LABA	x (x%)	x (x%)
Dual bronchodilator	xx (xx%)	xx (xx%)
Triple therapy	X (x%)	X (x%)
LAMA/ICS/LABA	x (x%)	0

PPD

13.12.15. Example Shell 15

Protocol: XYZ100001
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of On-Treatment COPD Maintenance (Step-up) Therapy

Therapy category	Treatment A (N=81)	Treatment B (N=79)
Any Step-up Therapy	70 (86%)	50 (63%)

PPD

13.12.16. Example shell 16

Protocol: XYZ100001
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of OCS use

	Treatment A (N=81)	Treatment B (N=79)
OCS use for index exacerbation	81 (100%)	79 (100%)
Total number of Days of OCS use		
Mean	Xx	xx
SD	Xx	xx
Median	Xx	xx
Min.	Xx	xx
Max.	Xx	xx
On-treatment OCS use	xx (xx%)	xx (xx%)
Total number of Days of OCS use		
Mean	Xx	xx
SD	Xx	xx
Median	Xx	xx
Min.	Xx	xx
Max.	Xx	xx

PPD

13.12.17. Example Shell 17

Protocol: ABC123456 Page 1 of x
Population: Safety

Table X
Summary of Post-Inhalation Cough by Visit

Visit: VISIT 2 (RANDOMISATION)

	Placebo (N=43)	GSK2269557 50 mcg (N=14)	GSK2269557 100 mcg (N=15)	GSK2269557 250 mcg (N=16)	GSK2269557 500 mcg (N=14)	GSK2269557 750 mcg (N=42)
Did subject experience PI cough? [1]						
n	20	10	12	15	12	35
Yes	7 (35%)	4 (40%)	6 (50%)	3 (20%)	6 (50%)	12 (34%)
No	13 (65%)	6 (60%)	6 (50%)	12 (80%)	6 (50%)	23 (66%)
Type of cough						
Single cough	4 (57%)	2 (50%)	1 (17%)	1 (33%)	1 (17%)	2 (17%)
Intermittent cough	2 (29%)	2 (50%)	5 (83%)	1 (33%)	4 (67%)	5 (42%)
Continuous cough	1 (14%)	0	0	1 (33%)	1 (17%)	5 (42%)
Severity of cough						
Mild	5 (71%)	3 (75%)	3 (50%)	2 (67%)	1 (17%)	6 (50%)
Moderate	2 (29%)	1 (25%)	2 (33%)	1 (33%)	5 (83%)	4 (33%)
Severe	0	0	1 (17%)	0	0	2 (17%)
Time to onset of PI cough (minutes)						
0-1	6 (86%)	3 (75%)	6 (100%)	3 (100%)	6 (100%)	12 (100%)
>1-2	1 (14%)	1 (25%)	0	0	0	0
>2-3	0	0	0	0	0	0
>3-4	0	0	0	0	0	0
>4-5	0	0	0	0	0	0
>5	0	0	0	0	0	0
Duration of PI cough (minutes)						
<=1	6 (86%)	3 (75%)	5 (83%)	3 (100%)	5 (83%)	11 (92%)
>1-2	1 (14%)	1 (25%)	1 (17%)	0	1 (17%)	1 (8%)
>2-3	0	0	0	0	0	0
>3-4	0	0	0	0	0	0
>4-5	0	0	0	0	0	0

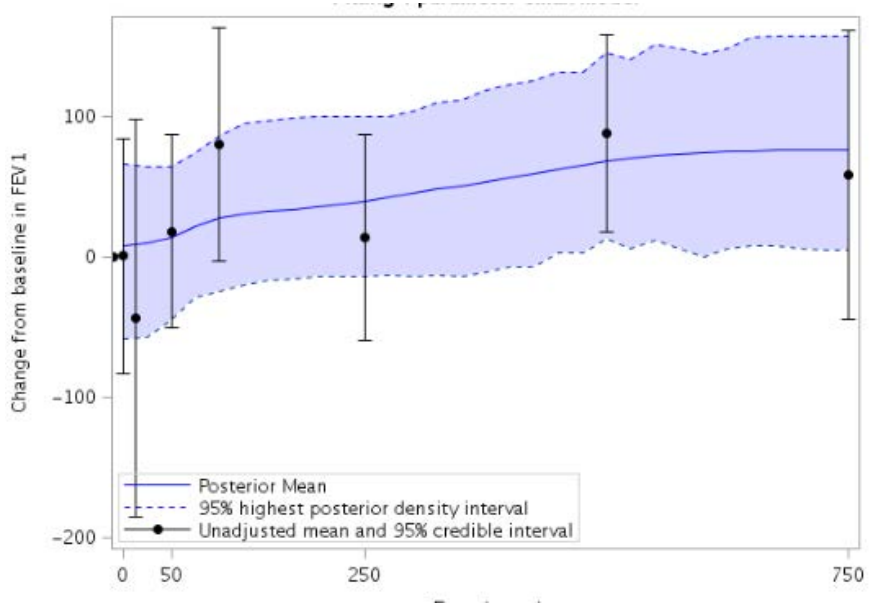
>5-10	x		x								
>10-30	x		x								
>30	x		x								
Number of subjects reporting cough as AE/SAE	2	(29%)	1	(25%)	4	(67%)	0		2	(33%)	3	(25%)
Mild	x	(x%)	x								
Moderate	x	(x%)	x								
Severe	x	(x%)	x								

[1] Percentages are calculated using the number of subjects evaluated at visit as the denominator.
All other percentages are calculated using the number of subjects with a PI cough at visit as the denominator.

13.12.18. Example shell 18

Protocol: ABC123456 Page 1 of x
Population: Intent-to-Treat/Safety/Other study specific

Figure X
Plot of Dose Response Model of Change from Baseline in FEV1



[Footnote to describe the fitted model]

PPD

13.12.19. Example Shell 19

Protocol: ABC123456 Page 1 of 3
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of COPD Related Unscheduled Healthcare Resource Utilization

		Treatment A (N=100)	Treatment B (N=100)
Unscheduled Healthcare Utilisation	Yes	97 (97%)	19 (19%)
	No	3 (3%)	81 (81%)
Number of Home Visits (day)	n	100	100
	0	90 (90%)	92 (92%)
	1	4 (4%)	4 (4%)
	2	0	0
	3	0	0
	>3	0	2 (<1%)
	Total [1]	4	4
Number of Home Visits (night)	n	100	100
	0	100 (100%)	100 (100%)
	1	0	0
	2	0	0
	3	0	0
	>3	0	0
	Total [1]	0	0

[1] Total number of contacts across all subjects.
[2] Total number of days across all subjects.

PPD

Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of COPD Related Unscheduled Healthcare Resource Utilization

		Treatment A (N=100)		Treatment B (N=100)	
Number of Office/Practice Visits	n	911		899	
	0	846	(93%)	808	(90%)
	1	42	(5%)	58	(6%)
	2	13	(1%)	23	(3%)
	3	7	(<1%)	8	(<1%)
	>3	3	(<1%)	2	(<1%)
	Total [1]	103		140	
Number of Urgent Care/Outpatient Visits	n	911		899	
	0	886	(97%)	882	(98%)
	1	15	(2%)	10	(1%)
	2	3	(<1%)	2	(<1%)
	3	3	(<1%)	3	(<1%)
	>3	4	(<1%)	2	(<1%)
	Total [1]	54		37	
Number of Emergency Room Visits	n	911		899	
	0	906	(>99%)	893	(>99%)
	1	5	(<1%)	5	(<1%)
	2	0		1	(<1%)
	3	0		0	
	>3	0		0	
	Total [1]	5		7	

[1] Total number of contacts across all subjects.
[2] Total number of days across all subjects.
PPD

Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of COPD Related Unscheduled Healthcare Resource Utilization

		Treatment A (N=100)	Treatment B (N=100)
Number of Days in Intensive Care	n	911	899
	0	910 (>99%)	894 (>99%)
	1	0	0
	2	0	1 (<1%)
	3	0	0
	>3	1 (<1%)	4 (<1%)
	Total [2]	12	40
Number of Days in General Ward	n	911	899
	0	896 (98%)	878 (98%)
	1	0	2 (<1%)
	2	1 (<1%)	1 (<1%)
	3	0	0
	>3	14 (2%)	18 (2%)
	Total [2]	119	258

[1] Total number of contacts across all subjects.
[2] Total number of days across all subjects.

PPD

13.12.20. Example Shell 20

Protocol: ABC123456 Page 1 of x
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Non-COPD Related Unscheduled Healthcare Resource Utilization

		Treatment A (N=100)	Treatment B (N=100)
Unscheduled Healthcare Utilisation	Yes	97 (97%)	19 (19%)
	No	3 (3%)	81 (81%)
Number of Days in Accident and emergency	n	100	100
	0	90 (90%)	92 (92%)
	1	4 (4%)	4 (4%)
	2	0	0
	3	0	0
	>3	0	2 (<1%)
	Total	4	4
Number of Days in General Ward	n	100	100
	0	100 (100%)	100 (100%)
	1	0	0
	2	0	0
	3	0	0
	>3	0	0
	Total	0	0

PPD

13.12.21. Example Shell 21

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Exacerbation Related Hospitalizations

	Treatment A (N=100)	Treatment B (N=100)
Index exacerbation		
Participants with hospitalization	x.xx	x.xx
Number of hospitalizations	x.xx	x.xx
Mean duration (days)	x.xx	x.xx
SD	x.xx	x.xx
Median duration (days)	x.xx	x.xx
Minimum duration (days)	x.xx	x.xx
Maximum duration (days)	x.xx	x.xx
Subsequent exacerbations		
Participants with hospitalization	x.xx	x.xx
Number of hospitalizations	x.xx	x.xx
Mean duration (days)	x.xx	x.xx
SD	x.xx	x.xx
Median duration (days)	x.xx	x.xx
Minimum duration (days)	x.xx	x.xx
Maximum duration (days)	x.xx	x.xx

PPD

13.12.22. Example Shell 22

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Re-hospitalization Within 30 days of Index Exacerbation

		Treatment A (N=100)	Treatment B (N=100)
Re-hospitalization Within 30 days	Yes	97 (97%)	19 (19%)
	No	3 (3%)	81 (81%)

PPD

13.12.23. Example Shell 23

Protocol: XYZ100001
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Subsequent Exacerbation Treatment

	Treatment A (N=81)	Treatment B (N=79)
Subsequent exacerbation	70 (86%)	50 (63%)
OCS	X (x%)	X (x%)
Antibiotics	x (x%)	x (x%)
OCS and antibiotics	X (x%)	X (x%)

PPD

13.12.24. Example Shell 24

Protocol: ABC123456 Page 1 of 1
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of Time from Resolution of Index Exacerbation to Next Exacerbation

	Treatment A (N=100)	Treatment B (N=100)
Subsequent exacerbation	x.xx	x.xx
Mean duration (days)	x.xx	x.xx
SD	x.xx	x.xx
Median duration (days)	x.xx	x.xx
Minimum duration (days)	x.xx	x.xx
Maximum duration (days)	x.xx	x.xx

PPD

13.12.25. Example Shell 25

Protocol: ABC123456 Page 1 of x
Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of ECG Abnormalities for Participants with Any Abnormal Clinically Significant ECG Interpretation

	Treatment A (N=100)	Treatment B (N=100)
Visit 2 (Day 1)		
Abnormal – Clinically significant	10 (10%)	15 (15%)
Any finding	5 (50%)	5 (33%)
ST depression	5 (50%)	5 (33%)
Short PR Interval	0	5 (33%)
T wave inversion	0	5 (33%)
…….		

Includes Scheduled, unscheduled and Early Withdrawal visits.
Participants may have more than one abnormality at each visit.

PPD

13.12.26. Example Shell 26

Protocol: ABC123456 Page 1 of n
Population: Intent-to-Treat/Safety/Other study specific

Table X
Statistical Analysis of Change from Baseline in FEV1 (mL) (Dose Response Model)
Measured post-bronchodilator

	Placebo (N=xx)	DNX 5mg (N=xx)	DNX 10mg (N=xx)	DNX 25mg (N=xx)	DNX 35mg (N=xx)	DNX 50mg (N=xx)
n [1]	xx	xx	xx	xx	xx	xx
Posterior Mean Change	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
(SD)	(x.xxx)	(x.xxx)	(x.xxx)	(x.xxx)	(x.xxx)	(x.xxx)
Posterior Median Change	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx
95% Credible Interval	(x.xx,x.xx)	(x.xx,x.xx)	(x.xx,x.xx)	(x.xx,x.xx)	(x.xx,x.xx)	(x.xx,x.xx)
Column vs. Placebo						
Posterior Difference		x.xx	x.xx	x.xx	x.xx	x.xx
80% Credible Interval		(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)	(x.xx, x.xx)
Prob(Difference>0)		xx%	xx%	xx%	xx%	xx%
Predictive probability (%) [2] *[only if required]*		xx%	xx%	xx%	xx%	xx%

[1] Number of subjects with data contributing to the analysis.
[2] Predictive posterior probability of success at end of study, where success is Pr(Difference>0)>90%.
Note: Model fitted was a…..[insert as appropriate].

PPD

13.12.27. Example Shell 27

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Population: Intent-to-Treat/Safety/Other study specific

Table X
Summary of QTc(F) (msec) Categories

	Treatment A (N=100)		Treatment B (N=100)	
Screening				
n	xx		xx	
<=450	xx	(xx%)	xx	(xx%)
>450 to <=480	xx	(xx%)	xx	(xx%)
>480 to <=500	xx	(xx%)	xx	(xx%)
>500	xx	(xx%)	xx	(xx%)
Day 1 (Baseline)				
n	xx		xx	
<=450	xx	(xx%)	xx	(xx%)
>450 to <=480	xx	(xx%)	xx	(xx%)
>480 to <=500	xx	(xx%)	xx	(xx%)
>500	xx	(xx%)	xx	(xx%)
Day 14				
n	xx		xx	
<=450	xx	(xx%)	xx	(xx%)
>450 to <=480	xx	(xx%)	xx	(xx%)
>480 to <=500	xx	(xx%)	xx	(xx%)
>500	xx	(xx%)	xx	(xx%)

PPD

13.12.28. Example Shell 28

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Population: Safety

Table X
Summary of Post-Inhalation Cough by Visit and Cough Type

Visit 2 (Day 1) Type of cough: Single cough	Treatment A (N=100)
Did subject experience event [1]?	12 (24%)
Cough severity	
Mild	6 (50%)
Moderate	5 (42%)
Severe	1 (8%)
Time to onset of PI cough (minutes)	
0-1	2(17%)
>1-2	3(25%)
>2-3	4(33%)
>3-4	3(25%)
>4-5	0
>5	0
Duration of PI cough (minutes)	
<=1	7(58%)
>1 - 2	2(17%)
>2 - 3	3(25%)
>3 - 4	0
>4 - 5	0
>5 - 10	0
>10 - 30	0
>30	0

[1] Percentages are calculated using the number of subjects evaluated at visit as the denominator.
All other percentages are calculated using the number of subjects with particular cough type at visit as the denominator.

Protocol: ABC123456
Population: Safety

Table X
Summary of Post-Inhalation Cough by Visit and Cough Type

Visit 2 (Day 1) Type of cough: Single cough	Treatment A (N=100)
Number of subjects reporting cough as AE/SAE	4 (33%)
Mild	2 (17%)
Moderate	2 (17%)
Severe	0

Protocol: ABC123456
Population: Safety

Table X
Summary of Post-Inhalation Cough by Visit and Cough Type

Visit 2 (Day 1) Type of cough: Intermittent cough	Treatment A (N=100)
Did subject experience event [1]?	11 (22%)
Cough severity	
Mild	2 (18%)
Moderate	6 (55%)
Severe	3 (27%)
Time to onset of PI cough (minutes)	
0-1	1(9%)
>1-2	4(36%)
>2-3	6(55%)
>3-4	0
>4-5	0
>5	0
Duration of PI cough (minutes)	
<=1	0
>1 - 2	3(27%)
>2 - 3	6(55%)
>3 - 4	1(9%)
>4 - 5	0
>5 - 10	0
>10 - 30	1(9%)
>30	0

Protocol: ABC123456
Population: Safety

Table X
Summary of Post-Inhalation Cough by Visit and Cough Type

Visit 2 (Day 1) Type of cough: Intermittent cough	Treatment A (N=100)
Number of subjects reporting cough as AE/SAE	5 (45%)
Mild	1 (9%)
Moderate	2 (18%)
Severe	2 (18%)

Protocol: ABC123456
Population: Safety

Table X
Summary of Post-Inhalation Cough by Visit and Cough Type

Visit 2 (Day 1) Type of cough: Continuous cough	Treatment A (N=100)
Did subject experience event [1]?	4 (8%)
Cough severity	
Mild	1 (25%)
Moderate	2 (50%)
Severe	1 (25%)
Time to onset of PI cough (minutes)	
0-1	3(75%)
>1-2	1(25%)
>2-3	0
>3-4	0
>4-5	0
>5	0
Duration of PI cough (minutes)	
<=1	0
>1 - 2	0
>2 - 3	0
>3 - 4	1 (25%)
>4 - 5	1 (25%)
>5 - 10	0
>10 - 30	1 (25%)
>30	1 (25%)

Protocol: ABC123456
Population: Safety

Table X
Summary of Post-Inhalation Cough by Visit and Cough Type

Visit 2 (Day 1) Type of cough: Continuous cough	Treatment A (N=100)
Number of subjects reporting cough as AE/SAE	2 (50%)
Mild	1 (25%)
Moderate	1 (25%)
Severe	0

REPEAT FOR EACH VISIT

13.12.29. Example Shell 29

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Population: Intent-to-Treat

Listing X
Listing of Subjects who Received Incorrect Medication

Randomized Treatment	Centre/ Subj	Start Date of Dosing	End Date of Dosing	Duration (Days)	Dispense Visit	Dispense Date	Actual Treatment Dispensed
GSK2269557 500 mcg	PPD	XXXXXXXXX	XXXXXXXXX	XX	Visit 3 (Week 0)	XXFEB2013	GSK2269557 500 mcg
		XXXXXXXXX	XXXXXXXXX	XX	Visit 5 (Week 4)	XXMAR2013	GSK2269557 100 mcg
		XXXXXXXXX	XXXXXXXXX	XX	Visit 6 (Week 8)	XXAPR2013	GSK2269557 500 mcg

PPD