Statistical Analysis Plan Amendment 3

Study ID: 208657

Official Title of Study: A multi-center, randomized, double-blind, parallel-group, placebo-controlled study of mepolizumab 100 mg SC as add-on treatment in participants with COPD experiencing frequent exacerbations and characterized by eosinophil levels (Study 208657)

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TITLE PAGE

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Abbreviated Title:	**M**epolizumab as **A**dd-on **T**reatment **IN** participants with COPD characterized by frequent **E**xacerbations and **E**osinophil Level
Acronym:	MATINEE

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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	28 Jul 2022	Amendment 6 (06-Dec-2021)	Not Applicable	Original version
SAP Amendment 1	16 Nov 2023	Amendment 6 (06-Dec-2021)	• Definition of Extended Treatment Population updated to include all participants who receive at least one dose of trial medication. Population for selected Study Population and Safety summaries, not Efficacy summaries.	• Definition amended to accommodate Extended Treatment population being applied to Study Population or Safety summaries.
			• Change in handling of intercurrent events of prohibited medication.	• Change to handle all occurrences of the intercurrent event of prohibited medication with treatment policy regardless of association with disruptions or restrictions imposed due to the COVID-19 pandemic per feedback from regulatory authority.
			• Addition of sensitivity analysis for primary endpoint regarding Site_239718.	• Due to concerns over data quality at site, sensitivity analysis was added to determine

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
				effect of site results on primary endpoint.
			• Addition of clarification that time to event analyses are carried out for data up to week 104.	• Provide further clarity for analysis.
			• Change in safety display presentations to include all data up to Week 104, with specific displays summarizing data separately for participants enrolled for 52 weeks only and those in the Extended Treatment population.	• Facilitate assessment of the overall effect of mepolizumab on safety.
			• Updated the SMQ to be used to identify adverse events of pneumonia, this will be Infective Pneumonia SMQ.	• The Pneumonia SMQ is no longer present in the current version of MedDRA.
			• Amendment of wording in Immunogenicity section.	• Wording changed to provide further clarity on the testing process.
			• Addition of time to first adjudicated MACE analysis section.	• Additional analysis to further explore difference in MACE occurrence in

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
				the two treatment groups.
			• Addition of PK/PKPD analysis.	• To document a PK/PKPD analysis may be conducted if deemed appropriate.
			• Addition of details regarding early release of unblinded PK data.	• Early release of PK data to be carried out to aid in refinement of the population PK model.
			• Addition of subgroup (symptoms of chronic bronchitis) and removal of subgroups (screening eosinophil categories and other comorbidity).	• Subgroup analyses of subjects with symptoms of chronic bronchitis determined to be of importance. Screening eosinophil categories were deemed unnecessary with screening eosinophil thresholds available. Other comorbidity was deemed not to provide a meaningful analysis.
			• Update of countries defining geographic regions.	• Incorporating additional countries participating in MATINEE to their respective

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
				geographic regions.
			• Addition of analyses for Chinese, East Asia, South Korea and India subpopulations.	• Documentation of planned subpopulation analyses.
			• Addition of outline of time to withdrawal from IP summary.	• Added for clarity (no change to analysis).
SAP Amendment 2	18 Jul 2024	Amendment 6 (06-Dec-2021)	• Addition of baseline definition for CAT and SGRQ questionnaires.	• Added to clarify differences to other baseline definitions.
			• Amendment of wording in the sensitivity analysis for primary endpoint section.	• Added clarity on defining the on and off treatment data used for imputation.
			• Minor amendments and clarifications added to secondary, pharmacodynamic analyses and other analyses.	• Added to clarify time periods for summaries, populations for summaries and methodologies used.
			• Amendment of PK and PKPD analysis objectives to remove covariate exploration.	• Model to be used is well established - covariate selection is not expected to be required and will only occur if original model is not deemed suitable.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			• Change of subgroup definitions – removed screening eosinophil thresholds, added screening eosinophil categories. Added <40 to age subgroup.	• Analysis by screening blood eosinophil threshold no longer required, analysis by screening blood eosinophil categories (<500, ≥500 cells/µL) added as more informative. Additional age subgroup level added for further information.
			• Subgroup analyses updated to include additional analyses for secondary and other endpoints and shrinkage methods in primary endpoint.	• Additional analysis to provide further context behind main analyses.
			• Amendment of definitions for Chinese, East Asia, South Korea and India subpopulations	• Definitions aligned to data categories collected in eCRF.
			• Minor amendments and clarifications added to study population analyses.	• Added to clarify summaries and methodologies used.
			• Addition of text in demographics section regarding requirements for de-identified summaries.	• Added in accordance with new company guidance.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			• Addition of eCOA compliance appendix.	• Added in accordance with new company guidance.
SAP Amendment 3	20 Aug 2024	Amendment 6 (06-Dec-2021)	• Updates to formatting.	• Applied in line with QC check.
			• Addition of further exploratory analyses to assess smoking variables.	• Additional analysis to further explore the impact of smoking in COPD.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report for Study 208657.

1.1. Objectives, Estimands and Endpoints

1.1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of mepolizumab 100 mg subcutaneous (SC) compared to placebo, given every 4 weeks in liquid formulation by safety syringe (SS) to COPD participants at high risk of exacerbations despite the use of optimized COPD maintenance therapy.	• Annualized rate of moderate/severe exacerbations
Secondary	
• To evaluate mepolizumab 100 mg SC compared to placebo given every 4 weeks in liquid formulation by SS on additional efficacy assessments, health related quality of life (HRQoL), health care utilization, and symptoms	• Time to first moderate/severe exacerbation • Proportion of COPD assessment test (CAT) responders (≥2 unit reduction in CAT score from baseline) at Week 52 • Proportion of St. George's Respiratory Questionnaire (SGRQ) total score responders (measured using the St. George's Respiratory Questionnaire for COPD [SGRQ-C], and defined as ≥4 point reduction in SGRQ total score from Baseline) at Week 52 • Proportion of Evaluating Respiratory Symptoms in COPD (E-RS: COPD) responders (≥2 unit reduction in total score from Baseline) at Week 52 • Annualized rate of exacerbations requiring Emergency Department (ED) visit and/or hospitalization

Objectives	Endpoints
Other	
• To further investigate other endpoints	CCI [redacted]
	• Change from Baseline in pre-bronchodilator forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) • CAT responders at Week 24 • CAT change from baseline at Week 24 and 52 • SGRQ responders at Week 24 • SGRQ change from Baseline at Week 24 and 52 • Proportion of Evaluating Respiratory Symptoms in COPD (E-RS: COPD) responders at Week 24 • Proportion of E-RS: COPD responders: sub-scales of breathlessness, cough and sputum and chest symptoms at Week 24 and 52 • Change from Baseline in E-RS: COPD Total Score at Week 24 and 52 • CCI [redacted]
CCI [redacted]	

Objectives	Endpoints
Safety	
• To evaluate the safety of mepolizumab in participants with COPD	• Incidence of AEs/SAEs including systemic reactions. • Incidence of adjudicated SAE reports and MACE events (CV death, non-fatal myocardial infarction, and non-fatal stroke) • Vital signs including blood pressure (BP), body temperature, pulse rate • ECG assessments • Mortality (all cause including respiratory and cardiovascular causes of death) • Presence of anti-drug antibodies (ADA) to mepolizumab • Hematological and clinical chemistry parameters
Health Outcomes	
• To further evaluate the effect of mepolizumab 100 mg SC on health care utilization.	• Healthcare utilization for COPD including hospitalization, ED, and physician office/clinic visits
Pharmacokinetics Sub-study: China and US only	
• To evaluate the PK of mepolizumab 100 mg in liquid formulation administered subcutaneously by SS in Chinese participants and to assess potential PK ethnic differences between non-Asian participants in the US and Chinese participants in China	• Plasma mepolizumab concentrations

1.1.2. Primary Estimand

The primary estimand is the difference between mepolizumab 100 mg SC and placebo (both added to optimized standard of care) in the annualized rate of moderate/severe exacerbations in participants with COPD experiencing frequent exacerbations and characterized by eosinophil levels, regardless of IP discontinuation/interruption or changes in background medication/starting a prohibited medication, in the absence of COVID-19 pandemic related intercurrent events.

The primary estimand is described by the following attributes:

Population: Participants with COPD experiencing frequent exacerbations and characterized by eosinophil levels

Treatment condition: Mepolizumab 100 mg SC vs. placebo (both as add-on treatment to optimized standard of care)

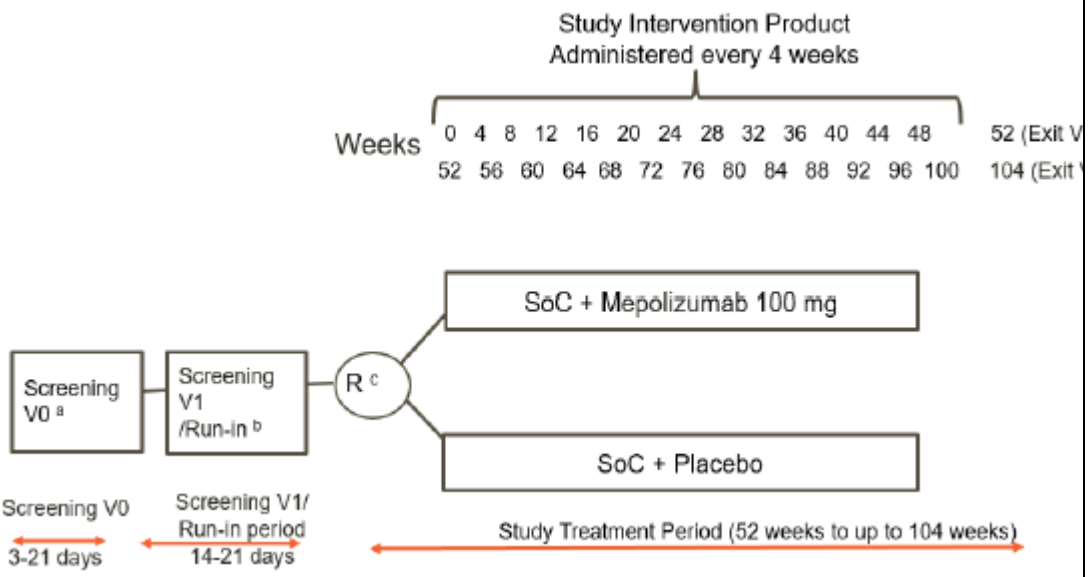
Variable: Number of moderate or severe exacerbations

Intercurrent events: The anticipated intercurrent events in this trial are discontinuation of interventional product (IP), interruption of 2 or more consecutive doses of IP, use of prohibited medications and change in background medication.
A treatment policy strategy will be used to handle the intercurrent events of discontinuation of IP and interruption of 2 or more consecutive doses of IP when not associated with disruptions or restrictions (e.g. lockdown measures, social distancing) imposed due to the COVID-19 pandemic. Under this strategy exacerbations and time in study will be included in the analysis regardless of the intercurrent event. A hypothetical strategy will be used to handle these intercurrent events when they are known to be associated with disruptions or restrictions imposed due to the COVID-19 pandemic.
A treatment policy strategy will be used to handle the intercurrent events of change in background medication and use of prohibited medications.

Rationale for estimand: The use of a hypothetical strategy recognizes any effect on exacerbations due to discontinuation or interruption of 2 or more consecutive doses of IP associated with disruptions or restrictions imposed due to the COVID-19 pandemic, may not have occurred in the hypothetical scenario of the absence of the pandemic.

1.2. Study Design

Overview of Study Design and Key Features



[a] Participants must have an eosinophil count of ≥300 cells/µL at Screening Visit 0 to proceed to Visit 1. They are also required to have a documented historical eosinophil count of ≥150 cells/µL in the 12 months prior to Screening Visit 0.

[b] Participants with no historical eosinophil counts of ≥150 cells/µL must have an eosinophil count ≥150 cells/µL at Screening Visit 1.

[c] R = Randomization: Randomization criteria should be assessed at Week 0 (Visit 2) prior to randomization.

[d] For participants enrolled in the study for 52 weeks, the Exit Visit will be at Week 52, 4 weeks after the last dose.

[e] For participants receiving study treatment beyond 52 weeks, the Exit Visit will be at Week 104 or aligned to the date the last randomized participant is scheduled to complete their Week 52 Exit Visit, whichever is sooner, see Protocol Section 4.4. The Exit Visit will be 4 weeks after the last dose.

Design Features	This is a multi-center, randomized, placebo-controlled, double-blind, parallel group trial evaluating mepolizumab 100 mg compared with placebo given every 4 weeks as a liquid formulation in a pre-filled safety syringe through SC injection as an add-on to optimized maintenance COPD therapy in participants with COPD characterized by eosinophil levels Study participants will remain in the study for at least 52 weeks and up to a maximum of 104 weeks. All participants will be expected to complete at least 52 weeks of the study. The last randomized participant will be scheduled to complete only 52 weeks of the study. More specifically,

Overview of Study Design and Key Features	
	○ For participants enrolled for 52 weeks, their Exit Visit will occur at Week 52, 4 weeks after the last scheduled dose of IP. ○ For participants enrolled for (or reconsented to) an extended treatment duration beyond 52 weeks, their Exit Visit will be at Week 104 or at a scheduled visit that occurs on or before the date the last randomized participant is scheduled to complete their Week 52 Exit Visit, whichever is sooner. The Exit Visit will occur 4 weeks after the participants last scheduled dose of IP.
Study intervention	Interventional product will be administered as a single SC injection given every 4 weeks at each study visit (except for the Exit Visit), beginning at the Randomization Visit (Visit 2). Participants are to continue on their baseline optimized COPD medications throughout the study.
Study intervention Assignment	Eligible participants will be randomized 1:1 to receive mepolizumab 100 mg or placebo in accordance with a randomization schedule generated using a validated randomization software, separate randomization schedules will be created for each country.
Blood Eosinophil Inclusion Criteria	Participants must have a blood eosinophil count of ≥300 cells/µl at Screening Visit 0 **and** a documented historical blood eosinophil count of ≥150 cells/µl in the 12 months prior to Screening Visit 0 (or at Screening Visit 1).
Off-treatment data	The protocol objective is to collect data over the full study period whether participants continue on IP or prematurely withdraw from IP. Unless otherwise specified, data from participants who agree to continue in the study after premature withdrawal from IP will be included in the analysis of efficacy endpoints.
Interim Analysis	No formal interim analyses of efficacy data are planned for this study. See Section 5 for details regarding blinded sample size evaluation.

2. STATISTICAL HYPOTHESES

This study is designed to test the superiority of mepolizumab 100 mg SC vs placebo. The treatment comparison of interest for the primary and secondary endpoints is mepolizumab 100 mg SC vs placebo in the modified Intent-to-Treat (mITT) population, the significance test will be considered statistically significant at the two-sided 5% alpha level (one-sided 2.5%).

2.1. Multiplicity Adjustment

A hierarchical testing procedure will be used to provide strong control of Type I error for multiplicity arising from the primary and multiple secondary endpoints. This will be carried out using a step-down closed testing procedure where inference for an endpoint in the predefined hierarchy will be dependent on statistical significance having been achieved for the previous endpoints in the hierarchy.

For example, for the primary endpoint, mepolizumab will be compared to placebo at a two-sided α=0.05 (one-sided α=0.025). The next endpoint in the hierarchy (i.e. the first secondary endpoint) will be tested only if the test for the primary endpoint is significant at the one-sided 2.5% level. Testing will continue down the hierarchy for the remaining endpoints in an equivalent manner only if the previous endpoint in the hierarchy achieves statistical significance.

The hierarchy of the primary and secondary endpoints to be tested is as follows:

1. Annualized rate of moderate/severe exacerbations (primary endpoint)
2. Time to first moderate/severe exacerbation
3. Proportion CAT score responders at Week 52
4. Proportion of SGRQ total score responders at Week 52
5. Proportion of E-RS: COPD responders at Week 52
6. Annualized rate of exacerbations requiring ED and/or hospitalization

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
All Participants Enrolled Population	All participants for whom a record exists on the study database.	Reasons for Screen Failures and Run-in Failures
Modified Intent-to-Treat Population (mITT)	All randomized participants who receive at least one dose of trial medication. Participants will be analyzed by randomized treatment.	Efficacy endpoints
mITT Population excluding past/concurrent Asthma (mITT2)	All participants in the mITT population with no evidence of a past history or concurrent diagnosis of asthma. Participants will be analyzed by randomized treatment.	Primary and secondary efficacy endpoints

Analysis Set	Definition / Criteria	Analyses Evaluated
Safety Population (Safety)	All randomized participants who receive at least one dose of trial medication. Participants will be analyzed based on actual treatment received for more than 50% of treatment administrations.	Safety endpoints
Per-Protocol Population (PP)	All participants in the mITT population not identified as protocol deviators with respect to criteria that are considered to impact the primary efficacy endpoint. The decision to exclude a participant from the PP Population will be made prior to the unblinding of treatment codes.	Supplementary analysis of primary endpoint
Pharmacokinetic (PK)	All participants enrolled in the PK sub-study who received at least one dose of trial medication and for whom at least one pharmacokinetic sample was obtained, analyzed and was measurable. Population for the PK sub-study analysis Data will be reported according to actual treatment received for more than 50% of treatment administrations.	Pharmacokinetics endpoints
Extended Treatment Population	All participants who receive at least one dose of trial medication and who consented to participate in the extended treatment period beyond 52 weeks. Participants within this population are enrolled for up to 104 weeks with variable duration.	Selected Study Population, Efficacy, Safety summaries

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Confidence intervals will use 95% confidence levels unless otherwise specified.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum, and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

The efficacy analyses will be based on the mITT/mITT2 population. Where available, data up to Week 104 will be summarized for the mITT/mITT2 Population; where specified, additional displays will present information separately for participants in the

Extended Treatment population. Extended Treatment population study population and efficacy displays will be summarized based on randomized treatment. Details of covariates are provided in Section 4.10.1.

4.1.2. Baseline Definition

For the majority of visit-based assessments the baseline value will be the last measurement collected prior to the first dose of interventional product. This will be the pre-dose assessment taken at Visit 2, or if missing the immediately preceding value if available, including from an unscheduled assessment. (Where time is collected, an assessment is valid for use as baseline if the date and time is prior to or the same as the date and time of first dose.)

For CAT and SGRQ assessments, the baseline value is defined as the last measurement taken prior to, or on same date as, first dose of interventional product.

For blood eosinophils, the screening value is defined as the value from the blood sample taken at Screening Visit 0, this pre-dose value is aligned with the blood eosinophil levels required for inclusion into the study. If missing the next available value prior to the first dose of interventional product will be used, however values from the blood sample taken at Screening Visit 1 will not be included in the determination of the screening value. The baseline value will be the measurement defined as the screening value.

For entry into the study, historical blood eosinophils recorded in the 12 months prior to Screening Visit 0 and aligned with the study inclusion criteria are required. For participants who do not have a documented historical blood eosinophil count prior to Screening Visit 0, the value from the blood sample taken at Screening Visit 1 is used.

For data collected every evening using the electronic diary (eDiary), the baseline value will be determined as the average of the 7 days of diary card data collected from the week prior to first dose (i.e., data collected between Day -7 and Day -1 inclusive).

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

4.1.3. Visit Windows

It is expected that all visits should occur according to the protocol schedule. No assessment windows are defined for visit based assessments. Detail of premature withdrawal and unscheduled visit assignments is found in Section 6.2.5.

4.1.4. Study Completion

The study is designed to collect data after premature discontinuation of treatment. Participants are considered to have completed the study if they meet the following criteria regardless of premature discontinuation of interventional product.

Participants enrolled for 52 Weeks

A participant is considered to have completed the study if they continue to participate in the study until the Exit Visit at Week 52.

Participants enrolled beyond 52 Weeks (or reconsented to continue beyond 52 Weeks)

A participant is considered to have completed the study if they continue to participate in the study until the earlier of:

The Exit Visit at Week 104

OR

A scheduled visit that is on or immediately before the date of the Exit Visit at Week 52 of the last participant to have been randomized into the study.

By study design, the duration of study will vary for the participants enrolled beyond 52 Weeks (or reconsented to continue beyond 52 Weeks).

4.2. Primary Endpoint Analyses

4.2.1. Definition of Primary Endpoint/Estimand

The primary endpoint is the annualized rate of moderate or severe exacerbations occurring during the study period. The study is designed to continue collecting exacerbation data for participants who have prematurely discontinued from IP and remain in the study.

For analysis, moderate exacerbations are defined as clinically significant exacerbations that require treatment with oral/systemic corticosteroids and/or antibiotics. Severe exacerbations are defined per protocol as clinically significant exacerbations that require in-patient hospitalization (i.e., ≥24 hrs.) or result in death. The study inclusion criteria required at least 2 moderate COPD exacerbations treated with systemic corticosteroids (intramuscular (IM), intravenous, or oral) with or without antibiotics or at least one severe exacerbation in the 12 months prior to Screening Visit 1.

Moderate and severe exacerbations occurring from the start of interventional product (IP) will be included in the primary analysis regardless of whether the exacerbation occurs after a participant prematurely discontinues from IP. For participants who complete the study (Section 4.1.4), all moderate/severe exacerbations occurring up to study completion will be included in the primary analysis. For participants who withdraw early from the study all moderate/severe exacerbations occurring up to the date of study withdrawal will be included in the primary analysis, these participants will be considered to have missing data from the date of study withdrawal up to their planned study completion date.

For all summaries and analyses, exacerbations occurring within 7 days of each other within a given participant will be handled as a continuation of the same exacerbation, assigned to the greatest severity.

The primary estimand is the difference between mepolizumab 100 mg SC and placebo (both added to optimized standard of care) in the annualized rate of moderate/severe exacerbations in participants with COPD experiencing frequent exacerbations and characterized by eosinophil levels, regardless of IP discontinuation/interruption or changes in background medication/starting a prohibited medication, in the absence of COVID-19 pandemic related intercurrent events.

The primary estimand is described by the following attributes:

Population: Participants with COPD experiencing frequent exacerbations and characterized by eosinophil levels

Treatment condition: Mepolizumab 100 mg SC vs. placebo (both as add-on treatment to optimized standard of care)

Variable: Number of moderate or severe exacerbations

Summary Measure: The summary measure of treatment effect will be the ratio of the frequency of exacerbations in the mepolizumab 100 mg treatment arm to the frequency in the placebo arm. Exacerbation rates will be expressed as an annualized exacerbation rate.

Intercurrent events: The anticipated intercurrent events for this trial are discontinuation of IP, interruption of 2 or more consecutive doses of IP, use of prohibited medications and change in background medication.

A treatment policy strategy will be used to handle the intercurrent events of discontinuation of IP and interruption of 2 or more consecutive doses of IP when not associated with disruptions or restrictions (e.g. lockdown measures, social distancing) imposed due to the COVID-19 pandemic, under this strategy exacerbations and time in study will be included in the analysis regardless of the intercurrent event. A hypothetical strategy will be used to handle these intercurrent events when they are known to be associated with disruptions or restrictions imposed due to the COVID-19 pandemic. Under this strategy exacerbations, and the period of time in study occurring after the intercurrent event, will be set to missing and handled as missing data.

A treatment policy strategy will be used to handle the intercurrent events of change in background therapy and use of prohibited medications.

Rationale for estimand: The use of a hypothetical strategy recognizes any effect on exacerbations due to discontinuation /interruption of 2 or more consecutive doses of IP associated with disruptions or restrictions imposed due to the COVID-19 pandemic, may not have occurred in the hypothetical scenario of the absence of the pandemic.

4.2.2. Main analytical approach

Statistical Methodology Specification

Endpoint / Variables
Annualized rate of moderate or severe exacerbations (mITT, mITT2 and Per Protocol).
Model Specification
Data from previous studies show the numbers of moderate/severe exacerbations follow a negative binomial distribution. The primary analysis of the annualized rate of moderate/severe exacerbations will use a negative binomial model, including both on-treatment and, where available, off-treatment exacerbation data. The analysis model will include covariates as shown below and an offset variable of $\log_e$ (length of time in study) which reflects the period of time in the study for which exacerbation data has been recorded for inclusion in the analysis model. Missing data will be considered as missing at random (MAR).

Fixed Categorical:	Treatment group, Geographic Region, Smoking Status
Fixed Continuous:	Baseline disease severity (as % predicted post-bronchodilator FEV_1), number of moderate/severe exacerbations in previous year (≤2, 3, ≥4 as ordinal)

- Participants with missing covariate information will be excluded from the analysis.

Model Checking & Diagnostics
• Missing data is assumed missing at random. Departures from this assumption will be tested for the primary endpoint (see Section 4.2.3). • Models will be checked for issues with convergence.
Model Results Presentation
• The model estimated mean annualized rate of exacerbations will be calculated using the observed marginal distributions of the study population covariates by inclusion of the OM (obsmargins) option in the LSMEANS statement of the GENMOD procedure. The estimated mean annualized rate of moderate/severe exacerbations for each treatment group and the rate ratio for mepolizumab vs. placebo with 95% confidence intervals and associated p-values will be presented in a table and associated figure.
Subgroup Analyses
Separate exploratory subgroup analyses of the primary endpoint (mITT) will be carried out as detailed in Section 4.10.1.

4.2.3. Sensitivity analyses

Sensitivity Analyses
Sensitivity Analysis for assumptions regarding missing data • Missing Data Imputation:

The negative binomial model assumes missing data is missing at random. To assess the robustness of the primary estimand to departures from this assumption, a sensitivity analysis in the mITT population will be performed where missing data will be imputed.

Participants who withdrew from the study early will have missing data imputed for the period of time between withdrawal from the study and their scheduled end of study. Missing data for these subjects will be imputed using observed off-treatment data collected from randomized participants (prior to occurrence of intercurrent events of IP discontinuation or interruption of 2 or more consecutive doses of IP associated with the COVID-19 pandemic) who continued in the study following discontinuation of randomized treatment.
Participants who have missing data due to occurrence of intercurrent events of IP discontinuation or interruption of 2 or more consecutive doses of IP associated with the COVID-19 pandemic will have missing data imputed for the period of time between occurrence of the intercurrent event and their scheduled end of study. Missing data after the occurrence of the intercurrent event will be imputed using both on-treatment and off-treatment data collected from randomized participants (on-treatment data prior to occurrence of intercurrent events associated with the COVID-19 pandemic, off treatment data from those not experiencing an occurrence of intercurrent events associated with the COVID-19 pandemic).

Missing data is imputed multiple times for each subject based on a combination of their respective covariates and the observed data. The imputed data is combined with the observed exacerbations and the data is analyzed as for the primary endpoint. This analysis is repeated multiple times and the results combined across imputations using Rubin's formulae [Rubin, 1987] as implemented in PROC MIANALYZE in SAS.

- Tipping Point:
  A tipping point sensitivity analysis will be performed for the primary endpoint of annualized rate of moderate/severe exacerbations in the mITT population. This will explore the impact of missing data by using differing assumptions regarding the exacerbation rate in participants with missing data. Participants who withdrew from the study or experienced intercurrent events of IP discontinuation or interruption of 2 of more consecutive doses of IP associated with the COVID-19 pandemic will have missing data imputed for the period of time from study withdrawal/occurrence of event to their scheduled end of study. The missing data will be imputed based on a range of increases in exacerbation rates relative to the estimated rates obtained within each arm under the MAR assumption. The imputed exacerbation rates will vary independently for the mepolizumab and placebo arms and will include scenarios where participants with missing data in the mepolizumab arm have worse outcomes than participants in the placebo arm. As before, multiple imputation methods will be used, and results will be combined across imputations using Rubin's method. The analysis results will be used to explore conditions under which there is no evidence of a treatment effect and clinical judgment will be applied as to the plausibility of the associated assumptions.

- Site 239718:
  A sensitivity analysis will be conducted excluding the three subjects randomized at Site 239718. This will explore the impact of patients from this site on the primary estimand. The analysis will otherwise be carried out as outlined within Section 4.2.2.

4.2.4. Additional estimands

Additional Estimands
Additional (supplementary) estimands for the primary endpoint will be presented for the mITT population whereby a treatment policy strategy will be used for all intercurrent events whether or not associated to the COVID-19 pandemic. Analysis will be as for the primary estimand and missing data due to study withdrawal will be handled as missing at random. In a separate analysis missing data will be imputed using observed off-treatment data collected from randomized participants who continued in the study following discontinuation of randomized treatment. These additional estimands estimate the difference between mepolizumab 100 mg SC and placebo (both added to optimized standard of care) in the annualized rate of moderate/severe exacerbations in participants with COPD experiencing frequent exacerbations and characterized by eosinophil levels, regardless of IP discontinuation/interruption, changes in background medication/starting a prohibited medication, or the impact of the COVID-19 pandemic.

4.2.5. Exploratory Modelling

The role of blood eosinophil counts on the effectiveness of mepolizumab with respect to the number of moderate/severe exacerbations will be investigated. The number of moderate/severe exacerbations will be predicted at each level of the screening $\log_e$ blood eosinophil count based on a model including a screening $\log_e$ blood eosinophil count main effect term and an interaction with treatment term.

The best fitting form of the interaction (i.e. which maximizes the likelihood function) between treatment group and screening $\log_e$ blood eosinophil count will also be explored.

4.3. Secondary Endpoint(s) Analyses

For all secondary endpoints the primary population of interest, the treatment condition, and handling of intercurrent events will be as described for the primary estimand (Section 4.2.1). Unless otherwise specified all analyses will include data regardless of discontinuation of interventional product as has been detailed for the primary endpoint.

4.3.1. Time to first moderate/severe exacerbation

4.3.1.1. Definition of Endpoint

The time to first moderate/severe exacerbation will be determined as the number of days from the date of first dose to the date of the first moderate or severe exacerbation:

Time to first exacerbation = date of first exacerbation – date of first dose +1

Partial dates related to exacerbations will be queried, in the event the full start date cannot be determined, imputation as described in Section 6.2.7 will be applied.

The variable of interest is the time to first moderate/severe exacerbation. Participants who complete the study without experiencing a moderate/severe exacerbation will be censored at their scheduled end of the study treatment period (see Section 6.2.2.1). Participants who withdrew early from the study or experienced an intercurrent event of IP discontinuation or interruption of 2 or more consecutive doses of IP associated with the COVID-19 pandemic before experiencing an exacerbation will be censored at the earliest of the date of study withdrawal and the start date of COVID-19 pandemic associated intercurrent event of IP discontinuation or interruption of 2 or more consecutive doses of IP.

The summary measure of treatment effect will be the hazard ratio, the ratio of hazards corresponding to treatment with mepolizumab compared with placebo. For this endpoint the hazard represents the probability of moderate/severe exacerbation for a participant at a given point in time following first dose of interventional product, given the participant has not experienced the event prior to that time. Data will be presented up to week 104 for this endpoint.

4.3.1.2. Main Analytical Approach

Statistical Methodology Specification

<table>
<tr><th>Endpoint / Variables</th></tr>
<tr><td>Time to first moderate/severe exacerbation (mITT and mITT2)</td></tr>
<tr><th>Model Specification</th></tr>
<tr><td>
• Analysis of time to first moderate/severe exacerbation will use a Cox proportional hazards model with covariates as shown. Missing values will be considered as censored at random (non-informative censoring).
<table>
<tr><td>Fixed Categorical:</td><td>Treatment group, smoking status, geographic region</td></tr>
<tr><td>Fixed Continuous:</td><td>Baseline disease severity (as % predicted post-bronchodilator FEV_1), number of moderate/severe exacerbations in previous year (≤2, 3, ≥4 as ordinal)</td></tr>
</table>
• Participants with missing covariate information will be excluded from the analysis.
</td></tr>
<tr><th>Model Checking & Diagnostics</th></tr>
<tr><td>A log(-log(survival)) plot by treatment group will be used to assess the assumption of proportional hazards.</td></tr>
<tr><th>Model Results Presentation</th></tr>
<tr><td>
• The number of participants with an event, the number censored due to study withdrawal, due to an intercurrent event associated to the COVID-19 pandemic, and at study completion will be presented by treatment arm.
• The hazard ratio with corresponding 95% CI and p-value from the Cox proportional hazards model will be presented.
A summary and graph of the Kaplan-Meier estimate of the cumulative proportion of participants with a moderate/severe exacerbation within each treatment arm over time will be produced.
</td></tr>
</table>

Subgroup Analyses
Separate exploratory subgroup analyses will be carried out as outlined in Section 4.10.1.

4.3.2. CAT Score Responders

4.3.2.1. Definition of Endpoint

The COPD Assessment Test (CAT) is an 8-item questionnaire used to measure the health status of patients with COPD, participants rate their experience on a 6-point scale, ranging from 0 (no impairment) to 5 (maximum impairment) with a scoring range of 0-40. Higher scores indicate greater disease impact.

The variable of interest is the proportion of CAT score responders at Week 52. A participant is considered a responder if they have a 2-point or more improvement (reduction) in CAT Score from baseline. Participants who withdrew from study prior to Week 52 will be included in the analysis as a non-responder.

Participants who experienced an intercurrent event of IP discontinuation or interruption of 2 or more consecutive doses of IP associated with the COVID-19 pandemic will be considered as having missing data from the time of the event. For these participants missing data will be imputed using a MAR assumption based on the observed on- and off-treatment scores recorded by randomized participants (prior to occurrence of any intercurrent events of IP discontinuation or interruption of 2 or more consecutive doses of IP associated with the COVID-19 pandemic), the response status of these participants will be determined based on the imputed value.

Imputed data will be combined with the observed data and analyzed multiple times using logistic regression analysis. The results of these analyses will be combined using Rubin's rule.

The summary measure of treatment effect will be the odds ratio which represents the relative odds of a participant being a responder at Week 52 in the mepolizumab arm compared with placebo.

4.3.2.2. Main Analytical Approach

Descriptive statistics by visit will be presented for the mITT population up to Week 104, regardless of treatment discontinuation. Responders will be summarized by visit up to Week 52 for the mITT and mITT2 populations, and by visit up to Week 104 for the Extended Treatment population.

Statistical Methodology Specification

Model Specification
• A logistic regression model will be used to compare the proportion of responders in the mepolizumab arm compared to placebo for the mITT and mITT2 populations. • The analysis model will include the following terms:

Fixed Categorical:	Treatment group, smoking status, geographic region
Fixed Continuous:	Baseline score

- Participants with missing covariate information will be excluded from the analysis

Model Checking & Diagnostics

- Models will be checked for issues with convergence.

Model Results Presentation

- The number and percentage of participants identified as responders, non-responders and the number with missing data imputed due to experiencing a COVID-19 pandemic related intercurrent event of IP discontinuation or interruption of 2 or more consecutive doses of IP prior to Week 52 will be displayed by treatment group, the non-responder group will be further categorized to display the number of participants withdrawn early from the study before Week 52 and the number with missing visit data.
- The estimated odds ratio, 95% CI and p-value comparing treatments from the logistic regression models will be displayed.
- A forest plot of the estimated odds ratio and 95% CI for the comparison of treatment groups will be provided by visit.

Subgroup Analyses

Separate exploratory subgroup analyses will be carried out as outlined in Section 4.10.1.

4.3.3. SGRQ total score Responders

4.3.3.1. Definition of Endpoint

The St George's Respiratory Questionnaire for COPD (SGRQ-C) is a 40-item questionnaire. A Total score and three component scores, a Symptoms score, Activity score and Impacts score will be calculated based on the scoring algorithm detailed in the SGRQ-C Manual Version 1.3. The total score is expressed as a percentage of overall impairment with 100 representing the worst possible health status and 0 the best possible health status. Higher scores indicate greater impairment of health.

The variable of interest is the proportion of SGRQ total score responders at Week 52. A participant is considered a responder if they have a 4-point or more improvement (reduction) in SGRQ total score from baseline. Participants who withdrew from study prior to Week 52 will be included in the analysis as a non-responder.

Participants who experienced an intercurrent event of IP discontinuation or interruption of 2 or more consecutive doses of IP associated with the COVID-19 pandemic will be considered as having missing data from the time of the event. Missing data will be imputed as described in Section 4.3.2.1.

The summary measure of treatment effect will be the odds ratio which represents the relative odds of a participant being a responder at Week 52 in the mepolizumab arm compared with placebo.

4.3.3.2. Main Analytical Approach

Descriptive statistics and summaries of responders for the SGRQ total score will be presented as detailed in Section 4.3.2.2. SGRQ total score responders will be analyzed as described in Section 4.3.2.2. Separate exploratory subgroup analyses will be carried out as outlined in Section 4.10.1.

4.3.4. E-RS: COPD total score Responders

4.3.4.1. Definition of Endpoint

The Evaluating Respiratory Symptoms in COPD (E-RS: COPD) consists of 11 items from the 14 item EXACT instrument (completed each evening using an eDiary). E-RS: COPD is intended to capture information related to the respiratory symptoms of COPD, i.e., breathlessness, cough, sputum production, chest congestion, and chest tightness. The E-RS: COPD has a scoring range of 0-40, higher scores indicate more severe symptoms. Three subscales of the E-RS: COPD are used to describe different symptoms (breathlessness, cough and sputum, and chest symptoms).

Daily data will be slotted to baseline and 4-week periods relative to the first dose of IP as defined in Section 6.2.5.4.

The variable of interest is the proportion of E-RS: COPD responders at Week 52, using data from the 4-week period prior to Week 52 (Weeks 49-52). A participant is considered a responder if they have a 2-point or more improvement (reduction) in their average E-RS: COPD total score during a 4-week period compared to baseline (*E-RS™: COPD User Manual*, 2016). Participants who withdrew from study prior to the start of the Weeks 49-52 time-period will be included in the analysis as a non-responder.

Participants who experienced an intercurrent event of IP discontinuation or interruption of 2 or more consecutive doses of IP associated with the COVID-19 pandemic prior to Weeks 49-52 will be considered as having missing data from the time of the intercurrent event. Missing data will be imputed based on the average 4-weekly scores as described in Section 4.3.2.1.

The summary measure of treatment effect will be the odds ratio which represents the relative odds of a participant being a responder at Weeks 49-52 in the mepolizumab arm compared with placebo.

4.3.4.2. Main Analytical Approach

Descriptive statistics and summaries of responders will be presented as detailed in Section 4.3.2.2. with the exception of the responder summary for the Extended Treatment Population. E-RS: COPD total score responders will be analyzed as described in Section 4.3.2.2.

4.3.5. Annualized Rate of Exacerbations Requiring ED visit and/or hospitalization

4.3.5.1. Definition of Endpoint

Frequency of exacerbations requiring ED visit and/or hospitalization over the study treatment period (up to 104 weeks) represented by an annualized rate, these exacerbations are relatively infrequent. Details regarding the estimand strategy for this endpoint are as described in Section 4.2.1.

4.3.5.2. Main Analytical Approach

The annualized rate of exacerbations requiring ED visit and/or hospitalization will be analyzed as described in Section 4.2.2.

4.4. Other Efficacy Analyses

The population, treatment condition and handling of intercurrent events as described for the primary estimand (Section 4.2.1) apply to all efficacy analyses unless otherwise specified.

4.4.1. Time to first exacerbation (ED/Hospitalization, Severe)

4.4.1.1. Definition of Endpoint

Time to first exacerbation requiring ED and/or hospitalization and time to first severe exacerbation will be determined as detailed in Section 4.3.1.1.

4.4.1.2. Main Analytical Approach

The approach to analysis will be as described in Section 4.3.1.2.

4.4.2. Annualized Rate of Exacerbations (Severe, Moderate/Severe By Type of Treatment Required)

4.4.2.1. Definition of Endpoint

Frequency of severe exacerbations and frequency of moderate/severe exacerbations by type of treatment required (corticosteroids alone, antibiotics alone or corticosteroids and antibiotics) over the study treatment period (up to 104 weeks) represented by an annualized rate as detailed in Section 4.2.1.

4.4.2.2. Main Analytical Approach

The approach to analysis will be as described in Section 4.2.2.

4.4.3. Daily eDiary data (Percentage of rescue medication free days, Percentage of nights with no awakenings, Mean number of occasions of rescue medication use/day)

4.4.3.1. Definition of Endpoint

Daily data collected via an eDiary will be slotted to baseline and 4-week periods relative to the first dose of IP as defined in Section 6.2.5.4.

The percentage of rescue medication free days will be calculated at baseline and for each 4-week period as:
(100 x [No. rescue medication free days /No. days with non-missing data]).

The percentage of nights with no awakenings due to COPD symptoms will be calculated at baseline and for each 4-week period as:
(100 x [No. nights with no awakenings /No. days with non-missing data]).

The mean number of occasions of rescue medication use per day will be calculated at baseline and for each 4-week period as:
(Total occasions of rescue medication use/No. days with non-missing data).

The summary measure of treatment effect for each endpoint will be the difference between mepolizumab and placebo in mean change from baseline at Weeks 49-52.

4.4.3.2. Main Analytical Approach

Statistical Methodology Specification

Endpoint / Variables

Percentage of rescue medication free days
Percentage of nights with no awakenings due to COPD symptoms
Mean number of occasions of rescue medication use per day

Model Specification

- This endpoint will be analyzed using a mixed model repeated measures (MMRM) analysis including data up to Weeks 49-52 and the following terms:

Fixed Categorical:	Treatment group, smoking status, geographic region, Time period
Fixed Continuous:	Baseline value
Repeated:	Time period
Interaction Terms:	Time period by baseline, Time period by treatment group.

  - Participants with missing covariate information will be excluded from the analysis

An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line. In the event that this model fails to converge, alternative correlation structures may be considered.

Model Checking & Diagnostics
• The Kenward-Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
Model Results Presentation
• The estimated means for each treatment group will be calculated from the model using the observed marginal distributions of the sample covariates (OM option in LSMEANS statement). • Model-estimates of the absolute and change from baseline values will be presented by treatment group. Estimated treatment differences (Mepolizumab-Placebo) with corresponding 95% CIs and p-values will also be presented.

4.4.4. Change from baseline (Pre-bronchodilator FEV_1, FVC, CAT Score, SGRQ Total Score, E-RS: COPD Total Score)

4.4.4.1. Definition of Endpoint

Change from baseline pre-bronchodilator FEV_1 at Week 52
Change from baseline pre-bronchodilator FVC at Week 52
Change from baseline CAT score at Weeks 24 and 52
Change from baseline SGRQ Total score at Weeks 24 and 52
Change from baseline ERS: COPD Total score at Weeks 21-24 and Weeks 49-52

For change from baseline CAT, SGRQ and E-RS: COPD: Participants who experienced an intercurrent event of IP discontinuation or interruption of 2 or more consecutive doses of IP associated with the COVID-19 pandemic will be considered as having missing data from the time of the event. Missing data will be imputed as described in Section 4.3.2.1.

The summary measure of treatment effect for each endpoint will be the difference between mepolizumab and placebo in mean change from baseline at the respective timepoints.

4.4.4.2. Main Analytical Approach

Statistical Methodology Specification

Endpoint / Variables

Change from baseline pre-bronchodilator FEV_1 at Week 52
Change from baseline pre-bronchodilator FVC at Week 52
Change from baseline CAT score at Week 24 and 52
Change from baseline SGRQ total score at Week 24 and 52
Change from baseline E-RS: COPD score at Weeks 21-24 and Weeks 49-52

Model Specification

- Endpoints will be analyzed using a mixed model repeated measures (MMRM) analysis including data up to Week 52/Weeks 49-52 and the following terms:

Fixed Categorical:	Treatment group, smoking status, geographic region, Visit/Time Period
Fixed Continuous:	Baseline value
Repeated:	Visit[1]/Time Period
Interaction Terms:	Visit[1]/Time Period by baseline, visit/time period by treatment group.

Participants with missing covariate information will be excluded from the analysis

1. FEV_1 and FVC recorded at Baseline, Week 24 and Week 52 only.

An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line. In the event that this model fails to converge, alternative correlation structures may be considered.

Model Checking & Diagnostics

- The Kenward- Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.

Model Results Presentation

- The estimated means for each treatment group will be calculated from the model using the observed marginal distributions of the sample covariates (OM option in LSMEANS statement).
- Model-estimates of the absolute and change from baseline values will be presented by treatment group. Estimated treatment differences (Mepolizumab-Placebo) with corresponding 95% CIs and p-values will also be presented.

Subgroup Analyses

Separate exploratory subgroup analyses for the change from baseline SGRQ total score will be carried out as outlined in Section 4.10.1.

4.4.5. Responders (CAT, SGRQ and E-RS: COPD Responders at Week 24, E-RS: COPD Subscale Responders at Weeks 21-24 and 49-52)

4.4.5.1. Definition of Endpoint

CAT score responders at Week 24: defined as a 2-point or more improvement (reduction) in CAT score from baseline.

SGRQ total score responder at Week 24: defined as a 4-point or more improvement (reduction) in SGRQ total score from baseline.

E-RS: COPD responder at Weeks 21-24: defined as a 2-point or more improvement (reduction) in average E-RS: COPD score from baseline.

E-RS: COPD Breathlessness Sub-Scale responder at Weeks 21-24 and Weeks 49-52: defined as a 1-point or more improvement (reduction) in average E-RS: COPD score from baseline.

E-RS: COPD Cough and Sputum Sub-Scale responder at Weeks 21-24 and Weeks 49-52: defined as a 0.7-point or more improvement (reduction) in average E-RS: COPD score from baseline.

E-RS: COPD Chest Symptoms Sub-Scale responder at Weeks 21-24 and Weeks 49-52: defined as a 0.7-point or more improvement (reduction) in average E-RS: COPD score from baseline.

4.4.5.2. Main Analytical Approach

Approach to analysis will be as described in Section 4.3.2.

4.4.6. Patient and Clinician Response to Therapy

4.4.6.1. Patient and clinician-rated response to therapy

Patient-rated and clinician-rated response to therapy are assessed separately. For each, a seven-point scale score is used with the following definitions: 1 = significantly improved; 2 = moderately improved; 3 = mildly improved; 4 = no change; 5 = mildly worse; 6 = moderately worse; and 7 = significantly worse.

Patient-rated and clinician-rated response to therapy will be summarized by visit up to Week 104. Data will be included in the summaries regardless of treatment discontinuation or occurrence of any other intercurrent events.

4.4.6.2. Patient's Global Rating of COPD

The Global Rating of COPD Severity is a single global question that asks participants to rate their severity of COPD on a four- point scale (mild, moderate, severe, very severe). The Global Rating of Change in COPD question is also completed by participants with response options being on a 7-point Likert scale ranging from much better to much worse.

Data will be summarized up to Week 104, and regardless of treatment discontinuation or occurrence of any other intercurrent events.

4.4.7. Healthcare Utilization

The following data will be collected regarding unscheduled use of health care resources:

- Number of Home Visits during Day and Night
- Number of Emergency Room Visits
- Inpatient days in General Ward and Intensive Care
- Number of office/practice visits
- Number of urgent care/outpatient visits

Healthcare utilization associated with an exacerbation will be summarized up to Week 52 only, and regardless of treatment discontinuation or occurrence of any other intercurrent events.

4.4.7.1. EuroQol questionnaire (EQ-5D-3L)

The EQ-5D-3L is a two-part self-assessment questionnaire. The first part consists of five items covering five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a three-point Likert scale (no problems, some problems and extreme problems). The second part is a vertical response scale (EQ-VAS) that has endpoints labelled “best imaginable health state” and “worst imaginable health state” anchored at 100 and 0, respectively.

A participant is classified into one of 243 distinct health states (each being referred to by a 5-digitcode based on the responses to each dimension in the descriptive system, e.g., 11111 or 33333). EQ-5D-3L health states are converted to a single summary index by applying a formula that essentially attaches weights to each of the levels in each dimension. The formula is based on the valuation of EQ-5D health states from general population samples.

The EQ-5D-3L health state is converted to a health state value, using the value set for the United Kingdom as described in [Dolan, 1997]. EQ-5D-3L health state values summarize how good or bad health problems are on a scale anchored at 1 (full health) and 0 (state equivalent to dead). Health states considered worse than dead are given values <0.

Valid non-missing responses are required to all questions for a health state value to be assigned, if there is a missing or ambiguous response in any dimension the health state value will be set to missing.

Both parts of the EQ-5D-3L questionnaire will be summarized by visit up to Week 104. Data will be included in summaries regardless of treatment discontinuation or occurrence of any other intercurrent events.

4.5. Safety Analyses

The safety analyses will be based on the Safety population. Data up to Week 104 will be summarized for the Safety Population; where specified, additional displays will present information separately for participants enrolled in the study for 52 weeks only and for those in the Extended Treatment population. Extended Treatment population safety displays will be summarized based on actual treatment received for more than 50% of administrations. Data separated by time of onset (before and after Week 52) will be summarized for the Safety population where specified.

4.5.1. Extent of Exposure

IP is administered approximately every 4 weeks and each dose viewed as providing therapeutic coverage for 4 weeks (28 days). Duration of exposure in months is calculated based on the therapeutic coverage as follows:

Duration of Exposure (months) = (IP Stop Date – IP Start Date + 29) *12/365.25

Patient years exposure is calculated as follows:

Patient Years Exposure = (IP Stop Date – IP Start Date + 29)/365.25

If the IP start date is missing and there is evidence the participant received at least one dose of IP, the IP start date will be taken to be the date of randomization.

Randomized participants with no evidence of receiving at least one dose of IP will be shown as having zero months of exposure.

Exposure will be summarized by treatment arm for all subjects in the safety population, for participants enrolled for 52 weeks only and for those in the Extended Treatment population. A listing of exposure data will also be produced.

4.5.2. Adverse Events

Summaries of adverse events (AEs), serious adverse events (SAEs) and other significant AEs will be based on GSK Core Data Standards. Summaries for the Safety Population will include AEs experienced up to Week 104. For on-treatment AEs, SAEs, common AEs and AESIs, separate displays will be produced for participants enrolled for 52 weeks only and for those in the Extended Treatment Population. Summaries of AEs, SAEs and AESIs will be produced by time of onset (before and after Week 52) where specified. Where applicable, exposure-adjusted rates will be included in summaries.

Adverse events will be coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA dictionary), with the maximum severity of each AE determined by the investigator (as mild, moderate, or severe). Unless otherwise specified, summaries are presented in descending order of frequency by system organ class and preferred term.

An overview summary of AEs will be generated, including counts and percentages of participants with any AE, AEs related to study treatment, AEs leading to permanent

discontinuation of study treatment, AEs leading to withdrawal from the study, SAEs, SAEs related to study treatment, fatal SAEs, and fatal SAEs related to study treatment.

Adverse events will be determined to be pre, on or post-treatment as described in Section 6.2.3.4. The number and percentage of participants experiencing AEs during the on-treatment and post-treatment periods will be summarized separately. Additionally, summaries of the number and percentage of participants with any on-treatment AEs by maximum severity will be produced. If an adverse event severity is missing, the severity will be populated as 'UNKNOWN'.

A separate summary will be provided for drug-related AEs. The summary will include events with the relationship to study intervention of 'Yes' or missing. On-treatment drug-related AEs will also be reported by maximum severity.

Summaries of SAEs, fatal and non-fatal SAEs, common AES defined as ≥3% (prior to rounding), AEs leading to discontinuation of study treatment, AEs leading to withdrawal from study, AEs reported on the day of dosing, and AEs by highest post-baseline anti-drug antibody result will be reported separately.

Adverse events of pneumonia will be summarized, these will be identified through matching of collected adverse event preferred terms with those from the Infective Pneumonia SMQ (narrow terms) prior to unblinding based on the latest version of the MedDRA dictionary available at the time of database lock for this study.

4.5.2.1. Adverse Events of Special Interest

Adverse events of special interest (AESIs) are adverse events which are to be closely monitored as the development of mepolizumab progresses. AESIs in the mepolizumab clinical development program are described in the mepolizumab BRMP/DRMP [GSK Document Number; 2020N436792]. The methods by which these events will be identified within this study reporting are detailed in Section 6.4.

AESIs of anaphylaxis reactions, systemic reactions, and local injection site reactions are collected via targeted eCRF. The AESIs of potential opportunistic infections, malignancies, serious CVT events and serious ischemic events will be identified from a list of relevant preferred terms maintained within a project level reference dataset; created based on the latest version of the MedDRA dictionary available at the time of database lock for this study.

Separate summary tables showing the number and percent of participants with each type of AESI, broken down by preferred term will be created. These summaries will be reported as part of the standard AE/SAE tables for the AESIs of infections, serious infections, neoplasms, cardiac disorders and serious cardiac disorders.

The relative risk and risk difference of each AESI between mepolizumab and placebo will be presented with 95% confidence intervals. A forest plot displaying the relative risk with 95% CI will also be produced.

For each AESI a profile summary table will be produced containing information on event characteristics including, but not be limited to, the number of participants with the AESI, the number of occurrences of the AESI, the number of participants with a serious event or a drug related event, maximum severity, outcome and action taken. Separate listings will be provided of participants with systemic reactions identified by the investigator as meeting the criteria for anaphylaxis, systemic reactions categorized as allergic (type I hypersensitivity), systemic reactions categorized as other, and all other AESIs.

4.5.2.2. Adjudication of Adverse Events and MACE

External adjudication of all serious cases will be completed in a blinded manner by case-based adjudication, with classification of primary cause of death for fatal cases or a classification of the primary event in the non-fatal cases.

For all cases with a fatal SAE, the Clinical Endpoint Committee (CEC) members will indicate the primary cause of death. Additionally, the CEC members will determine if the death is associated with the participant's known COPD.

For all non-fatal SAE cases, the CEC members will be asked to categorize the primary SAE. If there is more than one event for a patient in the same SAE report, the primary event will be the adverse event of greatest medical significance.

The categories will be as follows:

- Cardiovascular (sudden death (for fatal events only), myocardial infarction/ischemic heart disease, congestive heart failure, stroke or other cardiovascular cause)
    - Stroke is further categorized as hemorrhagic, thromboembolic or indeterminate
- Respiratory (COPD exacerbation with or without evidence of pneumonia, pneumonia/respiratory tract infection without COPD exacerbation, pulmonary embolism, other respiratory cause)
- Cancer (lung, breast, colorectal, unknown primary, other)
- Other
- Unknown (inadequate information or indeterminate).

Adjudication of all MACE (cardiovascular death, non-fatal acute MI, non-fatal acute stroke) will be completed by event-based adjudication in a blinded manner. MACE will be adjudicated based on criteria given in the CEC Charter Version3. Serious and nonserious events potentially representing acute MI and acute stroke will be identified for adjudication as events with a PT matching the list of PTs in pre-selected MedDRA SMQs.

Myocardial infarctions will be classified as:

- ST segment elevation myocardial infarction (STEMI)
- Non-ST segment elevation myocardial infarction (NSTEMI)
- Myocardial infarction, type (i.e., STEMI or NSTEMI) unknown

Strokes will be classified as intracerebral hemorrhage, subarachnoid hemorrhage, ischaemic (non-hemorrhagic) or undetermined. Events considered to not meet the charter definition of stroke but consistent with extra-axial hemorrhage will be classified as subdural, extradural or other.

All fatal events will be reviewed for adjudication of MACE component cardiovascular death. Cardiovascular deaths will be classified as acute MI (with sub-classifications as above), sudden cardiac death, heart failure, stroke (with sub-classifications as for stroke events above), cardiovascular procedure (with sub-classifications of PCI, CABG or other), cardiovascular hemorrhage (with sub-classifications of subdural, extradural, ruptured aortic aneurysm or other) or other cardiovascular cause (with sub-classifications of peripheral artery disease or other).

4.5.2.2.1. Time to first adjudicated MACE

Time to first adjudicated MACE will be analyzed and summarized. This will be determined as the number of days from the date of first dose to the date of the first adjudicated MACE:

Time to first adj. MACE = date of first adj. MACE – date of first dose +1

Partial dates related to adjudicated MACE will be queried, in the event the full start date cannot be determined, imputation as described in Section 6.2.7 will be applied.

The variable of interest is the time to first adjudicated MACE. For analyses of time to first 'on- and post-treatment' MACE, participants who complete the study or withdraw from the study prior to completion without experiencing a MACE will be censored at their respective completion or study withdrawal date. For analyses of time to first 'on-treatment' MACE, participants who do not experience a MACE prior to the end of their on-treatment period, as defined in Section 6.2.3.3 will be censored at their end of IP date + 28 days.

The analysis will be carried out using a Cox proportional hazards model with treatment group as the only categorical covariate. The model checking & diagnostics will follow the same strategy as outlined in Section 4.3.1.2. The number of participants with an event, the number censored due to study withdrawal and at study completion will be presented by treatment arm. The hazard ratio with corresponding 95% CI and p-value from the Cox proportional hazards model will be presented.

4.5.2.3. COVID-19 Assessment and COVID-19 AEs

The number of participants with suspected, probable, or confirmed for COVID-19 infection will be reported. This display will also summarize the number of participants with a COVID-19 diagnosis test performed and the number of participants with positive, negative, or indeterminate results.

The overall incidence of AEs of COVID-19 will be obtained from the standard AE summaries. Additionally, a summary and a listing of COVID-19 assessments and symptoms for participants with COVID-19 AEs will be generated.

4.5.3. Laboratory Data

Summaries of laboratory data including chemistry and hematology parameters, and liver function test data will be based on GSK Core Data Standards and unless otherwise specified will include on-treatment and post-treatment data.

Summaries of the number and percentage of participants with changes from baseline with respect to both the Normal Range (NR) and Potential Clinical Importance (PCI) criteria will be generated separately. Details of PCI criteria are provided in Section 6.2.1.1.

A listing of chemistry and hematology data will be presented for participants with laboratory values that meet any PCI criteria.

Summaries of hepatobiliary laboratory events including possible Hy's law cases will be provided in addition to what has been described above. Possible Hy's law cases are defined as events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin), or ALT ≥3 × ULN and international normalized ratio (INR) >1.5.

An e-DISH plot of maximum post baseline ALT versus maximum post baseline total bilirubin will be created.

4.5.4. Vital Signs

Descriptive statistics of change from baseline vital signs data [systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate] will be based on GSK Core Data Standards.

4.5.5. ECG

Summaries of ECG data will be based on GSK Core Data Standards. Summaries will include ECG findings showing the number of normal/abnormal 12-lead ECG results and descriptive statistics by visit and for any time post-baseline.

Individual QTc(F) values will be categorized and the number (percent) of participants with values in the following categories will be displayed for each visit and the highest post-baseline value: Grade 0 (≤450 msec), Grade 1 (>450 to ≤480 msec), Grade 2 (>480 to ≤500 msec) and Grade 3 (>500 msec).

Additionally, individual changes from baseline in QTc(F) values will be categorized and the number (percent) of participants with changes (msec) in the following categories will be displayed for each visit and the highest post-baseline value: <-60, ≥-60 to <-30, ≥-30 to <0, ≥0 to ≤30, >30 to ≤60, and >60.

A listing of ECG findings for participants with an abnormal interpretation or finding will be produced.

4.5.6. Cardiovascular Events

A summary of cardiovascular (CV) events will be presented in addition to patient profiles. CV events include myocardial infarction/unstable angina, congestive heart failure, arrhythmias, valvulopathy, pulmonary hypertension, cerebrovascular events/stroke and transient ischemic attack, peripheral arterial thromboembolism, deep venous thrombosis/pulmonary embolism, and revascularization (as specified in the trial Protocol Section 10.4.3).

4.6. Immunogenicity Data

An immune response to a therapeutic drug can lead to generation of anti-drug antibodies within the blood. For the immunogenicity assessment, two types of antibody assays will be performed, a binding anti-drug antibody (ADA) assay and a neutralizing antibody (NAb) assay.

For the binding ADA assay, there will be three testing steps: screening, confirmation, and titration. The screening assay produces a result of positive or negative relative to a screening cut point. Positive samples continue with the confirmation assay, which also produces a result of positive or negative relative to a confirmation cut point. Participants with a positive confirmation result are considered positive for anti-mepolizumab antibodies. Participants who test positive for the binding ADA assay will be tested in the titer assay to assess relative antibody concentrations (i.e., titer value) and will be tested for the NAb assay, which also reports results as positive or negative.

Immunogenicity data will be summarized for the Safety Population up to Week 52, and for the Extended Treatment Population using all data. For the binding ADA assay, confirmation results at each visit will be categorized as negative, transient positive (defined as a single positive immunogenic response that does not occur at the final study assessment) or persistent positive (defined as a positive immunogenic response for at least 2 consecutive assessments or a single result at the final study assessment). NAb assay results will also be summarized.

The highest binding ADA assay confirmatory result obtained post-baseline for a participant (including any off-treatment data), will be summarized, participants with both positive and negative results being identified in the positive category. Summary statistics for titre results will also be presented. In addition, the highest NAb assay result during the same period will be summarized (again participants with both positive and negative results will be identified in the positive category).

A summary of treatment emergent positive confirmatory binding ADA assay results in the subset of participants who did not have a positive confirmatory binding ADA assay result prior to the first dose of interventional product will also be presented.

All immunogenicity results (i.e. binding ADA screening and confirmatory assay results, titre values and NAb results) will be listed.

4.7. Pharmacodynamic Analyses

Blood eosinophils are collected as part of clinical laboratory assessments throughout the study.

4.7.1. Definition of Endpoint

Absolute and ratio to screening blood eosinophil counts will be summarized at each visit for the mITT population up to Week 104.

The summary measure of treatment effect will be the ratio of the effect at Week 52 of mepolizumab compared to placebo.

Only data collected while the participant was on-treatment will be used in the analysis (while on-treatment strategy). Blood eosinophil counts taken more than 28 days following last dose will not be included in the analysis.

4.7.2. Main Analytical Approach

Statistical Methodology Specification

Endpoint / Variables
• Ratio to screening blood eosinophils (mITT)
Model Specification
• Blood eosinophil counts will be log transformed (log_e) prior to analysis, transformations for values of 0 GI/L will be based on a value of 0.005 GI/L. • This endpoint will be analyzed using a mixed model repeated measures (MMRM) analysis including the following terms: Fixed Categorical: Treatment group, smoking status, geographic region, Visit Fixed Continuous: Baseline log_e blood eosinophil count, Repeated: Visit Interaction Terms: Visit by baseline, visit by treatment group. • Participants with missing covariate information will be excluded from the analysis • An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line. In the event that this model fails to converge, alternative correlation structures may be considered.
Model Checking & Diagnostics
• The Kenward-Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
Model Results Presentation
• The estimated means for each treatment group will be calculated from the model using the observed marginal distributions of the sample covariates (OM option in LSMEANS statement). • Model-estimates of the absolute mean and mean ratio to baseline will be back-transformed and presented as ratios with corresponding standard errors on the log scale for each treatment group by visit. Estimated treatment differences (Mepolizumab/Placebo) with corresponding 95% CIs and p-values will also be presented.

4.8. Population Pharmacokinetic (PopPK) Analyses

An optional PK Sub-study was performed for US and China participants only. The primary goal of this analysis is to characterize the population pharmacokinetics of mepolizumab administered subcutaneously in China and US participants with COPD in the PK sub-study. The analysis will be based on the most recent population pharmacokinetics model established with historical data from various indications. The influence of demographics, baseline characteristics, including disease activity, and co-medication on the pharmacokinetics of mepolizumab in this population may be investigated. These data will be used to explore potential ethnic differences between China and US participants mepolizumab exposure. The individual participant PK

parameters will be estimated and documented for the purposes of any subsequent exposure response (PK/PD) analyses.

The resultant primary and secondary PK parameters derived from the description of the sparse PK data by the model will be summarized as descriptive statistics by ethnicity. These data will serve as the basis for the comparison between ethnic groups. An assessment of similarity in PK will be performed by comparing summary of post-hoc primary PK parameters between ethnicities and whether the established model can describe the new data without modification.

Mepolizumab plasma concentration-time data [samples collected at Weeks 0, 4, 24 and 52; at the early withdrawal visit and IP discontinuation visit (if applicable)] will be analyzed by population methods using nonlinear mixed-effects modelling. The analysis will be carried out using appropriate software (e.g. NONMEM ™ or SAS ™).

In support of the analysis described below, a dataset will be generated for which specifications will be provided in a separate document.

Further to the details in the protocol regarding analysis of PK data, early release of PK data will be carried out to aid in refinement of the established population PK model. Under this process, individual participant-level, de-identified, unblinded, and scrambled (i.e., random reassignment of participant identification numbers) drug concentration information will be analyzed prior to unblinding the study. In that case, independent clinical PK analysts (who have no involvement in study conduct) will have access to an unblinded scrambled population PK-specific dataset (e.g., drug concentrations, actual dosing information, demographics, and laboratory details) at one or more time points (e.g., prior to the final analysis) throughout the study for population PK model development and refinement. No AE or efficacy data will be included and no unblinding eosinophil or immunogenicity data will be included as part of this early release.

4.8.1. Definition of Endpoint(s)

Blood for PK will be collected at Week 0 (prior to first dose initiation), Week 4 (pre-dose), Week 24 and Week 52 (or IP discontinuation/early withdrawal). Individual PK parameters and covariates will be log-transformed and standardized before analysis.

Based on previous knowledge of mepolizumab 100 mg SC pharmacokinetics, concentrations below the limit of quantification (BLQ) of the assay are not anticipated. Any such results will be treated as missing.

4.8.2. Main Analytical Approach

A population PK analysis of sparse concentration data will be performed. The population of interest will be the PK population.

The summary measure of interest will be the log-transformed mepolizumab plasma concentration. For participants prematurely discontinuing study treatment, all available

data will be included in the analysis. Participants who experience an intercurrent event will be handled using a treatment policy strategy.

Sparse blood sampling is implemented in this study for determination of mepolizumab plasma concentration, and subsequent data analysis by population PK methods using the most recent population pharmacokinetics model (meta-analysis PK model of data across indications described in CCI [redacted] The main objectives of this population PK analysis are:

- To evaluate mepolizumab pharmacokinetics in China and US participants with COPD in the PK sub-study following the subcutaneous administration of a 100 mg dose every 4 weeks;
- To obtain individual plasma concentration predictions for the timepoints at which PD is measured to allow the conduct of population PKPD analyses if deemed appropriate.

Outlier data will be assessed for plausibility; however, the aim is to use all available data whenever possible. Any decision to exclude data will be fully documented and specified in the clinical study report.

4.9. Population Pharmacokinetic/Pharmacodynamic (PopPKPD) Analyses

If deemed appropriate, a population pharmacokinetic/pharmacodynamic analysis will be conducted. Mepolizumab blood eosinophil count-time data will be analyzed by population methods using nonlinear mixed-effects modelling. The analysis will be carried out using appropriate software (e.g. NONMEM or SAS).

In support of the analysis described below, a specific dataset will be generated for which specifications will be provided in a separate document.

4.9.1. Definition of Endpoint(s)

Blood for PK are defined within Section 4.8.1.

Blood eosinophil counts are defined within Section 4.7.1.

4.9.2. Main Analytical Approach

The population of interest will be the PK analysis set and blood eosinophils measured in each visit in the PK sub-study. For participants prematurely discontinuing study treatment, all available data will be included in the analysis. Participants who experience an intercurrent event will be handled using a treatment policy strategy.

This PopPKPD analysis will be performed by population methods using the most recent population PKPD model CCI [redacted]

The objectives of the popPKPD analysis are:

- To evaluate mepolizumab pharmacodynamics in China and US participants with COPD in the PK sub-study following subcutaneous administration of a 100 mg dose every 4 weeks;

Outlier data will be assessed for plausibility; however, the aim is to use all available data whenever possible. Any decision to exclude data will be fully documented and specified in the clinical study report.

4.10. Other Analyses

4.10.1. Subgroup Analyses

For the primary endpoint, a separate exploratory analysis within each of the below subgroup categories will be carried out. Unless otherwise specified no formal hypothesis testing in subgroups of the population will be performed, exacerbation rates/year in each treatment arm together with the rate ratio and associated 95% CI will be displayed.

The following subgroups are of interest:

Subgroup	Categories
Age	<40, 40-<65, ≥65 years
Sex	Male, Female
Race	African American/African Heritage, White, Asian, Other
Baseline Body Mass Index (kg/m^2)	Low (≤20), Medium (>20-≤30), High (>30)
Geographic Region [1]	Europe (Belgium, Denmark, France, Germany, Greece, Ireland, Italy, Netherlands, Spain, Sweden, United Kingdom), Eastern Europe (Hungary, Poland), Asia (China, Republic of Korea, Taiwan), South America (Argentina, Brazil, Mexico), North America (United States, Canada), Rest of World (Australia, New Zealand, Israel, India)
Exacerbations in the previous year	≤2, 3, ≥4 exacerbations
Severe exacerbations in the previous year	0, ≥1 exacerbation
Screening blood eosinophil categories	<0.5 GI/L, ≥0.5 GI/L
Smoking status at Screening	Current, Former
Symptoms of Chronic Bronchitis	Yes (Participants with baseline response of "most days of the week" or "several days of the week" to both questions regarding cough and sputum on SGRQ-C questionnaire), No
Cardiovascular Disease Comorbidity	Any past or current medical condition under Cardiac Disorders
Modified Medical Research Council (mMRC) score at Screening	<2, ≥2
Severity of Airflow Limitation (GOLD Guidelines)	Mild, Moderate, Severe, Very Severe
Treatment Duration [2]	Fixed Duration ('Enrolled in study for 52 weeks', 'Enrolled in study for 52 weeks, Not agreed to extend up to 104 weeks'), Variable Duration ('Enrolled in study for 52 weeks, agreed to extend up to 104 weeks' or 'Enrolled in study for up to 104 weeks')

[1] If numbers of participants within the geographic regions are too small then regions may be further combined for analysis.
[2] From Treatment Duration Confirmation eCRF page. For participants who completed the study prior to release of Protocol Amendment 6, no information was entered into this eCRF page retrospectively, all such subjects were categorized as Fixed Duration.

If the number of participants is too small within a subgroup category, then the subgroup categories may be redefined prior to unblinding the study.

For secondary endpoints, exploratory analyses by screening blood eosinophil categories will be carried out for time to first moderate/severe exacerbation, CAT responders and SGRQ responders. Analysis by symptoms of chronic bronchitis and smoking status at screening will be carried out for time to first moderate/severe exacerbation, CAT responders, SGRQ responders and SGRQ change from baseline. Analysis by geographic region will be carried out for SGRQ responders and E-RS: COPD responders. No formal hypothesis testing in subgroups of the population will be performed.

Further exploratory analysis assessing the effect of smoking variables such as smoking duration in years and smoking intensity as measured by pack years may be carried out, this may include assessment of these variables as subgroups and/or as covariates of interest.

4.10.1.1. Shrinkage Estimation Methods

Additional to the conventional approach for the subgroup analyses specified for the primary endpoint, analyses using Bayesian Hierarchical Modelling will be carried out for all subgroups of interest, except for screening blood eosinophil categories, where the exchangeability assumption is not expected to hold. The rate ratios and standard errors from the standard subgroup analyses will be included in a Bayesian Hierarchical model to obtain shrinkage estimates of the subgroup-specific treatment effects.

The subgroup-specific rate ratios, μ_j (j=1, …, X) will be assumed to be distributed $\mu_j \sim N(\mu, \tau^2)$ where μ is the overall rate ratio and τ^2 is the between-subgroup variance. The following non-informative and weakly-informative priors respectively will be used in the model:

- $\mu \sim N(0, SD = 100)$
- $\tau \sim$ half-Normal$(SD = 1)$

The model will be fitted using MCMC with at least 50,000 iterations, a thin of 5 and a burn-in of at least 1000. The posterior rate ratios with 95% Credible Interval will be presented by subgroup in a forest plot alongside the conventional estimates.

A sensitivity analysis may be performed to assess the impact of the prior for τ on the degree of shrinkage by considering:

- $\tau \sim$ half-Normal$(SD = 0.5)$
- $\tau \sim$ half-Normal$(SD = 2)$

4.10.2. Subpopulation Analyses

The key study population, efficacy, safety analysis and some exploratory analysis will be repeated in the following subpopulations:

- Chinese subpopulation – All participants of a relevant Asian heritage (Asian – East Asian Heritage) enrolled at sites in China Mainland and Taiwan.
- East Asia subpopulation: All participants of a relevant Asian heritage (Asian – East Asian Heritage) enrolled at sites in China mainland, Taiwan, South Korea.
- South Korea subpopulation: All participants of a relevant Asian heritage (Asian – East Asian Heritage and Asian – South East Asian Heritage) enrolled at sites in South Korea.
- India subpopulation: All participants of a relevant Asian heritage (Asian – Central/South Asian Heritage, Asian – East Asian Heritage and Asian – South East Asian Heritage) enrolled at sites in India.

Any analyses involving statistical modelling will be carried out using the same approach as outlined in the relevant sections of this SAP (data permitting). Geographic region will not be included as a covariate within any of the models. Adaptions to the statistical models may be made in the case of any convergence issues.

4.11. Interim Analyses

No formal interim analyses of efficacy data are planned for this study. Details regarding planned blinded sample size evaluations are provided in Section 5.

4.12. Changes to Protocol Defined Analyses

Changes to the planned statistical analysis specified in the Protocol Amendment 6 (Dated: 06-DEC-2021) are detailed in Table 1

Table 1 Changes to Protocol Defined Analysis Plan

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
• Analysis populations defined as All Participants Enrolled (ASE), Modified Intent-to-Treat (mITT), Safety, Per-Protocol (PP) and PK	• Additional analysis population of mITT Population excluding past/concurrent Asthma (mITT2)	• Additional population excluding participants with past/concurrent asthma required for analysis of primary and secondary endpoints to assess the impact of inclusion of these patients.

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
• Other endpoint of Annualized rate of moderate/ severe exacerbation requiring systemic steroids	• Other endpoint of Annualized rate of moderate/ severe exacerbation by Type of Treatment Required (Corticosteroids alone, Antibiotics alone, Corticosteroids and Antibiotics)	• To provide further breakdown of exacerbations requiring differing treatment courses and effect of mepolizumab.
• For the primary estimand a treatment policy strategy will be used for the intercurrent events of discontinuation of study medication, use of medication prohibited by the protocol, and investigational product interruption of 2 or more doses, when these intercurrent events are not associated with disruptions or restrictions imposed due to the COVID-19 pandemic. A hypothetical strategy will be considered when these intercurrent events have occurred as a result of disruptions or restrictions (e.g. lockdown measures, social distancing) imposed due to the COVID-19 pandemic.	• For the primary estimand a treatment policy strategy will be used for the intercurrent events of discontinuation of study medication and investigational product interruption of 2 or more doses, when these intercurrent events are not associated with disruptions or restrictions imposed due to the COVID-19 pandemic. A hypothetical strategy will be considered when these intercurrent events have occurred as a result of disruptions or restrictions (e.g. lockdown measures, social distancing) imposed due to the COVID-19 pandemic.	• The change was made following regulatory feedback on the handling of the intercurrent event of prohibited medication use, a treatment policy strategy will be used for all occurrences of this intercurrent event.
• N/A (not in protocol)	• Individual participant-level, de-identified, unblinded, and scrambled (i.e., random reassignment of participant identification numbers) drug concentration information will be analyzed prior to unblinding the study. In that case, independent clinical PK analysts (who have no involvement in study conduct) will have access to an unblinded scrambled population PK-specific dataset (e.g., drug concentrations, actual dosing information, demographics, and	• The change was made to aid population PK model development and refinement.

Protocol Defined Analysis	SAP Defined Analysis	Rationale for Changes
	laboratory details, but no AE or efficacy data) at one or more time points (e.g., prior to the final analysis) throughout the study	
• Evaluation of similarity in exposure will be guided by the confidence interval excluding at least a two-fold difference.	• An assessment of similarity in PK will be performed by comparing summary of post-hoc primary PK parameters between ethnicities and whether the established model can describe the new data without modification.	• This was deemed to be a more meaningful analysis for comparing the similarity of PK across the US and China participants.

5. SAMPLE SIZE DETERMINATION

The primary analysis is based on comparing the annualized rate of moderate/severe exacerbations in participants treated with mepolizumab 100 mg SC vs. placebo.

The null hypotheses used to test the superiority of mepolizumab 100 mg compared to placebo will be:

H0: $\mu_i = \mu_p$

where μ_i is the annualized exacerbation rate on the mepolizumab 100 mg SC arm and μ_p is the annualized exacerbation rate on the placebo arm.

The (one-sided) alternative hypothesis is that the annualized exacerbation rate is lower on the mepolizumab arm:

Ha: $\mu_i < \mu_p$

The estimated annualized rate of moderate/severe exacerbations in the placebo arm was 1.7 exacerbations (based on exacerbation data observed from studies MEA117113 and MEA117106 [High Stratum], which were conducted prior to the COVID-19 pandemic).

Based on a true population reduction of 23% in the annualized rate of moderate/severe exacerbations following treatment with mepolizumab 100 mg SC compared to placebo, it was estimated that 400 participants per arm (800 participants in total) are required to provide 90% power to detect a statistically significant reduction at the 2-sided 5% level of significance. The smallest observed effect which is predicted to result in a statistically significant difference between mepolizumab 100 mg SC compared to placebo is 15%.

To account for the loss of patient years' data from participants who withdraw early from the trial and no longer provide any data (on- or off-treatment), the sample size includes an additional 44 patients to account for approximately 5.5% of patient-years data being missing, this being the level of missing data encountered in study MEA117113.

The sample size estimate is based on the number of moderate/severe exacerbations per year following a negative binomial distribution [Keene, 2007]. The estimate of 1.7 moderate/severe exacerbations per year in the placebo arm and of 0.55 for the dispersion parameter are based on data observed from studies MEA117113 and MEA117106 (High Stratum). Overall, in this study, a total of approximately 800 participants will be randomized with a randomization ratio of 1:1 placebo: mepolizumab 100 mg SC.

Blinded re-evaluations of the sample size will be carried out prior to randomizing the 800th participant to assess whether, based on the overall annualized rate of moderate/severe exacerbations and the level of dispersion seen within the available data, the initial planned sample size of 800 randomized participants would continue to provide 90% power for this study. The sample size re-estimation will follow the method described in [Friede, 2010]. A negative binomial distribution will be fitted to the blinded exacerbations from the available data with participant follow-up time as an offset, and estimates obtained for the overall exacerbation rate and the dispersion (shape) parameter. These estimates will be used to re-calculate the sample size that would be required to provide 90% power. If the re-estimated sample size is less than or equal to the currently planned 800 randomized participants, the study will continue as planned; otherwise the study sample size may be increased to that indicated by the re-estimation, with a potential maximum increase to 1400 participants. Further blinded re-evaluations will be conducted to monitor whether the sample size continues to be appropriate given the emerging event rate. The total sample size will be between 800 as originally planned up to a potential maximum of 1400 participants.

The sample size is based on an assumed exacerbation rate of 1.7 exacerbations per year in the placebo group and an expected reduction of 23% in this rate for participants treated with mepolizumab. If the true placebo exacerbation rate or the expected reduction with mepolizumab differ from these assumptions then, at the given sample size, there will be an effect on the power of the study. Table 2 illustrates the effect on the power for the treatment comparison (based on 756 participants, excluding the additional 44 participants to account for early study withdrawals), and a dispersion parameter k=0.55.

Table 2 Effect of placebo rate and expected rate reduction with mepolizumab on the power of the study

% reduction in annualized exacerbation rate with mepolizumab	Placebo: Annualized Exacerbation Rate					
	0.9	1.1	1.3	1.5	**1.7**	1.9
	Study Power[a]					
21%	67	73	78	81	84	86
22%	72	77	81	85	87	90
23%	76	81	85	88	**90**	92

a. Power estimate based on a 52-week follow-up for each participant

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

The study population analyses will be based on the modified Intent-to-Treat (mITT) Analysis Set, unless otherwise specified. Please see Section 3 of the SAP for details of the analysis sets. Displays for the Extended Treatment population will be analyzed by randomized treatment.

Study population summaries of participant's disposition, treatment discontinuation, protocol deviations, demographic and baseline characteristics, medical conditions, prior and concomitant medications will be based on GSK Core Data Standards.

6.1.1. Participant Disposition

Reasons for screening and run-in failures will be summarized for the All Participants Enrolled analysis set.

A summary of participant disposition with reasons for premature withdrawal from study will be provided along with the number of participants who consented to continue in the trial beyond Week 52. A summary of reasons for treatment discontinuation will be provided. The number of participants by region, country and center will also be provided.

Time to withdrawal from IP will be summarized. For this, the variable of interest is the time to withdrawal from IP. Participants who complete the study without withdrawing from IP will be censored at the date of their final administered dose of IP. Participants who withdraw from study prior to their final scheduled dose of IP without having previously withdrawn from IP will be censored at their date of final administered dose of IP.

An additional summary information showing the amount of time within the study period considered as on-treatment, off-treatment and missing will be presented.

6.1.2. Demographic and Baseline Characteristics

Demographic characteristics, race and racial combination details will be summarized, summaries of COPD history and baseline disease characteristics will be provided as well as summaries of history of tobacco use, and screening and baseline lung function including pre- and post-bronchodilator FEV_1, FVC, ratio of FEV_1/FVC and percent predicted FEV_1 as well as reversibility. A summary of age ranges using the EMA clinical trial results disclosure requirement categories based on the All Participants Enrolled analysis set will be provided.

Medical conditions will be summarized following GSK Core Data Standards.

6.1.2.1. De-identification of Demographic Data

Where required for the purposes of public disclosure, de-identified versions of summaries of demographic data which meet the criteria for de-identification (i.e. contain categories

with non-zero cells of n<11 or a standard deviation of 0) will be provided. For de-identified versions all non-zero cells within the table will contain n≥11 and where applicable a standard deviation of >0)

6.1.3. Protocol Deviations

Important protocol deviations will be summarized.

Protocol deviations will be tracked by the study team throughout the conduct of the study and reviewed in accordance with the Study Deviations Rules Document dated 24 August 2022 (Version 5) or later. Protocol deviations classified as important are detailed in the Study Deviations Rules Document and those requiring exclusion from the Per-Protocol (PP) population are provided in Section 6.3.

- Data will be reviewed prior to unblinding and locking the database to ensure all important deviations are captured and categorized in the protocol deviations dataset.
- Protocol deviations related to study treatment assignment will be confirmed as protocol deviations following unblinding for participants who received incorrect treatment according to the randomized treatment.
- This dataset will be the basis for the summaries of important protocol deviations.

Protocol deviations which result in exclusion from the per-protocol analysis set will also be summarized.

Data will be reviewed prior to unblinding and locking the database to ensure all deviations leading to analysis population exclusions are captured and categorized in the protocol deviations ADaM dataset (note these exclusions are not captured in the SDTM dataset).

6.1.4. Prior and Concomitant Medications

Concomitant medications will be coded using both the GSK Drug and WHO Drug dictionaries. Summaries will be based on the GSK Drug dictionary only.

Medications identified as being taken for COPD on the CRF will be categorized into and summarized by respiratory medication classes (RMCs) as detailed in Section 4.5.2 of the supporting Output and Programming Specification (OPS) document.

In addition, tables showing use of Long Term Oxygen Therapy (long term use defined as 40 days or more of consecutive use) in the 12 months prior to Screening will be provided.

6.1.5. Intercurrent Events

Number and percentage of participants with intercurrent events will be summarized.

Changes to background COPD medications will be identified programmatically and confirmed by blinded clinical review of concomitant medications. Instances of use of prohibited medications will be identified programmatically using protocol deviation

information under the category “Excluded medication, vaccine or device”, these will be confirmed by blinded clinical review.

The following intercurrent events are categorized by association with disruptions/restrictions imposed due to the COVID-19 pandemic:

- Discontinuation of interventional product will be identified using the study treatment discontinuation eCRF
- IP interruptions of ≥2 consecutive missed doses are identified using the study treatment eCRF.

6.1.6. Additional Analyses Due to the COVID-19 Pandemic

To assess the impact of the COVID-19 pandemic on study participation, the following study population summaries will be provided:

- Summary of recruitment by country and site relative to COVID-19 pandemic measures
- Summary of participant status and participant disposition by relationship to COVID-19 pandemic
- Summary of treatment status and reasons for discontinuation of study treatment by relationship to COVID-19 pandemic
- Important protocol deviations by relationship to COVID-19 pandemic
- Summary of visits impacted by COVID-19 pandemic
- Country level listing of Waves of COVID-19 pandemic measures

6.1.7. Change in Smoking Status

Smoking and eCigarette status is recorded at Baseline, Week 24, Week 52, Week 76 and Week 104. Smoking and eCigarette use at baseline and changes in smoking and eCigarette status at Week 24, Week 52, Week 76 and Week 104 will be presented.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Criteria for Potential Clinical Importance

6.2.1.1. Laboratory Values of Potential Clinical Concern

Haematology				
Laboratory Parameter	**Units**	**Age Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	12+	0.201	0.599
Hemoglobin	G/L	12+	71	199
Platelet Count	GI/L	1+	31	1499
While Blood Cell Count (WBC)	GI/L	12+	1.1	

Clinical Chemistry				
Laboratory Parameter	**Units**	**Age Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
ALT	U/L	3-12		>143
	U/L	13+		>239
Calcium	mmol/L	3+	1.50	3.24
Glucose	mmol/L	1+	2.2	27.8
Phosphorus, Inorg	mmol/L	3+	0.32	
Potassium	mmol/L	3+	2.8	6.5
Sodium	mmol/L	0+	120	160

6.2.2. Study Period

6.2.2.1. Analysis Period

The analysis period for exacerbations and efficacy endpoints is defined as the period of time over which exacerbations and efficacy assessments will be included in the on- and/or off-treatment phases (See Section 6.2.3.1). The start and end of the analysis period is defined as follows:

Analysis Period for Exacerbations and Efficacy Endpoints		
Study Completion	**Start Date of Analysis Period**	**End Date of Analysis Period** [1]
Participants enrolled for 52 weeks		
Completed	First dose of interventional product (Day 1)	Earlier of Date of Week 52 Exit Visit or Day 372
Withdrew Early	First dose of interventional product (Day 1)	Earlier of Date reported on the study conclusion page [2] or Day 372
Participants consented to participate for more than 52 weeks		
Completed	First dose of interventional product (Day 1)	Earlier of Date of Week 104 Exit visit or Day 736 or scheduled visit on or immediately before the date of Week 52 Exit Visit of the last participant to have been randomized into the study
Withdrew Early	First dose of interventional product (Day 1)	Earlier of Date reported on the study conclusion page or Day 736

[1] Allowing for the ±7 day visit window in the protocol; Day 372/736 is defined as 371/735 days (364+7 days / 728+7 days) after the first dose of interventional product.
[2] eCRF completion guidelines state 'COPD exacerbation details are collected from Screening Visit 1 through to last follow up (study conclusion date)'

6.2.2.2. Length of Time in Phase

The length of time in a phase reflects for each participant the period of time over which exacerbation data has been recorded and included in the negative binomial analysis model. The analysis model will incorporate this information as an offset of $\log_e$ (length of time (years) in phase).

Length of time (years) will be calculated as Length of time (Days)/365.25.

The length of time a participant contributes information in each phase is detailed below. For participants who completed the study and did not withdraw early from interventional product, the on-treatment period is the full analysis period; these participants have no off-treatment data. For participants who withdrew early from interventional product the on-treatment and off-treatment periods are as described in the table below:

Exacerbations – Length of Time in Phase	
Phase	Length of time (Days) in Phase
On- and Off-treatment	(Date of End of Analysis Period – IP Start Date) +1
On-treatment	If End of Analysis Period ≤28 days after last dose: (Date of End of Analysis Period – IP Start Date) +1 If End of Analysis Period >28 days after last dose: (IP Stop Date – IP Start Date) +29
Off-treatment	If End of Analysis Period ≤28 days after last dose: 0 days If End of Analysis Period >28 days after last dose: Date of End of Analysis Period – [IP Stop Date + 28 days]

Participants who withdrew early from the study with an analysis period which ends prior to their planned study completion date (see Section 4.1.4), will be considered to have missing data for the period of time from the end of the analysis period to their planned study completion date.

6.2.3. Treatment Phases

Assessments and events will be classified according to the time of occurrence relative to the first dose of interventional product.

6.2.3.1. Treatment Phases for Exacerbations

Treatment State	Definition
Pre-Treatment	Event start date < IP start date
On-Treatment	*For participants who did not prematurely withdraw from IP:* Event onset date is on/after IP start date & on/before the end of analysis period. (IP Start Date ≤ Event Start Date ≤ end of analysis period) *For participants who prematurely withdrew from IP:* Event onset date is on/after IP start date & on/before earlier of the IP stop date +28 days/end of analysis period. (IP Start Date ≤ Event Start Date ≤ earlier of IP Stop Date + 28 days/end of analysis period)
Off-Treatment	Event onset date is after IP stop date +28 days and on/before the end of analysis period. (IP Stop Date + 28 days < Event Start Date ≤ end of analysis period)
Post-treatment	Event onset date is after the end of analysis period. (Event Start Date > end of analysis period)
Duration of Exacerbation (Days)	Event resolution date – Event onset date + 1

Treatment State	Definition
Analysis period as defined in Section 6.2.2 If the IP stop date is missing or the event start date is partial/missing then unless there is evidence to the contrary the event will be considered to be On-Treatment (see Section 6.2.7)	

6.2.3.2. Treatment Phases for Visit Based Efficacy Assessments

Treatment State	Definition
Pre-Treatment Visit	Assessment Date ≤ Interventional Product Start Date
On-Treatment Visit	*For participants who did not prematurely withdraw from IP:* Assessment date is after IP start date & on/before the end of analysis period. (IP Start Date < Assessment Date ≤ end of analysis period) *For participants who prematurely withdrew from IP:* Assessment date is after IP start date & on/before earlier of the IP stop date +28 days/end of analysis period. (IP Start Date < Assessment Date ≤ earlier of IP Stop Date + 28 days/end of analysis period)
Off-Treatment Visit	IP stop date + 28 days < Assessment date ≤ end of analysis period
Post-Treatment Visit	Assessment date > end of analysis period
Analysis period as defined in Section 6.2.2 Where time of an assessment is recorded, the time of assessment and time of first dose will be considered to differentiate between Pre-treatment and On-treatment events.	

6.2.3.3. Treatment Phases for Visit Based Safety Assessments

Treatment State	Definition
Pre-Treatment	Assessment Date ≤ IP Start Date
On-Treatment	IP Start Date < Assessment Date ≤ IP Stop Date +28 days
Post -Treatment	Assessment Date > IP Stop Date + 28 days

6.2.3.4. Treatment Phases for Adverse Events

Treatment State	Definition
Pre-Treatment	Event Start Date < IP Start Date
On-Treatment	Event onset date is on/after IP start date & on/before IP stop date +28 days. (IP Start Date ≤ Event Start Date ≤ IP Stop Date + 28 days)
Post-Treatment	Event onset date is after the IP stop date + 28 days. (Event Start Date > IP Stop Date + 28 days)
Onset Time Since 1st Dose (Days)	If event onset date < IP start date = IP start date - Event onset date If event onset date ≥IP start date = Event onset date – IP start date +1 Missing otherwise.

Treatment State	Definition
Duration (Days)	Event resolution date – Event onset date + 1

NOTES:
If the IP stop date is missing or the event start date is partial/missing then unless there is evidence to the contrary the event will be considered to be On-Treatment (see Section 6.2.7).
Where time of event is recorded, the time of event and time of first dose will be considered to differentiate between Pre-treatment and On-treatment events.

6.2.3.5. Treatment Phases for Concomitant Medication Start Dates

Treatment State	Definition
Started Prior to Screening	Concomitant medication (CM) start date < Screening (Visit 1) Date
Pre-Treatment (Started prior to treatment)	Concomitant medication (CM) start date < IP start date
On-Treatment (Started during Treatment)	If CM start date is on/after IP start date & on/before IP stop date +28 days. (IP Start Date ≤ CM Start Date ≤ IP Stop Date + 28 days)
Post-Treatment	If CM start date is after the IP stop date + 28 days. (CM Start Date > IP Stop Date + 28 days)
Onset Time Since 1st Dose (Days)	If CM start date < IP start date = IP start date - CM start date If CM start date ≥ IP start date = CM start date – IP Start Date +1 Missing otherwise.
Duration (Days)	CM end date – CM start date + 1

NOTES:
If the IP stop date is missing and CM start date is on/after IP start date then CM considered on-treatment (started during treatment)
If CM start date is missing then CM considered on-treatment (started during treatment)

6.2.3.6. Treatment Phases for Concomitant Medication Usage Dates

Treatment State	Definition
Taken Prior to Screening	If CM start date < Screening (Visit 1) Date
Taken Prior to Treatment	If CM start date < IP Start Date
Taken During Treatment	If CM start date ≤ IP start date and CM stop date ≥ IP start date If IP start date ≤ CM start Date ≤ IP Stop Date + 28 days
Taken Post-Treatment	If CM start date < IP stop date+28 days and CM stop date ≥ IP stop date +28 days If CM start Date > IP stop date + 28 days

NOTES:
If the IP stop date is missing and CM start date is on/after IP start date then CM considered taken during treatment
If CM start date is missing, then CM considered to be taken during treatment

6.2.4. Study Day and Reference Dates

Study day is calculated as the number of days from the first dose of study medication (IP start date), as detailed below:

Assessment Date = Missing	Study Day = Missing
Assessment Date < IP Start Date	Study Day = Assessment Date – IP Start Date
Assessment Date ≥ IP Start Date	Study Day = Assessment Date – IP Start Date + 1

6.2.5. Assessment Windows

6.2.5.1. Visit Based Assessments

No assessment windows are defined for visit based assessments. Clinic visits as scheduled are subject to a ±7-day window, however assessments performed outside of these visit windows will still be included in analyses. Nominal visits will be used for reporting and analysis.

6.2.5.2. Premature Withdrawals from Interventional Product or Study and Scheduled Exit Visits at End of Study

Participants who withdrew prematurely from treatment or from the study and participants with a scheduled exit visit at end of study (i.e. where the exit visit is scheduled to occur on or before the date the last randomised participant is scheduled to complete their Week 52 Exit Visit) may have data recorded under either a nominal visit at which it was scheduled for collection, a nominal visit at which it was not scheduled for collection, or a withdrawal visit.

Data recorded under a visit at which it was not scheduled for collection, under a withdrawal visit or under a scheduled exit visit at end of study will be re-assigned to the next nominal visit at which collection was scheduled. This data will be summarized and analyzed (as appropriate) together with other data recorded as scheduled at the nominal visit. Data will be re-assigned according to the Schedule of Activities table, to the next visit where the data was scheduled for collection, unless data already exists at that visit.

For example, if a participant prematurely withdraws from treatment or the study at Week 16 (Visit 6) and completes an Early Withdrawal Visit which includes an ECG assessment, the ECG data collected will need to be re-assigned to a visit where ECG data is next scheduled for collection. In this case the ECG data will be reassigned to Week 24 as this is the next nominal visit at which collection of ECG data is scheduled.

6.2.5.3. Unscheduled Visits

Data recorded at an unscheduled visit will be re-assigned to the closest available nominal visit at which collection of the data was scheduled unless information already exists at that visit. Pre-treatment unscheduled data will be re-assigned to pre-treatment nominal

visits. Additionally, post-baseline data will be re-assigned to post-baseline nominal visits. If an unscheduled visit occurs between two scheduled visits for which data has been reported, the data will remain in the unscheduled visit and will not be included in any by visit summary tables; it will however be included in relevant summaries of any time post-baseline data and listings.

6.2.5.4. Daily Data from eDiary

Daily data collected every evening via eDiary will be summarized and analyzed in 4-week periods, data will be slotted to a 4-week period up to Week 104.

Analysis Window[1]		Analysis Timepoint
Beginning Timepoint	**Ending timepoint**	
-7	-1 (day prior to first dose)	Baseline
1 (day of first dose)	28	Weeks 1-4
29	56	Weeks 5-8
57	84	Weeks 9-12
85	112	Weeks 13-16
113	140	Weeks 17-20
141	168	Weeks 21-24
169	196	Weeks 25-28
197	224	Weeks 29-32
225	252	Weeks 33-36
253	280	Weeks 37-40
281	308	Weeks 41-44
309	336	Weeks 45-48
337	364[2]	Weeks 49-52
365	392	Weeks 53-56
393	420	Weeks 57-60
421	448	Weeks 61-64
449	476	Weeks 65-68
477	504	Weeks 69-72
505	532	Weeks 73-76
533	560	Weeks 77-80
561	588	Weeks 81-84
589	616	Weeks 85-88
617	644	Weeks 89-92
645	672	Weeks 93-96
673	700	Weeks 97-100
701	728 (or Week 104 visit if earlier)	Weeks 101-104

Notes:
[1] All analysis window timepoints are relative to first dose of IP.
[2] For patients enrolled for 52 weeks the Weeks 49-52 timeslot will be defined as 337 – 364 (or Week 52 visit if earlier)

6.2.6. Multiple measurements at One Visit

If there is more than one assessment reported under a nominal visit (for example data reported at the nominal and associated unscheduled visits), the first assessment will be used for summary tables and analyses. All assessments will be listed.

For safety assessments such as ECG the most abnormal result will be reported for the visit based on the following hierarchy: Abnormal-Clinically Significant > Abnormal – not clinically significant > Normal.

Where triplicate ECG measures are taken, the average of the triplicates will be used for summary statistics, and in the evaluation of the highest post-baseline measure.

For laboratory assessments, participants with post-baseline safety data in both High and Low categories with respect to the Normal Range/Potential Clinical Concern will be counted in each of the categories for the "Any visit post-baseline" row of related summary tables.

6.2.7. Handling of Partial Dates

Element	Reporting Detail	
General	Partial dates will be displayed as captured in participant listing displays. However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study phases or for specific analysis purposes as outlined below.	
Exacerbations and Adverse Events	Partial dates for exacerbations and AEs recorded in the CRF will be imputed using the following imputations:	
	Partial Start Date	'01' will be used for a missing day and 'Jan' will be used for a missing month. If this results in a date prior to the start of study treatment then the treatment start date will be used. The event will then be considered to be 'On-treatment' as per Section 6.2.2.
	Partial End Date (for Exacerbations)	'28/29/30/31' will be used for a missing day (dependent on the month and year) and 'Dec' will be used for a missing month. If this results in a date after the exit visit date, then the exit visit date will be used.

Element	Reporting Detail	
	Partial End Date (for Adverse Events)	'28/29/30/31' will be used for a missing day (dependent on the month and year) and 'Dec' will be used for a missing month. If this results in a date after the study treatment stop date +28 days, then the study treatment stop date + 28 days will be used.
	Completely missing start/end date	No imputation is applied.
Concomitant Medications/ Medical History	Partial dates for any concomitant medications or medical history conditions recorded in the CRF will be imputed using the following convention:	
	Partial Start Date	'01' will be used for the day and 'Jan' will be used for the month.
	Partial End Date	'28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.
	Completely missing start/end date	No imputation is applied.

6.3. Appendix 3 Exclusions from Per-Protocol Population

The per-protocol population includes all participants in the mITT who do not have protocol deviations that may significantly impact the interpretation of efficacy results.

Specifically, a participant will be excluded from the per-protocol population if meeting any of the following criteria that could significantly impact the interpretation of efficacy results:

Number	Exclusion Description
01	Informed consent never signed
02	Did not meet at least one of the following inclusion criteria (as numbered in the protocol) 1. Participant must be at least 40 years of age at Screening Visit 1 3. COPD Diagnosis: Documented history of COPD of at least 1 year in accordance with the definition by the American Thoracic Society/European Respiratory Society 7. Smoking status: Current or former cigarette smokers
03	Met at least one of the following exclusion criteria (as numbered in the protocol) 1. Asthma: Participants with a past history or concurrent diagnosis of asthma 2. Other respiratory disorders: The Investigator must judge that COPD is the primary diagnosis 4. Lung resection: Participants with lung volume reduction surgery within the 12 months prior to Screening Visit 1. 10. Eosinophilic Disease: Participants with other conditions that could lead to elevated Eosinophils 11. Parasitic Infection: Participants with a known, pre-existing parasitic infestation within 6 months prior to Screening Visit 1. 15. Previous mepolizumab studies: Participants who have received interventional product in previous mepolizumab studies 17. Investigational Medications: Participants who have received an investigational drug within 30 days of Visit 1, or within 5 drug half-lives of the investigational drug
04	Did not meet the following randomization inclusion criteria (as numbered in protocol) 1. Blood eosinophil count: Participants that do not have a historical blood eosinophil count that satisfies screening inclusion criterion 2 (Protocol Section 5.1) must have Screening Visit 1 blood eosinophil count $\geq$150 cells/μL.
05	Use of prohibited medication during the study [1]
06	Occurrence of any one of the following treatment related deviations for $\geq$2 consecutive doses or $\geq$3 doses at any time during the study: Received study treatment to which they were not randomized Study treatment not administered per protocol Expired study treatment administered

Number	Exclusion Description
	Use of study treatment impacted by a temperature excursion which was not reported or approved, or which was disapproved for further use
07	Participant/investigator is unblinded

[1] See Section 6.5.3 of protocol for prohibited medications.

6.4. Appendix 4: Adverse Events of Special Interest

6.4.1. Systemic Allergic (Type I Hypersensitivity) and Other Systemic Reactions

Systemic reactions will be collected via a targeted eCRF and are required to be assessed against Sampson's diagnostic criteria for anaphylaxis [Sampson, 2006].

Events reported on the eCRF as systemic reactions will be further categorized by the investigator as an 'allergic (type I hypersensitivity) reaction' or 'systemic other' reaction. Investigators are instructed to report systemic reactions with the best diagnosis/event term that describes the event.

6.4.2. Alterations in immune response (infections)

All infections and serious infections will be reported under the MedDRA system organ class of 'Infections and Infestations'.

Specific events of interest are Opportunistic Infections which will be identified through matching of collected adverse event preferred terms with those from:

- Opportunistic infections standard MedDRA query (SMQ) (narrow terms)
- Herpes zoster preferred term

6.4.3. Alterations in immune response (malignancies)

All neoplasms will be reported under the MedDRA system organ class of 'Neoplasms, benign, malignant and unspecified (including cysts and polyps)'.

Specific events of interest are Malignancies which will be identified through matching of collected adverse event preferred terms with those from:

Sub-SMQs under the Malignancies SMQ

- Malignant tumours sub-SMQ (narrow terms)
- Tumours of unspecified malignancy sub-SMQ (narrow terms)

6.4.4. Alterations in cardiovascular safety

Cardiac disorders and serious cardiac disorders will be reported under the MedDRA system organ class of 'Cardiac Disorders'.

Specific events of interest are Serious cardiac, vascular, and thromboembolic (CVT) events and Ischemic events. Serious CVT events will be identified as all serious adverse events classified under the MedDRA system organ classes of 'Cardiac Disorders' or 'Vascular Disorders', and thromboembolic events will be identified through matching of collected adverse event preferred terms with those from:

Sub-SMQs under the Embolic and thrombotic events SMQ

- Embolic and thrombotic events, arterial sub-SMQ (narrow terms)
- Embolic and thrombotic events, venous sub-SMQ (narrow terms)
- Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous sub-SMQ (narrow terms)

Sub-SMQs under the Ischaemic Heart Disease SMQ

- Myocardial infarction sub-SMQ (narrow terms)
- Other Ischaemic heart disease sub-SMQ (narrow terms)

Sub-SMQs under the Central Nervous System Vascular Disorders SMQ

- Ischaemic central nervous system vascular conditions sub-SMQ (narrow terms)
- Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic sub-SMQ (narrow terms)

Serious Ischemic adverse events, will be a subset of the Serious CVT events identified above through matching of collected adverse event preferred terms with those from:

Sub-SMQs under the Ischaemic Heart Disease SMQ

- Myocardial infarction sub-SMQ (narrow terms)
- Other Ischaemic heart disease sub-SMQ (narrow terms)

Sub-SMQs under the Central Nervous System Vascular Disorders SMQ

- Ischaemic central nervous system vascular conditions sub-SMQ (narrow terms)
- Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic sub-SMQ (narrow terms)

6.4.5. Local Injection Site Reactions

Local injection site reactions will be collected via a targeted eCRF.

6.5. Appendix 5: Electronic Clinical Outcome Assessment (eCOA) Compliance

The compliance of eCOA data will be derived at a participant level and reported across all participants and by treatment group.

An eCOA will be considered complete if there is no missing data within the assessment.

Visit-based assessments that are present at a visit due to visit slotting will be considered as complete assessments, however if a subject failed to complete an eCOA assessment at a visit that would have been slotted (e.g. at an early withdrawal visit), the visit the data would have been slotted to will be considered incomplete.

6.5.1. Study Level compliance

Overall eCOA compliance will be calculated based on the following patient-reported assessments: CAT, SGRQ, patient global rating of COPD severity, patient global rating of change in COPD and patient rated response to therapy which are all visit based assessments and daily symptom diary data. The target compliance for the study is 75%.

On a study level, overall eCOA compliance will be calculated as:

$$\frac{Total\ number\ of\ complete\ eCOAs\ across\ all\ participants}{Total\ expected\ number\ of\ complete\ eCOAs\ across\ all\ participants} \times 100$$

Where expected number of complete eCOAs is calculated as:

$$Expected\ number\ of\ complete\ eCOAs = \sum_{i=1}^{n}\sum_{j=1}^{c} data\ points\ expected\ for\ eCOA_j(participant\ i)$$

where *c* represents the total number of eCOAs collected and *n* represents the total number of participants.

Overall compliance will also be categorized, with the number of subjects who are <40% compliant, 40-<60% compliant, 60-<80% compliant and ≥80% compliant given.

6.5.2. Endpoint Level compliance

Compliance will be derived separately at a participant level for the secondary endpoints: CAT, SGRQ and E-RS: COPD; and summarized for all participants as well as by treatment group

Compliance for visit-based assessments (CAT and SGRQ) will be based on whether the participant completed the assessment for the expected number of visits. The compliance will be summarized for each visit time-point. The target compliance for these assessments is 85%.

Compliance for E-RS: COPD (based on daily diary data) will be based on whether the participant completed the expected number of daily diaries within the baseline and 4-weekly windows used in the endpoint definition. The compliance will be categorized, with the number of subjects who are <40% compliant, 40-<60% compliant, 60-<80% compliant and ≥80% compliant given for each time window. The target compliance for this assessment is 80%.

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