Statistical Analysis Plan

Study ID: 201536

Official Title of Study: A randomized, double blind, parallel group study of the efficacy and safety of Mepolizumab as adjunctive therapy in patients with severe asthma with eosinophilic inflammation

NCT number: NCT03562195

Date of Document: 24-SEP-2022

Information Type	:	Statistical Analysis Plan

TITLE PAGE

Protocol Title: A randomized, double blind, parallel group study of the efficacy and safety of Mepolizumab as adjunctive therapy in patients with severe asthma with eosinophilic inflammation

Study Number: 201536

Compound Number: SB-240563

Abbreviated Title: Not Applicable

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	**ID**
Not Applicable	Not Applicable

SAP Author(s):

Author
PPD Principal Statistician, China Biostatistics

SAP Biostatistics Line Approval (Pharma TMF eSignature):

Approver
PPD
PPD

TABLE OF CONTENTS

PAGE

Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
Reporting and Analysis Plan (RAP) Critical Component	24 Sep 2022	Version 01 (Date: 2018-MAR-28)	Not Applicable	Original version

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses and output to be included in the Clinical Study Report (CSR) for Study 201536. Details of the planned final analyses are provided.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of mepolizumab 100 mg subcutaneous (SC) every 4 weeks versus placebo on the frequency of clinically significant exacerbations in adult and adolescent Chinese subjects with severe asthma with eosinophilic airway inflammation.	• Frequency of clinically significant exacerbations of asthma over the 52-week treatment period. Clinically significant exacerbations are defined as: Worsening of asthma which requires use of systemic corticosteroids and/or hospitalizations and/or Emergency Department (ED) visits. For all subjects, oral corticosteroid for at least 3 days or a single IM Corticosteroid (CS) dose is required. For subjects on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days is required.
Secondary	
• To evaluate the effects of mepolizumab compared with placebo on a range of clinical markers of asthma control, including exacerbations, lung function, and quality of life.	• Time to first clinically significant exacerbations
	• Mean change in St. George's Respiratory Questionnaire (SGRQ) at Week 52
	• Frequency of exacerbations requiring hospitalisation (including intubation and admittance to an ICU) or ED visits over the 52-week treatment period
	• Frequency of exacerbations requiring hospitalisation over the 52-week treatment period
	• Mean change from baseline in clinic pre-bronchodilator FEV1 at Week 52
Safety	
• To evaluate the safety and tolerability of mepolizumab compared with placebo, in subjects with severe asthma with	• Adverse Event including systemic (i.e. allergic [type I hypersensitivity] and Other systemic) and injection site reactions reported throughout the 52-week treatment period
	• Haematological and clinical chemistry parameters

Objectives	Endpoints
eosinophilic inflammation	• Vital signs (pulse rate and systolic and diastolic blood pressure)
	• 12-lead ECG
	• Frequency of subjects with anti-mepolizumab antibody positive results
Others	
• To evaluate the effects of mepolizumab compared with placebo on asthma control	• Mean change from baseline compared to placebo in Asthma Control Questionnaire (ACQ-5) score at Week 52
	• Percent of subjects evaluated as responders as measured by ACQ-5 score at Week 52
	• Percent of subjects evaluated as responders as measured by SGRQ score at Week 52
	• Percent of subjects recording a favourable treatment response as measured by the Subject Rated Response to Therapy at Week 52
	• Percent of subjects evaluated as having a favourable treatment response as measured by the Clinician Rated Response to Therapy at Week 52
	• Mean change from baseline in daily salbutamol/albuterol use
	• Mean change from baseline in daily asthma symptom scores
	• Mean change from baseline in awakening at night due to asthma symptoms requiring rescue medication use
	• Mean change from baseline in morning PEF
	• Mean change from baseline in clinic post-bronchodilator FEV1 at Week 52
	• Mean number of days with oral corticosteroids taken for clinically significant exacerbations
	• Total prednisone (or equivalent) exposure for clinically significant exacerbation over the 52-week treatment period
	• Frequency of all exacerbations
	• Time to first exacerbation
	• Time to withdrawal from study treatment due to asthma exacerbations
	• Time to first exacerbation requiring hospitalization or ED visit

Objectives	Endpoints
	• Unscheduled healthcare resource utilization (for clinically significant exacerbations and other asthma related health care) over the 52-week treatment period • Mean days of School/Work missed over the 52-treatment period
Pharmacodynamics	
• To evaluate the PD of SC mepolizumab in Chinese subjects with severe asthma with eosinophilic airway inflammation	• Blood eosinophil ratio to baseline
PK Sub-Study	
• To evaluate the PK of SC mepolizumab in Chinese subjects with severe asthma with eosinophilic airway inflammation	• PK parameter estimates of mepolizumab

Primary estimand

The primary clinical question of interest is: What is the effect of adding mepolizumab to standard of care when compared with placebo plus standard of care on the rate of exacerbations over 52 weeks in Chinese participants with severe eosinophilic asthma? This question is to be addressed in the absence of study treatment discontinuation.

The estimand is described by the following attributes:

- Population: Chinese participants with severe eosinophilic asthma.
- Treatment condition: mepolizumab 100mg SC given every 4 weeks compared to placebo every 4 weeks, both treatments given on top of standard of care. Further details on standard of care can be found in Section 6 of Protocol.
- Variable: number of clinically significant exacerbations over 52 weeks.
- Summary measure: annualised rate of exacerbations. Comparison between the mepolizumab arm and placebo will be assessed with the rate ratio.
- Intercurrent events:
  - Study treatment discontinuation-hypothetical strategy
- Rationale for estimand:

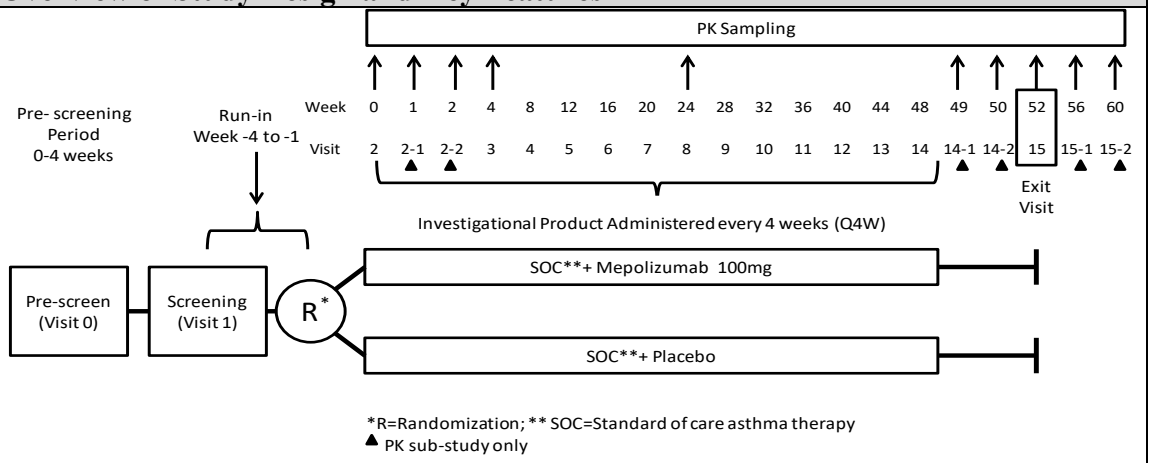
  Interest lies in the treatment effect when medication is taken as directed. For participants discontinuing randomised medication, use of a hypothetical strategy

addresses treatment effects attributable to mepolizumab in the hypothetical scenario where participants would not discontinue from treatment.

Since this is a bridging study, the results from MEA115588 will be borrowed and compared with the data from this study. To ensure comparability between two studies, the Estimand framework including analysis models will be similar with MEA115588.

1.2. Study Design

Overview of Study Design and Key Features



Design Features	• This is a bridging study. • Multi-centre, randomized, placebo-controlled, double-blind, parallel-group design. • In the main study, there will be a total of 16 clinic visits conducted on an outpatient basis. • Subjects who discontinue study treatment will not be automatically withdrawn, but will be encouraged to stay in the study and complete all remaining protocol specified visits and be followed-up as per the protocol until the completion of the follow-up assessments. • The total duration of subject participation in the main study, including run-in will be 53 to 56 weeks. • Subjects will remain on their current maintenance therapy throughout the run-in and double-blind treatment administration periods.
Study intervention	• Subjects will be randomized on Day 1 to receive mepolizumab (100 mg) SC or placebo SC added onto their existing therapy for asthma every 4 weeks for a total of 13 doses
Study intervention Assignment	• Randomization to study treatment will be stratified by blood eosinophil count at screening(≥300 cells/μL and <300 cells/μL). • Subjects will be randomized in a 1:1 ratio to receive either mepolizumab SC or placebo SC.
Interim Analysis	• No formal interim analysis is planned

Overview of Study Design and Key Features	
	• Blinded evaluation of exacerbation rates is planned for this study. This will be done under blinded situation and will not treated as formal interim analysis.

2. STATISTICAL HYPOTHESES

This is a bridging study designed to determine the effect of Mepolizumab 100mg SC on clinically significant exacerbation events, compared with placebo among Chinese subjects.

The Chinese patient data collected in this study will be supplemented with data on the treatment effect for the same exacerbation endpoint from the global PhIII study MEA115588, using a Bayesian Dynamic Borrowing approach to analysis of the study (Schmidli, 2014). The potential to borrow information from the global dataset is based on the premise that the underlying disease, its general management and the response to mepolizumab is similar in Chinese and non-Chinese patients. A bridging approach is proposed because of the expected similarity of the treatment effect in Chinese patients and the global population (supported by similarities in the epidemiology, pathophysiology, pharmacology and clinical management of patients and consistency of treatment differences across key demographic factors including ethnicity), and similar study design specially the study population (supported by similarities in key eligibility criteria) between MEA115588 and this China study, hence there is low probability of the null effect being true.

A frequentist hypothesis test will not be performed. Instead, the posterior distributions of the primary endpoint, i.e. rate ratio of events between Mepolizumab 100mg SC vs. placebo will be derived based on the Bayesian analysis including the global PhIII study MEA115588 information and the data collected on Chinese patients in this study. The hypothesis of interest for treatment comparison is that the rate ratio is less than 1, and the study will be considered to have shown evidence that supports this hypothesis if the posterior probability that the rate ratio is less than 1 is at least 95% (a “positive result”).

There is no adjustment for multiplicity in this study.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
All Subjects Enrolled (ASE)	All subjects enrolled and for whom a record exists on the study database	Summarizing reasons for screen and run-in failures
Modified Intent-to-Treat (MITT)	All randomized subjects who receive at least one dose of trial medication	The primary population for all analyses of efficacy and safety data
Per Protocol (PP)	All subjects in the Modified Intent-to-Treat population not identified as full protocol deviators with respect to criteria that are considered to impact the primary efficacy analysis.	Supplementary analysis of the primary endpoint
Pharmacokinetic (PK)	All subjects in the PK sub study* who received at least one dose of study medication and for whom at least one pharmacokinetic sample was obtained, and analyzed.	Primary population for assessing PK

* The subjects in the PK sub study means the subjects who signed ICF of PK sub study. One subject (ID: PPD) signed ICF for PK sub-study but withdraw the ICF for PK sub-study at Visit 2 since the number of subjects for PK sub study was full, therefore this subject will not be included in PK population.

4. STATISTICAL ANALYSES

4.1. General Considerations

Since this is a bridging study, the results from MEA115588 will be borrowed and compared with the data from this study. To ensure comparability between two studies, the Estimand framework including analysis models will be similar with MEA115588 unless otherwise specified.

4.1.1. General Methodology

In the case of wrong stratification assigned at the time of randomization, the analyses will be performed based on the actual stratum per data collected in the CRF.

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

Unless otherwise specified, the following will apply:

- Continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum, 25th percentile, 75th percentile and maximum.
- Categorical data will be summarized as the number and percentage of participants in each category.
- The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, 25th percentile, and 75th percentile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. A maximum of four decimal places will be used. Percentages will be presented to one decimal place. A count of zero will have no corresponding percentage.
- When the data are summarized by visit, only scheduled visits will be presented.

4.1.2. Baseline Definition

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

For data collected via the eDiary device (i.e. morning peak flow, usage of rescue medication (i.e. salbutamol/albuterol), asthma symptom score and frequency of awakening due to asthma symptoms), the baseline for analyses of averaged 4-weekly data will be calculated using values from the run-in period as shown in Section 4.2 in protocol.

Parameter	Study Assessments can be Considered as Baseline			Baseline Used in Data Display
	Screening	Day -6 to Day 1 (Pre-Dose)	Day 1 (Pre-Dose)	
[Efficacy]				
Salbutamol/albuterol use		X		Average of measurements from Day -6 to Day 1 pre-dose
Asthma symptom scores		X		Average of measurements from Day -6 to Day 1 pre-dose
Awakening at night		X		Average of measurements from Day -6 to Day 1 pre-dose
Morning PEF		X		Average of measurements from Day -6 to Day 1 pre-dose
[Safety]				
12-Lead ECG	X			Screening

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

4.1.3. Definition of endpoint(s)/estimands

The primary endpoint is the frequency of clinically significant exacerbations (the same as protocol defined exacerbations) of asthma over the 52 weeks treatment period expressed as an exacerbation rate p.a.

Exacerbation from the start of treatment until 4 weeks after the last dose of study drug will be used in the analysis. Exacerbations which are separated by less than 7 days will be treated as a continuation of the same exacerbation.

The estimand is described by the following attributes:

- Population: Chinese participants with severe eosinophilic asthma.
- Treatment condition: mepolizumab 100mg SC given every 4 weeks compared to placebo every 4 weeks, both treatments given on top of standard of care. Further details on standard of care can be found in Section 6 of Protocol.
- Variable: number of clinically significant exacerbations over 52 weeks.
- Summary measure: annualised rate of exacerbations. Comparison between the mepolizumab arm and placebo will be assessed with the rate ratio.
- Intercurrent events:
    - Study treatment discontinuation-hypothetical strategy
- Rationale for estimand:

  Interest lies in the treatment effect when medication is taken as directed. For participants discontinuing randomised medication, use of a hypothetical strategy addresses treatment effects attributable to mepolizumab in the hypothetical scenario where participants would not discontinue from treatment.

Since this is a bridging study, the results from MEA115588 will be borrowed and compared with the data from this study. To ensure comparability between two studies, the Estimand framework including analysis models will be similar with MEA115588.

4.2. Primary Endpoint(s) Analyses

4.2.1. Main analytical approach

The primary efficacy analysis will evaluate the primary estimand in the Modified Intent-to-Treat population, by first using a generalized linear model with a log-link function to get an estimate of the logarithm of the rate ratio for mepolizumab vs. placebo and associated standard error. These estimates will then be combined with the global MEA115588 study using the pre-specified robust mixture prior to obtain the posterior distribution for the China rate ratio (on the log scale). A 95% posterior probability that the true rate ratio < 1 represents a high level of confidence for declaring a positive treatment benefit in Chinese patients in the context of a bridging study where substantial evidence of treatment benefit in global (non-Chinese) patients already exists.

Model Specification

- Generalized linear model assuming a negative binomial distribution
- Terms in the model:
  - **Response**: number of recorded, on-treatment, clinically significant exacerbations experienced per subject.
  - **Categorical**: treatment group, baseline maintenance OCS therapy (OCS vs. no OCS),
  - **Continuous**: baseline disease severity (as % predicted FEV_1), number of exacerbations in previous year (as an ordinal variable)
  - **Offset**: logarithm of time on treatment

Since this is a bridging study, to ensure comparability between results in MEA115588 and this study, the analysis model including the covariates are the same with MEA115588.

Model Results Presentation

- Treatment group model estimated exacerbation rates, the treatment rate ratio and associated SE and 95% CI will be presented.
- The pairwise treatment rate ratios and associated 95% CIs will also be presented graphically

Bayesian Dynamic Borrowing

A Bayesian dynamic borrowing model (Schmidli, 2014) will be used to make inference about the logarithmic rate ratio of exacerbations in mepolizumab 100mg SC to Placebo in Chinese participants. The prior distribution will be a mixture with two components: the first component is based on the results from the MEA115588 study; the second component is a vague distribution centred on 0 representing 'no-effect'.

An initial (prior) weight of 50% is proposed for the informative global component of the robust mixture prior, with the remainder of the weight (50%) placed on the vague prior to reflect a conservative starting position regarding the assumed relevance of the global MEA115588 results to Chinese. Combining the two components and their respective weights gives the following 2-component mixture of normals:

$$p(\theta) = 0.5 * Normal(-0.7474\,, 0.1532) + 0.5 * Normal(0\,, 2.1256)$$

The prior mixture will be updated with the data from this study to obtain the posterior distribution. Assuming the standard error of the estimated logarithmic rate ratio in this study is known, the posterior distribution will also be a mixture of normal (see details below). The posterior weight given to the global MEA115588 study data is commensurate with the strength of evidence of similarity between the MEA115588 data and the China data. The BDB analysis [Schmidli, 2014] 'learns' how much of the global MEA115588 study information to borrow based on the consistency between the observed rate ratio in the China and global studies and updates the weight on the global MEA115588 results accordingly.

The mean, median,90% credible interval and 95% credible interval of this posterior distribution of the rate ratio will be reported, along with the probability that true rate ratio

Model Specification

is less than 1 (equivalent to the log rate ratio being less than 0). The mean and SE of log rate ratio will be presented as well.

The posterior distribution

The robust mixture prior was constructed as weighted average of global MEA115588 and weak priors, which followed the structure:

Robust mixture= $w \times Normal\left(m_{global}, \sqrt{v_{global}}\right) + (1-w) \times Normal(m_{vague}, \sqrt{v_{vague}})$

Where $m_{global} = -0.7474, v_{global} = 0.1532^2, m_{vague} = 0,\ v_{vague} = 2.1256^2$ and $w = 0.5$.

Assumed the observed log rate ratio from this study has the distribution with mean m_{china} and variance v_{china}, which were the point estimate and squared standard error of the log rate ratio from negative binomial regression defined previously. The sampling distribution for the observed data will be combined with robust mixture prior using standard conjugate Bayesian theory to obtain a posterior mixture distribution:

Posterior mixture=$w^* \times Normal\left(m^*_{global}, \sqrt{v^*_{global}}\right) + (1-w^*) \times Normal(m^*_{vague}, \sqrt{v^*_{vague}})$

where:

$$m^*_{global} = v^*_{global}\left(\frac{m_{global}}{v_{global}} + \frac{m_{china}}{v_{china}}\right) \text{ and } \frac{1}{v^*_{global}} = \frac{1}{v_{global}} + \frac{1}{v_{china}}$$

$$m^*_{vague} = v^*_{vague}\left(\frac{m_{vague}}{v_{vague}} + \frac{m_{china}}{v_{china}}\right) \text{ and } \frac{1}{v^*_{vague}} = \frac{1}{v_{vague}} + \frac{1}{v_{china}}$$

$$w^* = \frac{C_{global} \times w}{C_{global} \times w + C_{vague} \times (1-w)}$$

$$C_{global} = \frac{\exp\{-0.5(m_{china} - m_{global})^2/(v_{global} + v_{china})\}}{\sqrt{v_{global} + v_{china}}}$$

$$C_{vague} = \frac{\exp\{-0.5(m_{china} - m_{vague})^2/(v_{vague} + v_{china})\}}{\sqrt{v_{vague} + v_{china}}}$$

The posterior means and variances of each component are obtained from conjugate Bayesian updating of that individual prior component, and the posterior weight is a function of the prior weight and coefficients C_{global} and C_{vague} (Schmidli, 2014)

Subgroup Analyses

Subgroup analyses of the primary endpoint will be carried out to assess consistency of the intervention effect across the following subgroups:

- Age group: <65,≥ 65
- Sex: female vs male

Model Specification
• Weight: ≤=60 kg, >60-≤=75 kg, >75kg • Baseline predicted pre-bronchodilator FEV1: <=60%, >60%-80%, >80% • number of exacerbations in the year prior to screening (i.e., 2, 3, 4+) • Baseline use of maintenance oral corticosteroids • Baseline airway reversibility: reversible or not reversible defined in Section 6.2.9. • blood eosinophil count at screening: <150, ≥150-<300, ≥300-<500, ≥500 cells/μL • Randomization stratification factor: -<300, ≥300 cells/μL • If the number of participants is too small (less than [10%]) within a subgroup, then the subgroup categories may be redefined prior to unblinding the study.
Missing data imputation
• The primary analysis using the negative binomial model assumes that missing data is missing at random (MAR).

4.2.2. Sensitivity analyses

- Ordinarily, an analysis under a MAR assumption is implemented using direct likelihood, by introducing an offset into the log-linear model to allow for the length of the observation period. Using an underlying negative binomial model, missing data post study withdrawal of treatment will be imputed conditional upon the subjects own observed number of events prior to withdrawal of treatment under MAR assumption. This approach involves firstly fitting the negative binomial generalised linear model to the data, and sampling from the posterior distribution (likelihood function multiplied by a non-informative prior) of the estimated parameters (i.e. the betas) associated with the independent variables. The number of exacerbations that would have been seen based on various assumptions is then estimated for subjects who withdraw of treatment early. This number is combined with the observed exacerbations and the data is analysed as for the primary endpoint [Keene, 2014]. This analysis is repeated multiple times and the results combined using Rubin's formulae [Barnard, 1999] as implemented in PROC MIANALYZE in SAS.
- Since this is a bridging study, to keep consistent analysis model, the stratification variable EOS level at screening (≥300 cells/μL vs. <300 cells/μL) will be not included into the primary analysis. To test the impact of stratification variable for the model, further sensitivity analysis will be performed adding EOS level at screening (≥300 cells/μL vs. <300 cells/μL) into the primary negative binomial model, the missing data is assumed as missing at random (MAR).

All the sensitivity analyses will not use BDB method to implement.

4.2.3. Additional estimands

To examine the sensitivity of the results of primary analysis to departures from the assumption that Intercurrent Events (IEs) did not occur, treatment policy strategy will be used to IEs of study treatment discontinuation not related to the COVID-19 pandemic, the on- and off- treatment data will be included in the analyses.

Supplemental estimand 1:

The estimand is described by the following attributes:

- Population: Chinese participants with severe eosinophilic asthma.
- Treatment condition: mepolizumab 100mg SC given every 4 weeks compared to placebo every 4 weeks, both treatments given on top of standard of care. Further details on standard of care can be found in Section 6.
- Variable: number of clinically significant exacerbations over 52 weeks.
- Summary measure: rate ratio of exacerbations between the mepolizumab arm and placebo.
- Intercurrent events:
    - Study treatment discontinuation
        - Related to the COVID-19 pandemic: hypothetical strategy
        - Not related to the COVID-19 pandemic: treatment policy strategy

Handling of Missing Data:

Missing data will be imputed differently depending on the handling strategy for the specific intercurrent event.

- Missing data due to hypothetical strategy for intercurrent event of study treatment discontinuation (data collected after the occurrence of the IE will be excluded from the analysis), assuming that missing data is missing at random (MAR).

- Missing data due to study withdrawal. Study withdrawal before the completion of the study will create missing outcome data. This may occur concurrently or after the IE. The assumptions used to impute the missing part of the data for subjects who withdraw early from study will be as follows:
    a) Missing at Random (direct likelihood). Using the negative binomial model assumes that missing data is missing at random (MAR). The missing data will be imputed conditional upon the subjects own observed number of events, which are not missing, based on the negative binomial generalized linear model with offset variable.

    b) Missing at Random (multiple imputation). Using an underlying negative binomial model, post-withdrawal counts were imputed conditional upon the subject's own observed number of events prior to withdrawal.

    c) Jump to Reference. Missing counts will be imputed conditional upon the subjects own observed number of events prior to withdrawal. The impact of sampling from this conditional distribution is that if their event rate prior to withdrawal is worse than would be expected (positive residual) on mepolizumab, their imputed event rate after withdrawal will be worse than the expected event rate on placebo. Missing data in the placebo arm are imputed under randomised-arm MAR.

4.2.4. Supplementary Analyses

- As a supportive analysis to enable comparability of results with global MEA115588 study, the primary analyses may be repeated using the "Per-protocol" analysis population (see Section 6.2.13 for the definition).
- Impact of the Prior Weight of the robust mixture prior.
  Another supportive "tipping point" type of analysis will be conducted to assess the impact on the results of different prior weights given to the historical data in the robust mixture prior for primary endpoint.
  The prior weights of the informative global component of the prior will be varied from 0 to 1 in the increment of 0.05 and the primary analysis will be repeated for each value of the weight. When the prior weight is 0 or 1, the mixture prior will become a normal distribution thus the Bayesian diagram will be the standard conjugate analysis.
  The posterior mean, median and 90% credible interval of the posterior distribution will be reported for each prior weight, along with the probability that true rate ratio is less than 1 (equivalent to the log rate ratio being less than 0)

4.3. Secondary Endpoint(s) Analyses

4.3.1. Key secondary endpoint(s)

- Time to first clinically significant exacerbations.
- Mean change in St. Georges Respiratory Questionnaire (SGRQ) at Week 52
- Frequency of clinically significant exacerbations requiring hospitalization (including intubation and admittance to an ICU) or ED visits over the 52-week treatment period
- Frequency of clinically significant exacerbations requiring hospitalization over the 52-week treatment period
- Mean change from baseline in clinic pre-bronchodilator FEV1 at Week 52

Definition of endpoint(s)/estimands

The principle of Estimand consideration for each key secondary endpoint is to keep a similar Estimand strategy for intercurrent events with study MEA115588, since it is a bridging study. To test the sensitivity of the results of the main estimand for key secondary endpoints, the supplemental estimand for these endpoints are defined in Section 4.3.2.

Endpoint(s)
• Time to first clinically significant exacerbation
Estimand
The estimand is described by the following attributes: • Population: Chinese participants with severe eosinophilic asthma

Endpoint(s)

- Treatment condition: mepolizumab 100mg SC given every 4 weeks compared to placebo every 4 weeks, both treatments given on top of standard of care.
- Variable: Time to first clinically significant exacerbations.
- Summary measure: Rate of first clinically significant exacerbation. Comparison between the mepolizumab arm and placebo will be assessed through the hazard ratio.
- Intercurrent events:
    - Study treatment discontinuation - hypothetical strategy

The handling strategy for the IEs of discontinuation of study intervention will be based on a hypothetical approach; specifically, the effects estimated will be under the hypothetical scenario where the IE did not occur. If a subject discontinues study treatment without any clinically significant exacerbations, the subject will be censored at the date of study treatment discontinuation which assumes censoring at random.

Endpoint(s)

- Mean change in St. Georges Respiratory Questionnaire (SGRQ) at Week 52

Estimand

The estimand is described by the following attributes:

- Population: Chinese participants with severe eosinophilic asthma
- Treatment condition: mepolizumab 100mg SC given every 4 weeks compared to placebo every 4 weeks, both treatments given on top of standard of care.
- Variable:
    - Mean change in St. Georges Respiratory Questionnaire (SGRQ) at Week 52.
- Summary measure:
    - LS Mean change in St. Georges Respiratory Questionnaire (SGRQ) between the mepolizumab arm and placebo.
- Intercurrent events:
    - Study treatment discontinuation- hypothetical strategy

The handling strategy for the IEs of discontinuation of study intervention will be based on a hypothetical approach; specifically, the effects estimated will be under the hypothetical scenario where the IE did not occur.

Endpoint(s)

- Mean change from baseline in clinic pre-bronchodilator FEV1 at Week 52

Estimand

The estimand is described by the following attributes:

- Population: Chinese participants with severe eosinophilic asthma
- Treatment condition: mepolizumab 100mg SC given every 4 weeks compared to placebo every 4 weeks, both treatments given on top of standard of care.
- Variable:
    - Change from baseline in clinic pre-bronchodilator FEV1 at Week 52
- Summary measure:
    - Mean change from baseline in clinic pre-bronchodilator FEV1. Comparison between the mepolizumab arm and placebo will be assessed with the mean difference.

Endpoint(s)
• Intercurrent events: o Study treatment discontinuation-hypothetical strategy The handling strategy for the IEs of discontinuation of study intervention will be based on a hypothetical approach; specifically, the effects estimated will be under the hypothetical scenario where the IE did not occur.
Endpoint(s)
• Frequency of clinically significant exacerbations requiring hospitalization (including intubation and admittance to an ICU) or ED visits over the 52-week treatment period • Frequency of clinically significant exacerbations requiring hospitalization over the 52-week treatment period
Estimand

The estimand is described by the following attributes:
• Population: Chinese participants with severe eosinophilic asthma
• Treatment condition: mepolizumab 100mg SC given every 4 weeks compared to placebo every 4 weeks, both treatments given on top of standard of care.
• Variable:
  o Number of clinically significant exacerbations requiring hospitalization (including intubation and admittance to an ICU) or ED visits over 52 weeks.
  o Number of clinically significant exacerbations requiring hospitalization over 52 weeks.
• Summary measure:
  o Rate ratio of clinically significant exacerbations requiring hospitalization (including intubation and admittance to an ICU) or ED visits between the mepolizumab arm and placebo.
  o Rate ratio of clinically significant exacerbations requiring hospitalization between the mepolizumab arm and placebo
• Intercurrent events:
  o Study treatment discontinuation-hypothetical strategy
The handling strategy for the IEs will be the same with primary estimand defined in Section 4.2.1

4.3.2. Main analytical approach

Time to first clinically significant exacerbations

Endpoint / Variables
• Time to first clinically significant exacerbations
Model Specification
• Cox's proportional hazards model • Terms in the model:

Endpoint / Variables
• **Response**: time to first on-treatment, clinically significant exacerbation • **Categorical**: treatment group, baseline maintenance oral corticosteroids (OCS vs no OCS) • **Continuous**: baseline disease severity (as % predicted FEV1), number of exacerbations in the year prior to the study (as an ordinal variable (2, 3, 4+))
Model Checking & Diagnostics
• The proportional hazards assumption will be examined by obtaining the Kaplan-Meier estimates of the survival function S(t) over time separately for each treatment group. In addition, the ln {-ln[S(t)]} plot will be produced.
Model Results Presentation
• Hazard ratios and the percent reduction in risk of a first exacerbation at any time on-treatment during the study for the pairwise treatment comparisons with associated 95% CIs and p-values will be presented. • The probability of having an on-treatment clinically significant exacerbation at week 16，32 and 52and 95% CI for each treatment group will be presented.
Sensitivity and Supportive Analyses
• As a supportive analysis, the analysis will be repeated using the “Per-protocol” analysis population.
Additional estimands
A supplementary analysis will be performed using the “treatment policy” strategy for the intercurrent event of discontinuation of treatment. This analysis will include both on-treatment and off-treatment clinically significant exacerbation data from subjects who withdraw from treatment prior to W52. Exacerbations will be included provided the exacerbation onset date is before week 52. Participants that have not experienced a clinically significant exacerbation on or before the end of study date/early withdrawal/lost to follow up study/ date of death day are censored at the end of study date/early withdrawal/date of death.

SGRQ at Week 52

Endpoint / Variables
• Mean change in St. Georges Respiratory Questionnaire at Week 52 Details for how to score the SGRQ are outlined in the SGRQ manual (Mar, 2016).
Model Specification
• MMRM • Analysis performed using a mixed models repeated measures analysis (MMRM) adjusting covariates: baseline, baseline maintenance OCS therapy (OCS vs. no OCS), exacerbations in the year prior to the study (as an ordinal variable), baseline

Endpoint / Variables
% predicted FEV1, treatment and visit, plus interaction terms for visit by baseline and visit by treatment group • A dataset *om_dataset* will be constructed to reflect the data structure of no missing observations, i.e. had each subject been reported with the same visits.
Model Results Presentation
• Least-square (LS) means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors as well as 95% CIs. The estimated treatment difference along with corresponding standard error, 95% CI for each Week will be presented. • The treatment differences (and associated 95% CIs) at week 52 will also be presented graphically.
Missing data imputation
The analysis using the MMRM model assumes that missing data is missing at random (MAR).
Sensitivity and Supportive Analyses
• To compare with MEA115588 results, a sensitivity analysis will be analysed by analysis of covariance (ANCOVA) with covariates of baseline, baseline maintenance OCS therapy (OCS vs. no OCS), exacerbations in the year prior to the study (as an ordinal variable), baseline % predicted FEV1, and treatment. In this sensitivity analysis, the mean score for a subject at either timepoint (i.e. baseline or exit visit) will only be calculated if at least 75% of the questions were answered. If fewer than 75% of the questions were answered then the mean score for that subject at that timepoint will be considered missing. Only the observed data will be used and no imputation will be done for missing data. • Another sensitivity analyses of the MMRM will be performed using multiple imputation methods based on pattern mixture models. • A supportive analysis will be repeated using the “Per-protocol” analysis population • Another supportive analysis will be performed by domain: Symptoms domain, Activity domain and Impacts domain
Additional estimands
A supplementary analysis will be performed using the “treatment policy” strategy for the intercurrent event of discontinuation of treatment. This analysis will include both on-treatment and off-treatment value. For missing data imputation, the missing data are assumed as MAR.

Clinically significant exacerbations requiring hospitalization/ ED visits and clinically significant exacerbations requiring hospitalization

Endpoint(s)
• Frequency of clinically significant exacerbations requiring hospitalization (including intubation and admittance to an ICU) or ED visits over the 52-week treatment period • Frequency of clinically significant exacerbations requiring hospitalization over the 52-week treatment period
Model Specification, Checking & Diagnostics, Results, Presentation
• These endpoints will be analyzed using the same methodology as the primary analysis of Frequency of clinically significant exacerbations in Section 4.2.1.
Missing data imputation
The analysis using the negative binomial model assumes that missing data is missing at random (MAR).
Sensitivity and Supportive Analyses
• As a supportive analysis, the analysis will be repeated using the "Per-protocol" analysis population.
Additional estimands
The same additional estimand and similar methods for missing data imputation will be used as the primary endpoint in Section 4.2.3.

Pre-bronchodilator FEV1 at Week 52

Endpoint / Variables
• Mean change from baseline in clinic pre-bronchodilator FEV1 at Week 52
Model Specification
• Mixed Models Repeated Measures (MMRM) model. • Change from baseline in pre-bronchodilator FEV1 will be analyzed using a mixed models repeated measures analysis (MMRM) adjusting covariates of baseline, baseline maintenance OCS therapy (OCS vs. no OCS), exacerbations in the year prior to the study (as an ordinal variable), treatment and visit, plus interaction terms for visit by baseline and visit by treatment group. A dataset *om_dataset* will be constructed to reflect the data structure of no missing observations
Model Results Presentation
• Least-square (LS) means and LS mean change from baseline values for each treatment group will be presented with their associated standard errors as well as 95% CIs. The estimated treatment difference along with corresponding standard error, 95% CI for each Visit will be presented.

Endpoint / Variables
• The LS mean treatment differences (and associated 95% CIs) for all visits will also be presented graphically.
Missing data imputation
The analysis using the MMRM model assumes that missing data is missing at random (MAR).
Sensitivity and Supportive Analyses
• The sensitivity analyses of the repeated measures analyses will be performed for the FEV1 key secondary endpoint using multiple imputation methods under MAR based on pattern mixture models. The method is analogous to the multiple imputation of exacerbation events. • A supportive analysis of the repeated measures pre-bronchodilator FEV1 analysis will be performed, excluding all values captured within 6 hours of a SABA being administered or 12 hours of a LABA being administered to the subject. • Another supportive analysis will be repeated using the "Per-protocol" analysis population
Additional estimands
A supplementary analysis will be performed using the "treatment policy" strategy for the intercurrent event of discontinuation of treatment. This analysis will include both on-treatment and off-treatment value. For missing data imputation, the missing data are assumed as MAR.

4.4. Other Analyses

Endpoint(s)
• Mean change from baseline compared to placebo in Asthma Control Questionnaire (ACQ-5) score at Week 52 The ACQ-5 is a 5-item questionnaire developed as a measure of patient's asthma control. Response options for each question are on a 7-point scale ranging from 0 (CCI [redacted]) to 6 CCI [redacted]). The questions are equally weighted, and the ACQ-5 score is calculated as the mean of the 5 questions, ranging between 0 (CCI [redacted]) to 6 (CCI [redacted]), where higher scores indicate worse asthma control. • Mean change from baseline in clinic post-bronchodilator FEV1 at week 52
Model Specification, Checking & Diagnostics, Results, Presentation
• MMRM • These endpoints will be analyzed using a mixed models repeated measures analysis (MMRM) adjusting covariates: baseline, baseline maintenance OCS therapy (OCS vs. no OCS), exacerbations in the year prior to the study (as an ordinal variable), baseline % predicted FEV1, treatment and visit, plus interaction terms for visit by baseline and visit by treatment group. A dataset *om_dataset* will be constructed to reflect the data structure of no missing observations

Missing data imputation
For a given visit, if the response to one of the 5 questions is missing then the ACQ-5 score will be calculated as the mean of the available responses. If the response to more than one question is missing, then the ACQ-5 score will be set to missing. The analysis using the MMRM model assumes that missing data is missing at random (MAR).

Endpoint(s)
• Percent of subjects evaluated as responders as measured by ACQ-5 score at Week 52 ACQ-5 score responder is defined as the participant achieving a ≥0.5-point improvement (decrease) from baseline in ACQ-5 score. • Percent of subjects evaluated as responders as measured by SGRQ score at Week 52 SGRQ responder is defined as ≥ 4 points improvement (decrease) from baseline in total score.
Missing data imputation
Subjects with missing values at Baseline will be excluded from analyses. Any missing values at post-baseline visit will be included as non-responders.
Model Specification, Checking & Diagnostics, Results, Presentation
• Analysis will be performed using a logistic regression model adjusting for baseline, treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), number of exacerbations in previous year (as an ordinal variable), baseline disease severity (as % predicted FEV1) and baseline score. • For the baseline covariate, if the factor of baseline covariate fails to converge, it will be removed from the logistic model. If the model fails to converge, e.g. due to the limited event number, then the endpoints will be analysed by Fisher exact test only. • The number and percentage of patients identified as responders, non-responders or with missing data at Week 52 will be displayed for each treatment group. The model estimated ratio of the odds of being a responder in the mepolizumab treatment group compared to placebo will be presented with 95% confidence intervals and the associated p-value.

Endpoint(s)
• Percent of subjects recording a favorable treatment response as measured by the Subject Rated Response to Therapy at Week 52. • Percent of subjects evaluated as having a favorable treatment response as measured by the Clinician Rated Response to Therapy at Week 52
Missing data imputation
• Subjects with missing values at Week 52 will not be imputed and will be included in the analysis as category of significantly worse.

Endpoint(s)
Model Specification, Checking & Diagnostics, Results, Presentation
• These endpoints will be analyzed using a proportional odds model (multinomial (ordered) logistic generalized linear model), with terms for treatment group, baseline maintenance OCS therapy (OCS vs. no OCS), number of exacerbations in previous year (as an ordinal variable), baseline disease severity (as % predicted FEV1). • The number and percentage of patients identified as each category(including missing data) at Week 52 will be displayed for each treatment group. The model estimated ratio of the odds of being a responder in the mepolizumab treatment group compared to placebo will be presented with 95% confidence intervals and the associated p-value.

Endpoint(s)
• Mean change from baseline in daily salbutamol/albuterol use • Mean change from baseline in daily asthma symptom scores • Mean change from baseline in awakening at night due to asthma symptoms requiring rescue medication use • Mean change from baseline in morning PEF
Missing data imputation
No imputation will be done for missing data.
Model Specification, Checking & Diagnostics, Results, Presentation
• These endpoints will be summarized by descriptive statistics: mean, SD, median, min and max. • The daily data(excluding days with missing data)will be aggregated over 4-week periods (weeks 1-4, 5-8, …, 48-52). Data for each 4-week period, and change from baseline for each 4-week periods will be summarized by treatment group.

Endpoint(s)
• Mean number of days with oral corticosteroids taken for clinically significant exacerbations • Total prednisone (or equivalent) exposure for clinically significant exacerbations over the 52-week treatment period
Missing data imputation
Only the observed data before discontinuation of study treatment will be used and no imputation will be done for missing data.
Model Specification, Checking & Diagnostics, Results, Presentation
• Total number of days of oral corticosteroids use for clinically significant exacerbations per subject will be summarised by treatment arm

Endpoint(s)
• Total prednisone equivalent dose per clinically significant exacerbation per subject will be summarised by treatment arm. A summary table for OCS only and OCS plus other systemic routes of administration (oral, IV and IM) corticosteroids will be produced

Endpoint(s)
• Frequency of all exacerbations
Missing data imputation
The method for missing data imputation will be the same as the primary efficacy analysis (see Section 4.2.1 for details).
Model Specification, Checking & Diagnostics, Results, Presentation
• These endpoints will be analyzed using the same methodology as the primary analysis in Section 4.2.1

Endpoint(s)
• Time to first exacerbation • Time to withdrawal from study treatment due to asthma exacerbations • Time to first exacerbation requiring hospitalization or ED visit
Model Specification, Checking & Diagnostics, Results, Presentation
• These endpoints will be analyzed using the same methodology as the analysis of time to first clinically significant exacerbation in Section 4.3.2.

Endpoint(s)
• Unscheduled healthcare resource utilization (for clinically significant exacerbations and other asthma related health care) over the 52-week treatment period
Missing data imputation
No imputation will be done for missing data.
Model Specification, Checking & Diagnostics, Results, Presentation
• Healthcare resource use due to a clinically significant exacerbation and other asthma related health care will be summarized by treatment group

Endpoint(s)
• Days of school/work missed
Missing data imputation
No imputation will be done for missing data.

Model Specification, Checking & Diagnostics, Results, Presentation
• Number of days off school/work due to asthma symptoms for different groups will be summarized by mean, SD, median, minimum and maximum.

4.5. Safety Analyses

The MITT- population will be used for the analysis of safety data.
AEs will be considered on-treatment for at least 4 weeks (28 days) following the last dose of study treatment, AEs which occur more than 28 days following the last dose of study treatment will be considered as post-treatment, the detailed definition can be found in Section 6.2.3. All primary safety analysis will use the "While on Treatment" approach, i.e. any safety events which occur post discontinuation of study intervention will be excluded. For key safety outputs, post-treatment data will be included in analysis or displayed separately, detailed information will be defined in the following sections. The listings will cover all of pre-, on- and post- treatment data.
Generally, the missing data will not be imputed, except the AE severity and relatedness data. If an adverse event severity is missing, the severity is to be populated as 'UNKNOWN'. A worst-case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' or missing.

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

Subject years exposure is calculated as follows:
Subject Years Exposure = (IP Stop Date – IP Start Date + 29)/365.25
If the IP start date is missing and there is evidence the subject received at least one dose of IP, the IP start date will be taken to be the date of randomisation, and if the IP end date is missing it will be taken to be the last on-treatment visit attended.
Randomised subjects with no evidence of receiving at least one dose of IP will be shown as having zero days of exposure.
In addition, the number of subjects administered investigational product, the number of treatments administered, and the number of days over which treatment was administered will be summarized.

4.5.2. Adverse Events

Adverse events will be summarized by system organ class and preferred term .
AEs will be summarized for on-treatment period, unless otherwise specified.

The number and percentage of subjects experiencing at least one AE during on-treatment period of any type, AEs within each body system and AEs within each preferred term will be summarized for each treatment group.

- Overview of all AEs

The following summary tables will be produced:

- Summary of all AEs; (on-treatment, post-treatment)
- Summary of drug related AEs;
- Summary of Common (≥ 3% Incidence in any Treatment Group) Adverse Events by Overall Frequency
- Summary of AEs by maximum intensity
- Summary of Severe AEs (on-treatment, post-treatment)
- Summary of SAEs; (on-treatment, post-treatment)
- Summary of non-SAEs
- Summary of Common (≥ 3% Incidence in any Treatment Group) Non-Serious Adverse Events by Overall Frequency (on-treatment)
- Summary of drug related SAEs (on-treatment)
- Summary of non-fatal SAEs (on-treatment)
- Summary of Fatal Events (on-treatment, post-treatment)
- Summary of Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study
- Summary of Adverse Events Leading to Interruption of Study Drug
- Summary of AEs by ADA Assay Result Category (On-Treatment)
- Summary of AEs by NAb (On-Treatment)

The following listings will be produced:

- Listing of Subject Numbers for Individual Adverse Events
- Listing of all Adverse Events
- Listing of Non-Fatal Serious Adverse Events
- Listing of Fatal Adverse Events
- Listing of Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal from the Study

Exposure Adjusted Rate for Adverse Events

Exposure adjusted rate for adverse events represents the frequency of events per 1000 subject-years of exposure, which is calculated as:

(Total number of adverse events / Total Duration of Exposure in days)/365.25*1000

The summary of exposure adjusted for the events below will be provided:

- All Adverse Events (on treatment)
- Most frequent AEs reported by 3% or more subjects (on treatment)
- Drug related AEs (on treatment)
- Non-fatal SAEs (on treatment)

- Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study (on treatment)

Adverse Events of Special Interest

Systemic reactions and local injection site reactions are adverse events of special interest (AESIs) which are collected using target eCRF pages within the study, and will be summarized separately. The summary of symptoms associated with AEs defined by the investigator as being systemic/local injection site reactions will be displayed.

AESIs of potential opportunistic infections, malignancies, serious cardiac, vascular and thromboembolic (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 source data lock for this study. Further details of how relevant preferred terms are identified for the AESIs are given in the Program Safety Analysis Plan (PSAP).

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.

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.

COVID-19 Assessment and COVID-19 AEs

Listing of COVID-19 assessment and COVID-19 AEs will be provided.

Impact of COVID-19 Pandemic on Safety Results

The impact of the COVID-19 pandemic on the safety results will be assessed. Pandemic measures began in different countries at different times. The start date of pandemic in China was Jan. 24th. 2020, which was determined by the GSK country Issue Management Teams (IMT), will be used in the following summaries.

Summaries of the incidence rates of AEs, SAEs and severe AEs, before (AE onset date < pandemic measure start date) and after (AE onset date >= pandemic measure start date) the start of the COVID-19 pandemic will be produced.

4.5.3. Additional Safety Assessments

Cardiovascular events

The following cardiovascular events on treatment will be summarised and listed:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep vein thrombosis/pulmonary embolism
- Revascularization

Laboratory Data

The change from baseline values on- and post- treatment for clinical chemistry and haematology will be summarised. Summaries of the data outside the normal range and the changes from baseline relative to the normal range will also be produced, including 'any time post-baseline', which will include laboratory assessments taken at scheduled, unscheduled and Early Withdrawal visits and will report the most extreme value(s). Data from subjects who have values outside the normal range will be listed.

Urinalysis results (screening only) will be listed.

Vital Signs

Pre-dose systolic blood pressure, diastolic blood pressure and pulse rate including change from baseline for on- and post- treatment will be summarised and listed.

ECG

Actual and change from baseline (for post-baseline timepoints) values for QTc(F) and heart rate including on- and post- treatment will be summarised by treatment for Baseline, Week 24, Week 52 and Withdrawal visit. ECG results will also be listed. Abnormal findings and interpretations will be listed separately.

Individual maximum QTc(F) values will also be summarised to show the number of subjects with maximum values (msec) in the following categories:

- <= 450
- 450 < to <= 480
- 480 < to <= 500
- > 500

Additionally, individual maximum changes from baseline in QTc(F) values will be summarised to show the number of subjects with maximum changes (msec) in the following categories:

- Increase of <=30 msec
- Increase of >30-<=60 msec
- Increase of >60 msec

Liver Event

Liver event information on- and post- treatment will be summarised and all subjects who report a liver event will be listed.

Immunogenicity

For the immunogenicity assessment, two types of anti-drug antibody (ADA) assays will be performed: a binding antibody assay and a neutralizing antibody assay (NAb).

For the binding assay, there will be a three-tiered analysis: 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. For positive confirmation samples, a titre value will also be obtained to quantify the degree of binding in a titration assay, and the sample will be tested with the neutralizing antibody assay, which also reports results as positive or negative. A sample that is positive in the confirmation assay is considered positive for anti-SB-240563 antibodies.
A table will be produced summarising results for the ADA assay in the mITT Population. The highest binding ADA assay confirmatory result obtained post-baseline for a participant (including both on-treatment and post-treatment data, unscheduled and early withdrawal visits), will be summarised with a positive result being considered higher than a negative one, participants with both positive and negative results will be identified in the positive category. Descriptive statistics for titre results will also be presented. In addition, the highest NAb assay result during the same period will be summarised (again with a positive result being considered higher than a negative one and participants with both positive and negative results will be identified in the positive category).

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

A listing will also be produced results for the neutralising antibody assay in the mITT Population, by treatment group and visit. Neutralising antibody assay results will be categorised as follows:

1. Negative
2. Positive

4.6. Pharmacodynamic Analyses

Blood eosinophils on treatment will be summarised by treatment group and visit.

Ratio to baseline at W52 will be analysed using a mixed model repeated measures (MMRM) analysis adjusting for covariates of treatment group, baseline, baseline

maintenance oral corticosteroids (OCS vs no OCS), baseline % predicted pre-bronchodilator FEV1, exacerbations in the year prior to the study (as an ordinal variable (2, 3, 4+)), visit, plus interaction terms for visit by baseline and visit by treatment group. Blood eosinophil counts will be log transformed (loge) prior to analysis. The log transformation for values of 0 GI/L will be based on a value of 0.005 GI/L. Data will be log-transformed prior to analysis. Visit will be fitted as a categorical variable with the effect of treatment group and baseline varying at each visit (i.e. visit by baseline and visit by treatment group interactions will also be included in the model).

To assess the robustness of Blood eosinophils results from the impacts of missing dose, the summary of blood eosinophils without missing dose will also be provided. If the subject has dose missing, the data after the first missing dose will be excluded.

4.7. Pharmacokinetic Analyses

4.7.1. Pharmacokinetic Concentration

Concentrations will be determined at a number of time points over the whole treatment period, ranging from the first dose to last dose when steady state was achieved (Protocol Table 1).

To minimize the potential impact of missing dose on observed plasma concentrations, only the mepolizumab plasma concentrations for which no missing dose occurring within approximate 5 half-life prior to the time of the SC administration will be summarized by visit, i.e., the concentrations at V2-1, V2-2 and V3 without missing dose at V2; the concentrations at V8 without missing dose at V4-7, the concentrations at V14 without missing dose at V10-V13 and the concentrations at V14-1 to V15-2 without missing dose at V10-V14. Standard summary statistics will be calculated (i.e. mean, standard deviation, median, minimum, and maximum).

All the records of concentrations will be listed. Individual concentration-time profiles and median/mean profiles with all records will be plotted on both a linear and semi-log scale.

Protocol amendment 4 updated Study Day of V2-1 (from day 7 to day 8) and V2-2 (from day 14 to day15) to clarify the duration of PK sample collection in Section 1.2 of protocol. On final PK Sample ID form and related PK CRF forms in InForm System, “VISIT 2 PREDOSE” refers to “VISIT2 DAY1”, “VISIT 2 DAY7” refers “VISIT 2 DAY8”, and “VISIT 2 DAY 14” refers to “VISIT 2 DAY15” in SoA.

Concentrations that are below the LLQ (“lower limit of quantification”) are listed as NQ in the raw concentration data. For NQ at pre-dose at V2, it will be imputed as 0, for post first dose records, NQ will be imputed as NULL.

4.7.2. Pharmacokinetic Parameters

The pharmacokinetic parameters for PK data collected following the first dose (up to Day 28/ Visit 3) and at steady state (i.e., at Visit 14 and 15) will be calculated by standard

non-compartmental analysis according to current working practices and using Phoenix WinNonlin, version 6.3 or above.

- Pharmacokinetic parameters described in Table 1 will be calculated, if data permits. Particularly some directly determined parameters, e.g., Cmax or Tmax, might not be reported if the data are considered insufficient to produce.
- All non-compartmental parameters will be calculated based on actual sampling times.

Table 1 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
AUC(0-τ)	Area under the concentration-time curve during the dosing interval at steady-state, i.e., 4 weeks for the study
AUC(0-t)	Area under the concentration-time curve for the last dose, will be calculated from predose on Visit 14 to the time of the last quantifiable concentration (C(t)) based on data collected after last dose, using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid
Cmax	Maximum observed concentration after single dose, determined directly from the concentration data collected after the first dose
Cmax_ss	Maximum observed concentration at steady state, determined directly from the concentration data collected after last dose at Visit 14.
Cavg_ss	Averaged concentration during the dosing interval at steady state, i.e., 4 weeks for the study
Tmax	Time to reach Cmax after single dose, determined directly from the data collected after the first dose
Tmax_ss	Time to reach Cmax at steady state, determined directly from the data collected after last dose at Visit 14
Ctrough	Trough concentration prior to dose at Visit 3
Ctrough_ss	Trough concentration prior to dose at steady-state (Visit 14)
t½	Apparent terminal half-life will be calculated as (just for data collected after last dose at Visit 14): **t½ = ln(2) / lambda_z**
CL_ss/F	Apparent Clearance at steady state, calculated as: CL_ss/F = Dose / AUC(0-τ)
Vz/F	Apparent volume of distribution based on the terminal phase observed after last dose at Visit 14
λz, lambda_z	Terminal phase rate constant

All derived pharmacokinetic parameters described above will be summarised and listed. The parameters of Cmax, Tmax and Ctrough will be summarized at Visit 2, the rest of parameters in table 1 will be summarized at Visit 14. For each of these parameters the following summary statistics will be calculated: n, mean, 95% confidence interval for the mean, standard deviation, median, minimum, maximum, between coefficient of variation, geometric mean, 95% confidence interval for the geometric mean and standard deviation of log-transformed data. No statistical tests will be performed.

Between subject coefficient of variation (%CVb) for log-transformed data will be calculated according the following methods.

%CVb=SQRT(exp(SD^2)-1)*100

Where SD is the standard deviation of the log-transformed data.

4.7.3. Assessment of Accumulation Ratio

To assess the extent of accumulation following mepolizumab multiple doses, the observed accumulation ratio (Ro) for mepolizumab will be determined as ratio of Cmax_ss (Cmax observed after last dose) to Cmax (Cmax observed after the first dose) and ratio of Ctrough_ss (Ctrough before the last dose) to Ctrough (Ctrough after the first dose)

Ro(Cmax) = Cmax_ss / Cmax
Ro(Ctrough) = Ctrough_ss / Ctrough

Accumulation ratios of Cmax and Ctrough will be summarised using n, mean, 95% confidence interval for the mean, standard deviation, median, minimum, maximum, between coefficient of variation, geometric mean, 95% confidence interval for the geometric mean and standard deviation of log-transformed data, and listed.

This pharmacokinetic statistical analysis will only be performed if sufficient data are available.

4.7.4. Population Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Analysis

If deemed necessary, the pharmacokinetic and/or pharmacodynamic data collected from the study may be combined with data from other studies for a population pharmacokinetic or pharmacokinetic/pharmacodynamic analyses. In that case, an analysis plan will be prepared independently. All eligible pharmacokinetic or pharmacodynamic data collected from the study will be included into the analyses.

4.8. Interim Analyses

No formal interim analysis is planned.

4.9. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 04 (Dated: [18-NOV-2021]).

5. SAMPLE SIZE DETERMINATION

5.1. Sample Size Assumptions

The sample size of 300 participants (considering 256 evaluable participants and additional 44 subjects for drop-out) in a 1:1 ratio has been determined by the superiority testing of mepolizumab 100 mg SC vs. placebo, there will be 90% power to detect a 40% decrease in the exacerbation rate from 1.7 per annum (p.a.) on placebo to 1.02 p.a. on mepolizumab 100mg SC using a two sided 5% significance level. The calculation assumes the number of exacerbations per year follows a negative binomial distribution [Keene, 2007] with a dispersion parameter k=0.8.

During the blinded evaluation, the clinically significant exacerbations occurred during the treatment period were analyzed using a generalized linear model assuming a negative binomial distribution and covariates of baseline maintenance OCS therapy (OCS vs. no OCS), EOS level at screening (>=300 cells/μL vs. <300 cells/μL), number of exacerbations in previous year (as an ordinal variable) and baseline disease severity (as % predicted FEV1). The blinded evaluation concluded, the overall event rate under blinded was observed as 0.78 p.a., the dispersion was 2.0.

This reduction observed for overall events at blinded evaluation can be explained by a reduction in exacerbation events during the COVID-19 pandemic, which was not unique in China. , it is still expected that the treatment effect of Mepolizumab compared with placebo will be the same in Chinese SEA population as the original assumption. Therefore, according to the formula [Friede, 2010]

$$\bar{\lambda} = (\lambda_T + \lambda_P)/2$$

where $\bar{\lambda}$ is the overall events rate under blinded, the λ_T and λ_P are the event rates in the treatment and placebo groups, and assuming the reduction will keep the same as 40% under pandemic, the estimated event rates λ_T and λ_P for Mepolizumab 100mg SC and placebo are 0.585 and 0.975 p.a. respectively. On the other hand, there exists a difference for the estimate of dispersion when data is blinded or unblinded, so that the dispersion is adjusted by the difference between blinded and unblinded, which is 1.6=2.0 *(0.796 / 0.972), where the dispersion in MEA115588 study were 0.796 (unblinded) vs. 0.972 (blinded).

Therefore, based on the conclusion on blinded evaluation, assuming a 40% decrease in the exacerbation rate from 0.975 per annum (p.a.) on placebo to 0.585 p.a. on mepolizumab 100mg SC, they will lead to a power of 66% implying a high false negative rate of 34% in China study. If there is a true reduction of 40% in exacerbation rate in Chinese patients, based on use of Bayesian dynamic borrowing with an initial weight of 0.5 on global MEA115588 study result, there will be 88.6% probability to achieve a positive result (equivalent to the power of the study).

The 40% reduction in exacerbation rate has been selected as reductions of this magnitude or greater have been seen in previous mepolizumab studies MEA112997 and MEA115588. However, it should be noted that a smaller reduction in exacerbations could

be clinically significant. Under the same assumptions, there will be 99% probability of showing consistent trend, which is defined as the point estimation of rate ratio between Mepolizumab and placebo<1 in China study, with global MEA115588.

5.2. Sample Size Sensitivity

The sample size in Section 5.1 is based on an expected reduction in this rate for subjects treated with mepolizumab. If the expected reduction with mepolizumab differ then, at the given sample size there will be an effect on the probability of success of the study. Table 2 illustrates this effect on probability of success of varying reductions in rates with mepolizumab, assuming the sample size remains constant at 128 subjects in mepolizumab arm and 128 subjects in placebo arm, excluding the additional 44 subjects to account for early withdrawals from study treatment.

Table 2 Probability of meeting the success criterion conditional on various assumed true treatment effects

Reduction	0.45	0.4	0.35	0
Probabilities of Success	94.6%	88.6%	80.0%	11.8%*

*The probability of success will equal with Type I error when there is no treatment effect for Mepolizumab compared with placebo.

In the Table 2, the probabilities of meeting success are conducted under various assumed true treatment effects when overall event rate is fixed as 0.78 based on the blinded evaluation and dispersion is 1.6, e.g. when reduction is 40%, then the probability of success is calculated by the exacerbation rates for Mepolizumab 100mg SC and placebo as 0.585 and 0.975 p.a. respectively. Type I error is 11.8%, which is calculated when the event rate for each group is 0.78, adjusted dispersion is 1.6 based on analyses of blinded evaluation.

5.3. Sample Size Re-estimation or Adjustment

Blinded evaluation of exacerbation rates is planned for this study. A blinded evaluation of exacerbation rates for the purpose of sample size re-estimation will be done after 15 months of enrolment, or when 225 subjects have been randomized, whichever is earlier. If the exacerbation rates for the study are lower than planned, a sample size re-estimation may be conducted. Any subsequent change to the planned number of subjects randomized would be documented in a protocol amendment.

By the time of this protocol amendment, blinded evaluations of exacerbation rate were completed indicating the data deviate substantially from the assumptions made when we planned the trial, before the COVID-19 pandemic, thus supporting a protocol amendment to update the planned primary analyses without further adjustment of planned sample size.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

Unless otherwise specified, the study population analyses will be based on the MITT Analysis Set. A summary of the number of participants in each of the participant level analysis set will be provided.

6.1.1. Participant Disposition

A summary of the number of subjects included in each population will be produced.

The proportion of screen failures, the proportion who reported each reason for screen failure will be presented for the ASE population. The number of randomized subjects who did not receive treatment will be listed. The reason of Inclusion, Exclusion, Randomization Criteria is failed for screening will be summarized for ASE population. The deviations for these criteria will be presented as well on MITT analysis set.

The subject's completion status will be presented as percentage of withdrawals from the study as well as the reasons for withdrawal. The number and percentage of subjects who completed through Week 52 and who withdrew, including the primary reasons for withdrawal, will be displayed.

A summary of study treatment status will be provided. This display will show the number and percentage of participants who have completed the scheduled study treatment or have discontinued study intervention prematurely, as well as primary reasons for discontinuation of study intervention.

In addition, the subjects' study completion status and treatment status will be summarized by related to COVID-19 and not related to COVID-19 respectively.

The summary of study treatment impacted by COVID-19 will be provided.

Visits and assessments missed due to the COVID-19 pandemic, together with visits conducted remotely, will be listed.

The proportion of subjects in the MITT population at each centre will be presented.

A listing will be provided of subjects who interrupted or discontinued IP, including reason and date of interruption or discontinuation.

Subjects for whom the treatment blind was broken during the study will be listed.

A listing of planned and actual treatments will be provided for each subject by Site ID, and Investigator name.

6.1.2. Demographic and Baseline Characteristics

Demography

Demographic characteristics (age, sex, ethnicity, race, height, weight and body mass index) will be summarised and listed. For age group, it also will by categorised by group: 12-17 years, 18-29 years, 30-49 years, 50-64 years and >= 65 years.

Randomization stratification factor

Randomization stratification factor blood eosinophil count at screening(≥300 cells/μL and <300 cells/μL) will be presented by treatment group. A shift table of differences between stratification factor and as Randomized (data entered into the IWRS system) will be produced.

Stratification factors (randomized and actual strata) will be listed for all subjects by treatment group.

Medical Conditions

The proportion of subjects who report medical conditions in each medical condition class will be presented, for current and past conditions separately. Current and past medical conditions will be listed.

Cardiovascular Assessment

A summary of the baseline cardiovascular assessment will be presented. The proportion of subjects who report a family history of medical conditions that may indicate predisposition towards cardiovascular conditions will be summarised.

Asthma History and Tobacco Use

Asthma history including duration of asthma (including derived age of onset), OCS use and exacerbations in the 12 months prior to Visit 1 will be summarised and listed. Asthma disease characteristics and causes of exacerbations will be summarised and listed.

History of tobacco use will be summarised (i.e., non-smoker, former smoker).

Screening and Baseline Lung Function Tests

The following Screening (Visit 1) and (Visit 2) clinic lung function results will be summarised. Pre and post bronchodilator FEV1 will be listed in the same listing as the raw FEV1 listing in Section 4.3.2. The rest of the screening lung function results detailed below will be listed in a separate listing.

- Pre and post bronchodilator FEV1 (mL)
- Pre and post-bronchodilator percent predicted FEV1 (%)
- Reversibility (in mL and in %)
- Pre and post bronchodilator Forced Vital Capacity FVC (mL)
- Pre and post bronchodilator FEV1/FVC

6.1.3. Protocol Deviations

All protocol deviations, important protocol deviations and protocol deviations which will lead to exclusion from PP population will be summarized. Protocol deviations will also be listed for the MITT population.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations (where possible without knowing the study intervention details) are captured and categorised in the protocol deviations dataset.
- This dataset will be the basis for the summaries of important protocol deviations.

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

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

In addition to the overall summary of important protocol deviations, separate summaries will be produced for important protocol deviations related to COVID-19, and important protocol deviations not related to COVID-19 respectively.

The date of and the reason for breaking the study blind will be listed for the MITT population.

6.1.4. Prior and Concomitant Medications

The proportion of subjects reporting each concomitant medication will be presented. Multi-ingredient medications will be presented according to their combination ATC classification rather than the classifications of the ingredients. Summaries will be split into asthma and non-asthma concomitant medications, as well as into those taken pre-treatment, during treatment and post-treatment. Asthma medications will be grouped for Respiratory Medications Classes as well, which are based on pre-defined code lists derived from ATC classifications:

- Androgens and Estrogens
- Anti-IgE, Anti-IL5
- Antiinfectives (antibiotics, antiseptics)
- Antimycotics
- Antivirals
- Beta 2 Agonist
- Corticosteroid
- Leukotriene Receptor Antagonist
- Long-acting anticholinergic

- Long-acting beta-2 agonist – Group 2 (Once per day)
- Long-acting beta-2 agonist – Group 3 (Twice per day)
- Mucolytics
- Nedocromil or Cromolyn Sodium
- Oxygen
- PDE4 Inhibitors
- Short-acting anticholinergic
- Short-acting beta-2 agonist
- Theophylline
- Xanthine

Classification of a medication as pre-, on- or post-treatment will be made with reference to the study treatment start and stop dates and the medication start date. If the medication start date is missing or partial then the medication will be considered on-treatment unless there is evidence to the contrary (e.g. the month of the start date is present and is less than the month of the first dose of study medication). Medications with a start date of up to 4 weeks after the last dose of treatment will be considered on-treatment. Medications with a start date after this period will be considered post-treatment.

Pre- and on-treatment respiratory medications will be summarised separately.

A medication will be summarised in every period (pre/on-/post) in which it was taken, so a medication that was started in the run-in and stopped during active treatment will appear in both the pre-treatment and the during treatment tables.

The listings of all asthma and non-asthma concomitant medications will be provided.

6.1.5. Study Intervention Compliance

A summary of treatment compliance is not applicable to this study; however number of treatments received is summarised in the Extent of Exposure Section 4.5.1.

6.2. Appendix 2 Data Derivations Rule

6.2.1. Planned and Actual Treatment

For participants who received the correct treatment throughout the study, the actual treatment will be the same as the planned treatment. For participants who received an incorrect treatment, the actual treatment will be derived as follows:

- If the number of doses on an incorrect treatment is less than the number of doses on the planned treatment then the actual treatment is assigned as planned treatment.
- If the number of doses on an incorrect treatment is equal to or greater than the number of doses on the planned treatment then the actual treatment is assigned as the incorrect treatment.

6.2.2. Analysis Period for Exacerbations and Efficacy Endpoints

The analysis period defines the period of time over which exacerbations and efficacy assessments will be included in the on and/or off-treatment phases. The start and end of the analysis period is defined for subjects based on their study completion status as follows:

Study Completion	Start Date of Analysis Period	End Date of Analysis Period
Completed	First dose of investigational product (Day 1)	Earlier of Date of Week 52 visit or Date of last dose at Week 48 +35 days [1]
Withdrew early	First dose of investigational product (Day 1)	Earlier of Date reported on the study conclusion page or Date of last dose at Week 48 +35 days [1]

[1] Based on protocol Section 4.1, the Exit Visit (Visit 15) represents the last day of study (i.e. 4 weeks after the last dose given at Visit 14), allowing for the ±7 days visit window, date of last dose at week 48+35 days is defined as the upper bound of 7 days visit window for the date of last dose at week 48+28 days.

6.2.3. Study Period

Assessments and events will be classified according to the time of occurrence relative to the study treatment period.

Study treatment period for Exacerbation

Treatment period	Definition
Pre-Treatment	Event start date < IP start date
On-Treatment	Subjects who did not withdraw early 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) Subjects who withdrew early from IP: Event onset date is on/after IP start date & on/before the earlier of the IP stop date+28 days/end of analysis period. (IP Start Date ≤ Event Start Date ≤ 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)

Note: the IP stop date is missing or the event start date is missing then the event considered on-treatment

Study Treatment Period for Visit Based Efficacy Assessments

Applicable to all visit-based efficacy assessment such as FEV1, SGRQ, ACQ, Subject Rated Response to Therapy, Clinician Rated Response to Therapy.

Treatment period	Definition
Pre-Treatment	Visit date < IP start date
On-Treatment	Subjects who did not withdraw early from IP: Visit date is after IP start date & on/before the end of analysis period. (IP Start Date < Visit Date ≤ end of analysis period) Subjects who withdrew early from IP: Visit date is after IP start date & on/before earlier of the IP stop date +28 days/end of analysis period. (IP Start Date < Visit Date ≤ earlier of IP Stop Date + 28 days/end of analysis period)
Off-Treatment	(IP Stop Date + 28 days < Visit Date ≤ end of analysis period)
Post-Treatment	Visit Date > end of analysis period

Study treatment Period for Adverse Events

Treatment period	Definition
Pre-Treatment	Event start date < IP start date
On-Treatment	IP start date ≤ Event start date ≤ IP stop date +28 days
Post-Treatment	Event start date > IP stop date +28 days

Note: the IP stop date is missing or the event start date is missing then the event considered on-treatment

Study Treatment Period for Visit Based Safety Assessments

Applicable to all safety assessment such as vital signs, ECG, laboratory assessments:

Treatment period	Definition
Pre-Treatment	Visit date < IP start date
On-Treatment	IP start date ≤ Visit date ≤ IP stop date +28 days
Post-Treatment	Visit date > IP stop date +28 days

Study Treatment Period for Concomitant Medications

Treatment period	Definition
Pre-Treatment	Concomitant medication (CM) start date < IP start date
On-Treatment	IP start date ≤ CM start date ≤ IP stop date +28 days
Post-Treatment	CM start date > IP stop date +28 days

Note: the IP stop date is missing and CM start date is on/after IP start date then CM considered on-treatment
If CM start date is missing then CM considered on-treatment

6.2.4. Length of Time in Phase for Exacerbations

The length of time in a phase reflects for each subject 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 loge (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 subject contributes information in each phase is detailed below.

Phase	Length of time (Days) in Phase
On- and Off-treatment	(Date of End of Analysis Period – IP Start Date) +1
On-treatment	Subjects who did not withdraw early from IP: (Date of End of Analysis Period – IP Start Date) +1 Subjects who withdrew early from IP: (IP Stop Date – IP Start Date) +28+1
Off-treatment	Subjects who did not withdraw early from IP: 0 days Subjects who withdrew early from IP: Date of End of Analysis Period – [IP Stop Date + 28 days]

Subjects who withdraw early from the study with an analysis period which ends prior to Day 372 will be considered to have missing data for a period of time calculated as: (Day 372-Date of End of Analysis Period) +1.

6.2.5. Study Day and Reference Dates

The safety reference date is the study intervention start date and will be used to calculate study day for safety measures.

The efficacy reference date is the date of the study intervention start date and will be used to calculate study day for efficacy measures and baseline characteristics, as well as efficacy durations.

The study day is calculated as below:

Assessment Date = Missing → Study Day = Missing
Assessment Date < Reference Date → Study Day = Assessment Date – Ref Date
Assessment Data ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1

6.2.6. Assessment Window

Clinic visits are scheduled to take place as specified in the protocol. Measurements outside visit windows will not be excluded from analyses on any population. For all clinic visits, nominal visit days and times will be used for reporting, such that if a subject recorded values on the Week 4 visit that were actually made on Week 3 of treatment, they will be presented as Week 4 values.

If a subject withdraws at a scheduled visit, and these data were scheduled to be collected at that visit, the data will be summarised and analysed (as appropriate) together with data from subjects who did not withdraw. If a subject withdraws at a scheduled visit at which these data were not scheduled to be collected, or if a subject withdraws between scheduled visits, data will be slotted to the next visit where the data was scheduled to be collected according to the study flowchart. The protocol visit windows of ±7 days should be applied to the assignment of withdrawal visits, so that if a subject withdraws within the appropriate number of days from the last visit where that data was scheduled to be collected, they would get that data slotted to that visit and otherwise the data will be slotted to the next scheduled visit. The early withdrawal visit with then be re-labelled as the corresponding visit.

For unscheduled visits, excluding a subject's baseline visit (where IP is initiated) or exit visit, the same logic will be applied. If a subject has an unscheduled assessment within the appropriate number of days (±7 days) from a visit where that data was scheduled to be collected, this data would be slotted to that visit and otherwise the data will be slotted to the next scheduled visit. Liver event and log visits will be excluded from summary tables, but included in the 'any time post baseline' data.

If there is more than one assessment associated with a particular visit interval then the closest assessment will be used for summary tables and analyses. Where two or more ECG findings slot to the same visit interval, the most 'abnormal' results will be used, i.e. according to the following hierarchy: Abnormal-Clinically Significant > Abnormal – not clinically significant > Normal.

6.2.7. Multiple measurements at One Analysis Time Point

When triplicate ECG assessments are taken, mean of the measurement will be calculated first and summary statistics will be based on the calculated mean. This will apply to both baseline and post baseline assessments.

For lab tests on a study day, if more than one assessment is taken on the same day, the test from a central lab will be taken over the test from a local lab. If multiple assessments are taken from the same type of lab, the worst case will be used.

6.2.8. 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

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>imputed for ‘slotting’ data to study phases or for specific analysis purposes as outlined below.
• Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.</td></tr>
<tr><td>Adverse Events</td><td>• Partial dates for AE recorded in the CRF will be imputed using the following conventions:
<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.

Else if study intervention start date is not missing:

o If month and year of start date = month and year of study intervention start date, then

▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.

▪ Else set start date = study intervention start date.

Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.

Else if study intervention start date is not missing:

o If year of start date = year of study intervention start date, then

▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
▪ Else set start date = study intervention start date.
Else set start date = January 1.</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td>Missing end day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
<tr><td>Concomitant Medications/ Medical History</td><td>
Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.

Else if study intervention start date is not missing:

o If month and year of start date = month and year of study intervention start date, then
▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
▪ Else set start date = study intervention start date.
Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.

Else if study intervention start date is not missing:

o If year of start date = year of study intervention start date, then
▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
▪ Else set start date = study. intervention start date.</td></tr>
</table>
</td></tr>
</table>

Element	Reporting Detail		
		Else set start date = January 1.	
	Missing end day	A '28/29/30/31' will be used for the day (dependent on the month and year).	
	Missing end day and month	A '31' will be used for the day and 'Dec' will be used for the month.	
	Completely missing start date	No imputation	
	Completely missing end date	The date of last visit for this participant will be used	

6.2.9. Reversibility

Subjects' reversibility will be assessed at Screening (Visit 1). To determine reversibility, the subject will follow bronchodilator procedures as per the protocol.

Reversible is defined as an increase in FEV1 of ≥12% and ≥200mL following administration of albuterol/salbutamol.

Non-reversible is defined as a post-albuterol/salbutamol increase in FEV1 of <200mL or a ≥200mL increase that is <12% from pre-albuterol/salbutamol FEV1.

6.2.10. Evaluation Process of Clinically Significant Asthma Exacerbations

In order to provide an objective assessment of the circumstances linked to the clinical decision that defines asthma exacerbations, the investigator must take into account changes on one or more of the following parameters recorded in the subject's eDiary:

- decrease in morning peak flow
- increase in the use of rescue medication
- increase in the frequency of nocturnal awakening due to asthma symptoms requiring rescue medication use
- increase in overall asthma symptom score

This clinical verification process is designed to validate that the exacerbations recorded by the investigator are associated with objective evidence, such as the eDiary parameters described above.

The following steps will be followed for verification of asthma exacerbations:

1. Clinical Review will be performed to evaluate each exacerbation to determine the event meets the protocol definition. Follow up will be done with the Primary Investigator in the event that data needs to be queried.
2. The medical monitor will review each exacerbation in InForm and verify the exacerbation against eDiary data (extracted from the PHT Portal), to confirm the exacerbation was associated with one of the following:
    a. Decreases in peak flow:
        i. as flagged by an alert in the eDiary (Decrease in morning PEF ≥30% on at least two of three successive days, compared with baseline (last 7 days of run-in)) or;
        ii. any other decrease judged by the medical monitor to be clinically significant
    b. b. Increase in rescue medication use:
        i. as flagged by an alert in the eDiary (An increase of ≥50% in rescue medication on at least two of three successive days, compared with the average use for the previous week) or;
        ii. any other increase judged by the medical monitor to be clinically significant (e.g. ≥4 puffs in 2 or more consecutive days)
    c. Increase in nocturnal awakenings due to asthma symptoms requiring use of rescue
        i. as flagged by an alert in the eDiary (Awakening due to asthma symptoms requiring successive nights) or;
        ii. any other increase judged by the medical monitor to be clinically significant
    d. Changes in Asthma Symptoms (increase in overall asthma symptom score):
        i. as flagged by an alert in the eDiary (A symptom score of 5 for at least two of three successive days) or;
        ii. any other change judged by the medical monitor to be clinically significant (e.g. ≥4 during 2 or more consecutive days when baseline is 0)
3. The medical monitor will review data in the eDiary 10 days prior to the event start date and 5 days post the event start date in exceptional circumstances data from outside this window may be considered adequate evidence.
4. The medical monitor will tick the relevant check-box (i.e. peak flow; rescue med use; nocturnal awakenings; asthma symptoms) based on whether there is objective evidence available (as described above) and confirm that the exacerbation is clinically significant.
5. For each exacerbation for which objective evidence is not available in the eDiary data the medical monitor will follow up with the primary investigator to determine if there is alternative objective data (not in the eDiary) to support it being a clinically significant exacerbation.

6. A final decision will be made on whether exacerbations with no supporting eDiary data but possibly other objective data can be included as part of the primary endpoint analysis of clinically significant exacerbations.
7. If an exacerbation with no eDiary data to support it is deemed as having another source of objective evidence, this will be updated in the comments section of the InForm adjudication page to clearly specify what evidence is supporting the decision.

In the event that the primary investigator is unable to provide objective evidence to support the exacerbation, then the event will be reported as "Investigator- defined" exacerbation and it will only be included as part of the sensitivity analysis of the primary analysis. If the medical monitor deems the exacerbation to be clinically significant based on evidence provided by the primary investigator, it will be included as part of the primary endpoint analysis.

6.2.11. eDiary Data

The following assessments will be collected on a daily basis using an eDiary device: morning peak flow, usage of rescue medication (i.e. salbutamol/albutamol), asthma symptom score and frequency of awakening due to asthma symptoms requiring use of rescue medication. These data will be summarised in 4-weekly periods, as shown in the below table.

Reporting Period	First Day Included	Last Day Included
Baseline	7 days prior to day of first dose	Date of first dose
Weeks 1-4	Day after day of first dose	28 days after day of first dose
Weeks 5-8	29 days after day of first dose	56 days after day of first dose
Weeks 9-12	57 days after day of first dose	84 days after day of first dose
Weeks 13-16	85 days after day of first dose	112 days after day of first dose
Weeks 17-20	113 days after day of first dose	140 days after day of first dose
Weeks 21-24	141 days after day of first dose	168 days after day of first dose
Weeks 25-28	169 days after day of first dose	196 days after day of first dose
Weeks 29-32	197 days after day of first dose	224 days after day of first dose
Weeks 33-36	225 days after day of first dose	252 days after day of first dose
Weeks 37-40	253 days after day of first dose	280 days after day of first dose
Weeks 41-44	281 days after day of first dose	308 days after day of first dose
Weeks 45-48	309 days after day of first dose	336 days after day of first dose
Weeks 49-52	337 days after day of first dose	Week 52 visit date (or 364 days after day of first dose, if earlier)

6.2.12. Computation of Age

Each subject's age will be calculated based on their date of birth relative to the date of the screening visit. Where only a subject's year of birth is collected, their date of birth will be imputed with 30th June (30 Jun YYYY).

6.2.13. Reasons for Exclusion from the Per Protocol Analysis

Subjects with protocol deviations considered to potentially have an effect on efficacy will be removed from the Per Protocol (PP) population. Determination of the Per Protocol population will be done blinded to treatment before the database is frozen. The reason for exclusion for any subject will be documented.

Reasons for exclusion from the PP population may be included:

- No persistent airflow obstruction as indicated by pre-bronchodilator FEV1 <80% predicted (NHANES III) for subjects ⩾ 18 years of age recorded at Visit 1 (predicted pre-bronchodilator FEV1 <90% or FE1/FVC <0.8 for subjects 12 to 17 years of age) (see Inclusion Criterion 3)
- Absence of regular treatment with high dose ICS (ICS dose must be ⩾500 mcg/day fluticasone propionate (FP) or equivalent daily (for ICS/LABA combination preparations, Seretide 50/250 mcg bid and above or equivalent will meet this ICS criteria).) in the 12 months prior to Visit 1, of which at least 9 months accumulated documented is required (see Inclusion Criterion 5)
- Absence of current treatment with one or more additional controller medication, besides ICS, and at least one additional controller medication must have been regularly used for at least 3 months prior to Visit 1. (see Inclusion Criterion 6)
- No eosinophilic airway inflammation (see Randomization Criterion 1) as defined by:
    - Peripheral blood eosinophil level of ⩾300 cells/ μ L documented in the 12 months prior to visit 1 that is related to asthma OR
    - Peripheral blood eosinophil level of ⩾150 cells/ μ L demonstrated at Visit 1 that is related to asthma
- <2 asthma exacerbations in the 12 months prior to Visit 1 (see Inclusion Criterion7)
- No evidence of asthma (see Randomization Criterion 2) as documented by either:
    - Airway reversibility (FEV1⩾12% and 200ml) demonstrated at Visit 1 or Visit 2 OR
    - Airway reversibility (FEV1⩾12% and 200ml) documented in the 12months prior to visit 2 (randomization visit) OR
    - Airway hyperresponsiveness (PC20 of <8mg/mL or PD20 of <7.8 μmol methacholine/histamine or positive mannitol test) documented in the 12 months prior to visit 2 (randomization visit) OR
    - Airflow variability in clinic FEV1 ⩾20% between two clinic visits documented in the 12 months prior to visit 2 (randomization visit) (FEV1 recorded during an exacerbation will not be valid) OR
    - Airflow variability as indicated by >20% diurnal variability in peak flow observed on 3 or more days during the run-in
- Use of omalizumab (Xolair) within 130 days of Visit 1 (see Exclusion Criteria 14)
- Use of omalizumab (Xolair) or other prohibited medication during the study
- Breaking of the blind at any point during the study
- Receiving the wrong study treatment at any point during the study
- >=2 consecutive dose missing

6.2.14. Daily Corticosteroid Dose Administered for an Exacerbation

Only corticosteroids administered via oral, IV and IM routes are to be considered when calculating a subject's daily prednisone/prednisolone dose associated with an exacerbation. All steroids administered via a sublingual route will also be considered as oral.

The below corticosteroid conversion factors will be used, regardless of the route of administration, to scale each corticosteroid dose to a prednisone equivalent dose. These three routes of administration (oral, IV and IM) are to be considered equivalent as it has been noted that the bioavailability of methylprednisolone is considered to be roughly equivalent following administration as an oral, IV or IM steroid [Kenalog-40 prescribing information, 2011; Antal, 1983]. If there are seen to be two corticosteroid records associated with an exacerbation that are seen to overlap on a particular study day, these overlapping records will be summed in order to obtain a total prednisone/prednisolone equivalent dose for the day in question.

Standardized Medication Name	Scaling Factor
Betamethasone	8.33
Betamethasone Dipropionate	8.33
Betamethasone Sodium Phosphate	8.33
Cortisone	0.2
Cortisone Acetate	0.2
Cortivazol	17
Deflazacort	0.833
Dexamethasone	6.67
Dexamethasone Sodium Phosphate	6.67
Dexamethasone Acetate	6.67
Fludrocortisone Acetate	0
Hydrocortisone	0.25
Hydrocortisone Sodium Succinate	0.25
Hydrocortisone Sodium Phosphate	0.25
Meprednisone	1
Methylprednisolone	1.25
Methylprednisolone Acetate	1.25
Methylprednisolone Sodium Succinate	1.25
Methylprednisone	1.25
Methylprednisone Acetate	1.25
Prednisolone	1
Prednisolone Acetate	1
Prednisolone Hemisuccinate	1
Prednisolone Sodium Succinate	1

Standardized Medication Name	Scaling Factor
Prednisone	1
Prednisone Acetate	1
Triamcinolone	1.25
Triamcinolone Acetonide	1.25

6.2.15. Early PK Access Key Activities

No early PK access before database freeze.

6.3. Appendix 3 Model Checking and Diagnostic for Statistical Analyses

Endpoints	Exacerbation endpoints
Analysis	Negative Binomial Model
Missing data is assumed missing at random. Departures from this assumption will be tested for the primary endpoint. If model fails to converge due to limited events, the covariates in the model may be removed.	
Endpoints	Exacerbation endpoints
Analysis	Mixed Model Repeated Measures
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. An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line. If this model fails to converge, alternative correlation structures may be considered, e.g. Heterogeneous AR (type=ARH(1)) or Heterogeneous CS (type=CSH) or others if applicable.	

Endpoints	Time to first event (exacerbation)
Analysis	Cox proportional hazard method
The Kaplan Meier method for computing survival function estimates will be used (Method = KM).	

Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
WinNonlin
SAS

7. REFERENCES

Antal E.J., Wright III C.E., Gillespie W.R., Albert K.S. Influence of Route of Administration on the Pharmacokinetics of Methylprednisolone. *Journal of Pharmacokinetics and Biopharmaceutics.* 1983;11.6:561-576.

Barnard J, Rubin D. Small Sample Degrees of Freedom with Multiple Imputations. *Biometrika*. 1999;86:948-955.

Carpenter JR, Roger JH, Kenward MG. Analysis of Longitudinal Trials with Protocol Deviations: a Framework for Relevant, Accessible Assumptions, and Inference via Multiple Imputation. *Journal of Biopharmaceutical Statistics (accepted for publication).* 2013; N/A:N/A.

Friede T, Schmidli H. Blinded Sample Size Reestimation with Negative Binomial Counts in Superiority and Non-inferiority Trials. *Methods Inf Med.* 2010;49:618-624.

Keene ON, Jones M, Lane P, Anderson J. Analysis of Exacerbation Rates in Asthma and Chronic Obstructive Pulmonary Disease: Example from TRISTAN Study. *Pharm Stats*. 2007;6:89-97.

Keene ON, Roger JH, Hartley BF, Kenward MG. Missing Data Sensitivity Analysis for Recurrent Event Data Using Controlled Imputation. *Pharmaceutical Statistics.* 2014;13:258-264.

Kenalog-40 prescribing information, KENALOG®-10 INJECTION prescribing information.
http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/012041s039lbl.pdf. August 2011.

Schmidli H, Gsteiger S, Roychoudhury S, O'Hagan A, Spiegelhalter D, Neuenschwander B. Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics.* 2014;70:1023-1032.