# Statistical Analysis Plan

**Study ID:** 209682

**Official Title of Study:** A Phase 4, open-label, single arm, 24-week, study to evaluate the safety and efficacy of mepolizumab 100 mg SC administered every 4 weeks in Indian participants aged ≥18 years with Severe eosinophilic asthMa (PRISM)

**Date of Document:** 21-June-2023

# Statistical Analysis Plan

Protocol No. 209682

Version 2.0

A Phase 4, open-label, single arm, 24-week, phase 4 study to evaluate the safety and efficacy of Mepolizumab 100 mg SC administered every 4 weeks in Indian participants aged ≥18 years with Severe eosinophilic asthma requiring oral corticosteroid treatment to Maintain asthma control (PRISM)

**Author**: PPD

**Version Number and Date of Protocol: Amendment 04, 13 Aug 2022**

# Statistical Analysis Plan Signature Page

**Statistical Analysis Plan for Protocol 209682.**

Upon review of this document, the undersigned approve this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

| | Name | Signature | Date |
|---|---|---|---|
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# Modification History

| Version Number | Date of the Document Version | Author | Significant Changes from Previous Version |
|---|---|---|---|
| 1.0 | 17 Feb 2022 | PPD | Not Applicable – First Version |
| 2.0 | 8-JUN-2023 | PPD | As per Protocol Amendment 4 |

# Table of Contents

# 1. GLOSSARY OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ACQ | Asthma Control Questionnaire |
| ADA | Anti-Drug Antibodies |
| AE | Adverse Event |
| AESI | Adverse Events of Special Interest |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| BMI | Body Mass Index |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| CV | Cardiovascular |
| ECG | Electrocardiogram |
| ENR | Enrolled |
| EOS | End of Study |
| EOT | End of Treatment |
| FVC | Forced Vital Capacity |
| FEV | Forced Expiratory Volume |
| MCH | Mean Corpuscular Hemoglobin |
| MCV | Mean Corpuscular Volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | Mixed Model Repeated Measures |
| OCS | Oral Corticosteroid |
| PD | Protocol Deviation |
| PEF | Peak Expiratory Flow |
| PT | Preferred Term |
| PP | Per-Protocol |
| RBC | Red Blood Count |
| SAE | Serious Adverse Event |
| SAS | Statistical Analysis System |
| SAP | Statistical Analysis Plan |
| SC | Subcutaneous |
| SD | Standard Deviation |
| SOC | System Organ Class |
| WBC | White Blood Count |
| WHO DD | World Health Organization Drug Dictionary |
| WPAI-GH | Work Productivity and Activity Impairment Questionnaire: General Health |

# 2. INTRODUCTION

The purpose of this document is to provide a description of the statistical methods and procedures to be implemented for the analysis of data from GSK 209682 study. This document is based on the protocol version Amendment 4, dated 23 August 2022. This Statistical Analysis Plan (SAP) has been developed prior to database lock for final analysis. Any changes from the planned analysis as described in the protocol GSK 209682 and its amendments (as applicable) are detailed here, and any differences described here supersede the analysis presented in the protocol. Any additional analyses which are conducted to supplement the planned analyses and any deviations from the planned analyses described in this SAP will be documented in the Clinical Study Report (CSR).

## 2.1. RESPONSIBILITIES

Tech Observer will perform the statistical analyses and will be responsible for the production and quality control of all tables, figures and listings. This SAP only describes the study population, efficacy and safety analyses for this study.

## 2.2. TIMING OF ANALYSES

The primary analysis of efficacy and safety is planned after all subjects completed the final study visit or withdraw early from the study. No interim analysis is planned for this study.

# 3. STUDY OBJECTIVES

## 3.1. PRIMARY OBJECTIVE

The primary objective of this study is to evaluate safety and tolerability of mepolizumab in subjects with severe refractory asthma with elevated eosinophils.

## 3.2. SECONDARY OBJECTIVE

The secondary objective of this study is to evaluate the efficacy of mepolizumab in subjects with severe refractory asthma with elevated eosinophils.

## 3.3 EXPLORATORY OBJECTIVE

CCI [redacted]

# 4. ESTIMANDS

**Primary Endpoints:**

Incidence of on-treatment adverse events (AEs), serious adverse events (SAEs) and adverse events of special interest (AESIs).

The primary estimand for this endpoint is described by the following attributes:

- Population: Severe refractory asthma patients in India with elevated eosinophils.
- Treatment condition: Participants to receive Mepolizumab 100mg SC every 4 weeks during 24 weeks treatment period.
- Variable/endpoint: Incidence of on-treatment adverse events (AEs), serious adverse events (SAEs) and adverse events of special interest (AESIs).
- Summary measure: Counts and percentages for incidence of at least one AE will be summarised overall, by system organ class and by preferred term.
- Key Intercurrent events & Strategy:
    - Discontinuation of treatment (for any reason) - While on-treatment strategy will be used for treatment discontinuation. This will estimate the percentage of participants experiencing an AE, while receiving treatment. AEs will be defined as on-treatment between the first dose up to and including 28 days following the last dose of mepolizumab.

**Supplementary Estimand:**

This supplementary estimand will report all AEs regardless of the discontinuation of study treatment.

- Population: Severe refractory asthma patients in India with elevated eosinophils.
- Treatment condition: Participants to receive Mepolizumab 100mg SC every 4 weeks during 24 weeks treatment period.
- Variable/endpoint: Incidence of AEs and SAEs
- Key Intercurrent events & Strategy:

- Treatment discontinuation (for any reason) - Treatment policy strategy will be used for treatment discontinuation. This summary will therefore be inclusive of all on-treatment and post-treatment AEs.

**Secondary Endpoints:**

- Number of clinically significant exacerbations (including exacerbations requiring hospitalization or ED visits)
- Number of exacerbations requiring hospitalization or ED visits
- Number of exacerbations requiring hospitalization
- Change from baseline in clinic pre-bronchodilator FEV1 at week 24
- Change from baseline in clinic post bronchodilator FEV1 at week 24
- Change from baseline in ACQ-5 score at week 24
- Change from baseline in morning PEF during weeks 20 – 24

The estimand for the secondary endpoint are detailed here.

- Number of clinically significant exacerbations (including exacerbations requiring hospitalization or ED visits)
- Number of exacerbations requiring hospitalization or ED visits
- Number of exacerbations requiring hospitalization

The above listed secondary endpoint has estimand attributes given below.

- Population: Severe refractory asthma patients in India with elevated eosinophils.
- Treatment condition: Participants to receive Mepolizumab 100mg SC every 4 weeks during 24 weeks treatment period.
- Variable/endpoint:
    - Number of clinically significant exacerbations (including exacerbations requiring hospitalization or ED visits)
    - Number of exacerbations requiring hospitalization or ED visits
    - Number of exacerbations requiring hospitalization
- Summary measure: Rate ratio comparing events/year during the 24-week follow-up period compared to the 12 months prior to screening.
- Key Intercurrent events & Strategy:

- Discontinuation of treatment (for any reason) - Treatment policy strategy will be used for treatment discontinuation. This will estimate the treatment effect over the 24 week study period regardless of treatment discontinuation.

The estimand for the remaining secondary endpoints are detailed as following.

- Population: Severe refractory asthma patients in India with elevated eosinophils.
- Treatment condition: Participants to receive Mepolizumab 100mg SC every 4 weeks during 24 weeks treatment period.
- Variable/endpoint:
  - Change from baseline in clinic pre-bronchodilator FEV1 at week 24
  - Change from baseline in clinic post bronchodilator FEV1 at week 24
  - Change from baseline in ACQ-5 score at week 24
  - Change from baseline in morning PEF during weeks 20 – 24
- Summary measure:
  - Mean change from baseline in clinic pre-bronchodilator FEV1 at week 24
  - Mean change from baseline in clinic post-bronchodilator FEV1 at week 24
  - Mean change from baseline in ACQ-5 score at week 24
  - Mean change from baseline from baseline in morning PEF during weeks 20 – 24
- Key Intercurrent events & Strategy:
  - Discontinuation of treatment (for any reason) - Treatment policy strategy will be used for treatment discontinuation. This will estimate the treatment effect over the 24 week study period regardless of treatment discontinuation

**Exploratory Endpoints:**

CCI

[redacted]

CCI

[redacted]

**Health Outcome Endpoints: -**

Health outcome endpoints are Clinician and Participant-Rated response to therapy and WPAI-GH composite scores at week 24.

The estimand for this endpoint is described by the following attributes:

- Population: Severe refractory asthma patients in India with elevated eosinophils.
- Treatment condition: Participants to receive Mepolizumab 100mg SC every 4 weeks during 24 weeks treatment period.
- Variable/endpoint:
  - Clinician and Participant rated response to therapy at week 24
  - Change from baseline in each of the following WPAI-GH composite scores at week 24:
    - Percent work time missed due to general health
    - Percent impairment while working due to general health
    - Percent overall work impairment due to general health
    - Percent activity impairment due to general health
- Summary measure:
  - Counts and percentages of clinician response rate to the treatment at week 24
  - Counts and percentages of participant response rate to the treatment at week 24

- Mean change from baseline in percent work time missed due to general health at week 24
- Mean change from baseline in precent impairment while working due to general health
- Mean change from baseline in percent overall work impairment due to general health
- Mean change from baseline in percent activity impairment due to general health.

- Key Intercurrent events & Strategy: A treatment policy would be used if intercurrent event 'Discontinuation of study treatment for any reason' occurs. That is, if a subject discontinues the study treatment, the data for that subject will be analyzed as collected.

# 5. STUDY DESIGN

## 5.1. BRIEF DESCRIPTION

This is a Phase IV multi-center, open-label, single arm 24-week study to evaluate the safety and efficacy of mepolizumab in subjects with severe refractory asthma with elevated eosinophils. Assuming a 35% screen failure rate approximately 154 participants will be required to be screened in order for 100 participants to be enrolled onto the study treatment.

The study schema is provided below.

V1 V2* V3 V4 V5 V6 V7 V8

-2 weeks to -1 week ⟵ Mepolizumab 100 mg, SC ⟶

| | W0 | W4 | W8 | W12 | W16 | W20 | W24 |
|---|---|---|---|---|---|---|---|
| Screening visit (-2 weeks to -1 week) | Treatment Period | | | | | | End of study visit |

*All screening procedures will be performed at least -2 weeks to -1 week prior to first dose of mepolizumab at Visit 2 (Week 0). Screening visit would be at least 7 day prior to dosing visit.

V, visit; W, week; SC, subcutaneous

The primary estimand is the incidence of AEs, SAEs and AESIs in adult Indian participants with severe refractory asthma with elevated eosinophils while on-treatment with mepolizumab 100mg SC during a 24-week study.

### 5.1.1. Screening:

Participants who meet all eligibility criteria at the Screening visit (Visit 1) will enter the study and asked to come to the clinic after at least 1 week for Visit 2 (Week 0). Participants must understand and agree to use the study drugs for the treatment of asthma, or asthma exacerbation, for the duration of the study. OCS use and OCS dose adjustment in participants will be as per the investigator's discretion and clinical practice. At Visit 1, the screening visit, the screening ACQ-5 score will be captured. Participants who meet study eligibility criteria, are eligible to enter the Treatment period. All screening procedures will be performed -2 weeks to -1 week (screening visit would be at least 7 day prior to dosing visit) before first dose of mepolizumab (Visit 2, Week 0). The ACQ-5 questionnaire has been validated in several separate studies and the minimal clinically important difference value of +0.5 has been established to demonstrate a significant clinical change in asthma status.

### 5.1.2. Exacerbation Management:

Anytime during the study when a participant experiences an exacerbation the exacerbation should be treated according to the investigator's clinical practice.

### 5.1.3. Treatment period:

At Visit 2 (Week 0), participants who meet the Treatment Period eligibility criteria will receive Mepolizumab 100mg SC every 4 weeks. Subsequently, participants will continue to receive with mepolizumab 100mg SC every 4 weeks. During this period, participants will remain on their baseline asthma medications. OCS use and OCS dose adjustment in participants will be as per the investigator's discretion and clinical practice.

### 5.1.4. Exacerbation Management during Treatment Period:

Anytime during the study when a participant experiences an exacerbation the exacerbation should be treated according to the investigator's clinical practice.

The participant will return for each subsequent Visit, to receive their subsequent doses of open label study treatment, as scheduled.

### 5.1.4. IP Discontinuation Visit:

The IP discontinuation visit will be performed 4 weeks following the last dose of mepolizumab with a window of ±7 days. Also, if a participant permanently stops study intervention, the participant is not required to withdraw from the study. Every effort should be made by the PI/staff to keep the subject in the study to collect important efficacy and safety data. In the event of discontinuation of study, the end of study visit activities should be performed as specified in SoA table.

### 5.1.5. End of Study Visit:

A participant is considered to have completed study treatment if he/she has received a dose of mepolizumab at Visit 7 (Week 20) of the study. A participant is considered to have completed the study if he/she has completed the 24 week treatment period of the study including the end of study visit. The end of the study is defined as the date of the last visit of the last participant in the study.

## 5.2. SUBJECT SELECTION

### 5.2.1. Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Subject must be 18 to 65 years of age inclusive, at the time of signing the informed consent.
2. Evidence of asthma as documented by either:
    - Airway reversibility (FEV1≥12% and 200 ml) demonstrated at Visit 1 (screening), or Visit 2 (Week 0) OR documented in the previous 12 months OR
    - Airway hyper-responsiveness (methacholine: PC20 of <8mg/mL or histamine: PD20 of <7.8 µmol; mannitol: decrease in FEV1 as per the labelled product instructions) documented in the 12 months prior to Visit 2 (Week 0) OR
    - Airflow variability in clinic FEV1 ≥20% between two consecutive clinic visits documented in the 12 months prior to Visit 2 (FEV1 recorded during an exacerbation should not be considered for this criteria) OR
    - Airflow variability as indicated by >20% diurnal variability in peak flow observed on 3 or more days during the optimisation period

3. Participants with Eosinophilic asthma: prior documentation of eosinophilic asthma or high likelihood of eosinophilic asthma as

   FEV1: Persistent airflow obstruction as indicated by:

   For participants ≥ 18 years of age at Visit 1 (screening), or Visit 2 (Week 0), a prebronchodilator FEV1 <80% predicted

   For predicted FEV1 values NHANES III values will be used and adjustments to these values will be made for race [Hankinson, 1999].

4. Eosinophilic Phenotype: Airway inflammation characterized as eosinophilic in nature as indicated by one of the following characteristics:

   a. An elevated peripheral blood eosinophil level of ≥300 cells/μL that is related to asthma within the previous 12 months prior to Visit 2 (Week 0) OR

   b. Peripheral baseline eosinophil level ≥150 cells/μL between Visit 1 (screening) and Visit 2 (Week 0) that is related to asthma.

5. Patients eligible for mepolizumab treatment as per independent clinical judgment of treating physician in alignment with local prescribing information.

6. Inhaled Corticosteroids: requirement for regular treatment with high dose inhaled corticosteroid in the 6 months prior to Visit 1 (screening).

   For 18 years of age and older:

   • ICS dose must be ≥880 mcg/day fluticasone propionate (FP) (ex-actuator) or equivalent daily.

7. Controller Medication: Current treatment with an additional controller medication for at least 3 months OR having used and failed an additional controller medication for at least 3 successive months during the prior 12 months [e.g., long-acting beta2-agonist (LABA), leukotriene receptor antagonist (LTRA), or theophylline].

**Sex**

8. Male or eligible female
   Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
   Female Participants:

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a woman of childbearing potential (WOCBP)

OR

- Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 4 of the protocol during the intervention period and for at least 16 weeks after the last dose of study intervention. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- A WOCBP must have a negative highly sensitive (Appendix 2 of the protocol) pregnancy test (serum) within 8 weeks before the first dose of study intervention.
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2 of the protocol.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy

**Informed Consent**

**9.** Capable of giving signed informed consent as described in Appendix 1 of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

### 5.2.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

**Medical Conditions**

1. Concurrent Respiratory Disease: Presence of a clinically important lung condition other than asthma. This includes but is not limited to current infection, bronchiectasis, pulmonary fibrosis, bronchopulmonary aspergillosis, or diagnoses of emphysema or chronic bronchitis (chronic obstructive pulmonary disease other than asthma) or a history of lung cancer.
2. Malignancy: A current malignancy or previous history of cancer in remission for less than 12 months prior screening (Participants who had localized carcinoma (i.e. basal or squamous cell) of the skin which was resected for cure will not be excluded).
3. Liver Disease: Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, oesophageal or gastric varices or persistent jaundice), cirrhosis,

and known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

4. Cardiovascular: Participants who have severe or clinically significant cardiovascular disease uncontrolled with standard treatment. Including but not limited to:
   - Known ejection fraction of <30% OR
   - severe heart failure meeting New York Heart Association Class IV (Appendix 5 of the protocol) OR
   - hospitalized in the 12 months prior to Visit 1 for severe heart failure meeting New York Heart Association Class III (Appendix 5 of the protocol) OR
   - angina diagnosed less than 3 months prior to Visit 1 (screening) or at Visit 1
5. Other Concurrent Medical Conditions: Participants who have known, pre-existing, clinically significant endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, haematological or any other system abnormalities that are uncontrolled with standard treatment.
6. Eosinophilic Diseases: Participants with other conditions that could lead to elevated eosinophils such as Hypereosinophilic Syndromes, including Churg-Strauss Syndrome, or Eosinophilic Esophaghitis.
7. Participants with a known, pre-existing parasitic infestation within 6 months prior to Visit 1 (screening) are also to be excluded.

**Prior/Concomitant Therapy**

8. Omalizumab Use: Participants who have received omalizumab [Xolair] within 130 days of Visit 1 (screening)
9. Other Monoclonal Antibodies: Participants who have received any monoclonal antibody (other than Xolair) to treat inflammatory disease within 5 half-lives of Visit 1 (screening).
10. Investigational Medications: Participants who have received treatment with an investigational drug within the past 30 days or five terminal phase half-lives of the drug whichever is longer, prior to Visit 1 (this also includes investigational formulations of marketed products).

**Prior/Concurrent Clinical Study Experience**

11. Participants who have previously participated in any study of mepolizumab and received Investigational Product (including placebo).

**Diagnostic assessments**

12. ECG: ECG assessment QTcF > 450msec or QTcF > 480 msec for participants with Bundle Branch Block.

Participants are excluded if an abnormal ECG finding from the 12-lead ECG conducted at Screening (Visit 1) is considered to be clinically significant and would impact the participant's participation during the study, based on the evaluation of the Investigator.

13. Immunodeficiency: A known immunodeficiency (e.g. human immunodeficiency virus – HIV), other than that explained by the use of corticosteroids taken as therapy for asthma.

**COVID-19 Related Exclusion**

14. Participants that have a current active COVID-19 infection, either laboratory confirmed or according to the investigator's medical judgement.

    Note: Participants who have confirmed or suspected COVID-19 infection may be rescreened 4 weeks or more after the resolution of the COVID-19 infection and only after written approval from the study Medical Monitor.

15. Participants known to be in contact with active COVID-19 positive individuals within the past 14 days.

    Note: Participants may be re-screened 14 days or more following the contact, during which the participant should remain symptom free, and only after written approval from the study Medical Monitor.

**Other Exclusions**

16. Smoking history: Current smokers or former smokers with a smoking history of ≥10 pack years. A former smoker is defined as a participant who quit smoking at least 6 months prior to Visit 1 (screening)
17. Hypersensitivity: Participants with a known allergy or intolerance to a monoclonal antibody or biologic.
18. Pregnancy: Participants who are pregnant or breastfeeding. Patients should not be enrolled if they plan to become pregnant during the time of study participation.
19. Alcohol/Substance Abuse: A history (or suspected history) of alcohol misuse or substance abuse within 2 years prior to Visit 1 (screening).
20. Adherence: Participants who have known evidence of lack of adherence to controller medications and/or ability to follow physician's recommendations.

Re-screening of participants will be allowed only upon approval by the medical monitor.

## 5.3. DETERMINATION OF SAMPLE SIZE

The primary objective of the study is to evaluate the safety and tolerability of mepolizumab over 24 weeks of treatment. The primary endpoint is incidence of AEs, SAEs and AESIs. Sample size is determined based on the calculation of the probability of observing an AE. Table 3 provides the probabilities of observing various numbers of AEs based on a series of theoretical risks of an event occurring in a given patient in a study of 24 weeks' duration, given a sample size of 100. For example, for a theoretical risk of an AE of 2/100 (true proportion value of 0.02) in this 24-week study, we would have a greater than 86% chance of observing at least one subject having the AE.

Table Probabilities of observing a given number of subjects experiencing an adverse events or more (k) for given anticipated risks for a sample size of 100 patients.

| **Theoretical Risk of an Event*** | | | | | |
|---|---|---|---|---|---|
| No of AEs | 5% risk | 3% risk | 2% risk | 1% risk | 0.5% risk |
| K | 0.05 | 0.03 | 0.02 | 0.01 | 0.005 |
| 1 | 0.9941 | 0.9524 | 0.8673 | 0.6340 | 0.3942 |
| 2 | 0.9629 | 0.8053 | 0.5967 | 0.2642 | 0.0898 |
| 3 | 0.8817 | 0.5802 | 0.3233 | 0.0794 | 0.0141 |
| 4 | 0.7422 | 0.3528 | 0.1411 | 0.0184 | 0.0017 |
| 5 | 0.5640 | 0.1821 | 0.0508 | 0.0034 | 0.0002 |
| 6 | 0.3840 | 0.0808 | 0.0155 | 0.0005 | ≤ 0.0001 |
| 7 | 0.2340 | 0.0312 | 0.0041 | ≤ 0.0001 | ≤ 0.0001 |
| 8 | 0.1279 | 0.0106 | 0.0009 | ≤ 0.0001 | ≤ 0.0001 |
| 9 | 0.0631 | 0.0032 | 0.0002 | ≤ 0.0001 | ≤ 0.0001 |
| 10 | 0.0282 | 0.0009 | ≤ 0.0001 | ≤ 0.0001 | ≤ 0.0001 |

*Theoretical risk of an event occurring in a given patient in a study of 24 weeks' duration.

Assuming a 35% screen failure rate approximately 154 participants will be required to be screened in order for 100 participants to be enrolled onto the study treatment.

## 5.4. TREATMENT ASSIGNEMENT AND MASKING

This is an open-label study. All subjects enrolled in the induction phase will receive the study drug (100 mg mepolizumab SC every 4 weeks).

# 6. ANALYSIS POPULATIONS

For the purpose of analysis, the following population are defined:

## 6.1. ALL ENROLLED POPULATION

All participants enrolled and for whom a participant number exists on the study database. This population will be used for summarizing reasons for screen and run-in failures.

## 6.2. SAFETY POPULATION

All participants who take at least 1 dose of study intervention. This population will be used for all safety, efficacy and health outcomes.

# 7. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

## 7.1. GENERAL CONSIDERATIONS

Continuous data will be summarized using the number of subjects (n), arithmetic mean (mean), standard deviation (SD), median, minimum value (min), and maximum value (max) values unless otherwise specified. Categorical variables will be summarized using the frequency counts (n) and percentages (%) for each possible value. Where log-transformed data are used, the summary statistics will include geometric mean and geometric standard deviation (SD). Only data from protocol scheduled visits will be included in the summary tables. Data from unscheduled visits will not be included in the summary tables but will be included in the by-subject listings.

## 7.2. KEY DEFINITIONS

### 7.2.1. Study/Onset Day

The study/onset day will be defined as the number of days since the first dose of study drug, which is assigned as Day 1 for analysis purposes. Study/onset day is calculated using the formula below:

| Assessment Date Relative to First Dose of Study Drug | Study Day Calculation |
|---|---|
| Assessment/Event date < Date of first dose | Date of assessment - Date of first dose of study drug |
| Assessment/Event date ≥ Date of first dose | (Date of assessment – Date of first dose of study drug)+1 |

### 7.2.2. Baseline, Change from Baseline, Relative Change from Baseline and Ratio to Baseline

Baseline is defined as the value recorded at Visit 1 pre-dose assessment. For data collected via eDiary device, the baseline is defined as the average of 4-weekly data collected in the run-in period.

On Visit 2, where time of assessment is collected/available, this should be used to determine if the assessment was performed prior to the administration of the study drug. Where time of assessment is not collected/available it will be assumed that all assessments on Visit 2 occurred prior to the administration of the study drug.

Change from baseline, relative change from baseline and ratio to baseline are calculated as follows:

- Change from baseline = (Post-baseline value – Baseline value)
- Relative change from baseline (%) = (Post-baseline value – Baseline value)/(Baseline value)*100
- Ratio to baseline = Post-baseline value /Baseline value

### 7.2.3. Duration of Event

Where the duration of an event is to be calculated, it will be derived as: (Event stop/end date – Event start date) + 1.

### 7.2.4. Treatment Period

- Pre-treatment period = Date of Screening to Date of first dose minus 1
- On-treatment period = Date of first dose to Date of last dose plus 28 days inclusive
- Post-treatment period = End of last dose plus 29 days to End of study date

### 7.2.5. OCS Dose Reduction

Percent OCS Dose Reduction during Weeks 20 - 24 = 100 * (Baseline Dose – Maintenance Dose during Weeks 20 - 24)/Baseline dose.

Baseline dose is defined as the prescribed optimized prednisone/prednisolone dose following the OCS optimization run-in period and maintenance dose is defined as the mean average of all daily prednisone/prednisolone doses during the maintenance phase of Weeks 20 -24. The visit window for calculating OCS dose at each reporting period is described below:

| Reporting Period | First Day Included | Last Day Included |
|---|---|---|
| Optimised Dose | N/A | N/A |
| Baseline – Week 4 | Day after Week 0 visit | Day of Week 4 visit |
| Week 4 – Week 8 | Day after Week 4 visit | Day of Week 8 visit |
| Week 8 – Week 12 | Day after Week 8 visit | Day of Week 12 visit |
| Week 12 – Week 16 | Day after Week 12 visit | Day of Week 16 visit |
| Week 16 – Week 20 | Day after Week 16 visit | Day of Week 20 visit |
| Maintenance Dose (Week 20 – Week 24) | Day after Week 20 visit | Day of Week 24 visit |

### 7.2.6. Asthma Exacerbations

For the analysis of exacerbations, the exacerbation follow-up time is defined as:

- For subjects completed the study: Date of Week 24 visit – Date of Baseline (Week 0) visit +1
- For subjects with early withdrawals: Date of Withdrawal – Date of Baseline (Week 0) visit + 1

The on-treatment assessment period for exacerbations is calculated from date of Baseline (Week 0) visit to date of Week 24 visit or early withdrawal (inclusive).

### 7.2.7. Concomitant Medication Derivation

Taken Before the Run-In: If medication start date < Date of Screening visit (Visit 1) (or medication start date is missing)

Run-In Period Medications:

- Medication start date < date of Screening visit (Visit 1) (or medication start date is missing) and medication stop date ≥ date of Screening visit (or medication stop date is missing), or
- Date of Screening visit ≤ medication start date < Date of first dose of study drug

On-Treatment Medications:

- Medication start date < date of first dose of study drug (or medication start date is missing) and medication stop date ≥ date of first dose of study drug (or medication stop date is missing), or
- Date of first dose of study drug ≤ medication start date ≤ date of last dose of study drug + 28 days
- Date of last dose of study drug is missing and the medication start date is on or after the date of first dose of study drug
- Medication start or stop date is missing or partial then the con-med will be considered on-treatment unless there is evidence to the contrary (e.g. month/year of con-med stop date is present and is before the month/year of study treatment start date).

Post-Treatment Medications:

- Medication start date is after the date of last dose of study drug + 28 days
- Medication stop date > date of last dose of study drug + 28 days or medication stop date is missing

### 7.2.8. Common Calculations

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 30$^{th}$ June (30 Jun YYYY).

Body Mass Index (kg/m$^2$) = Weight (kg)/Height (m)$^{2.}$

The predicted normal FEV1 and reversibility values are recoded in the CRF as per the protocol assessment visits. The predicted normal FEV1 is based on the NHANES III equations as described in the protocol and Asian equation will be used for Asian race.

Reversible is defined as an increase in FEV1 of ≥12% and ≥200mL following administration of bronchodilator (albuterol/salbutamol) at any protocol assessment visit.

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

A subject is considered achieved asthma control between Week 20 and Week 24 if he/she does not have a clinically significant exacerbation during this period between W20 and W24. The process for assessing clinically significant exacerbations of asthma is provided in Appendix9. Visit Windows.

Where a subject does not prematurely withdraw from the study, or the subject withdraws prematurely from the study at a scheduled visit, there are no plans to derive visit windows; visits will be used in the analyses as reported on the CRF.

For subjects prematurely withdrawing from the study, the EOS, unscheduled or IP discontinuation visit will initially be remapped to the next scheduled protocol specific assessment visit for each parameter, if the visit falls ±7 days of next scheduled planned visit (see below). Otherwise, the data will be remapped to the next planned scheduled visit. If there are more than one assessment associated with a particular visit interval, then the visit will be remapped to that with the closest target day. If subject having multiple records on same day for parameter (lab, ECG etc), then for continuous parameter data average value and for categorical parameter data, worst value will be presented. Please reframe the text accordingly.

| Visit | Target Day | Window (Days) |
|---|---|---|
| Visit 3 (Week 4) | 28 | 21 to 35 |
| Visit 4 (Week 8) | 56 | 49 to 63 |
| Visit 5 (Week 12) | 84 | 77 to 91 |
| Visit 6 (Week 16) | 112 | 105 to 119 |
| Visit 7 (Week 20) | 140 | 133 to 147 |
| Visit 8 (Week 24) | 168 | 161 to 175 |

Unless otherwise stated, unscheduled visits will be included in the data listings only. If an unscheduled visit is present because of a visit/assessment missed due to COVID-19 factors, the unscheduled assessment may be used for remapping. The unscheduled visits may be used for summaries related to 'any time post baseline' assessment.

### 7.2.10. MedDRA and WHO Drug Coding Versions

Where applicable, safety data will be coded using the following coding dictionaries:

| Dictionary | Version |
|---|---|
| Medical Dictionary for Regulatory Activities (MedDRA) | 26.0 |
| World Health Organization Drug Dictionary (WHO-DD) | March 2020 B3 |

### 7.2.11. Software Version

All analyses will be conducted using SAS version 9.4 or higher.

# 8. INTERIM ANALYSIS

No interim analysis is planned for this study.

# 9. SUBJECT CHARACTERISTICS AND STUDY CONDUCT SUMMARIES

## 9.1. SUBJECT DISPOSITION

Subject disposition table will be summarized based on the safety population. The following summaries

will be included in the disposition table:

- Total number of subjects enrolled in the study
- Total number of subjects screen failure
- Total number of subjects re-screened
- Total number of subjects passed screen but not received the treatment
- Total number of subjects in safety population
- Number of subjects who completed the study treatment
- Number of subjects who completed the study
- Number and percentage of subjects who discontinued from the study
- Number and percentage of subjects who pre-maturely discontinued the treatment as well as from the study along with reason for discontinuation.

Percentages will be based on the number of subjects in the safety population or enrolled population. Number and percentages of the reasons for study discontinuation is based on the total discontinued subjects.

A summary of reasons for screen failure, rescreen and the number of subjects included in the analysis population (Safety) will be presented based on all enrolled population. The percentages will be based on the number of subjects in all enrolled population.

In addition, the following summaries will be generated based on the safety population:

- Summary of inclusion, exclusion and induction phase criteria deviations
- Summary of important protocol deviations
- Summary of important protocol deviations related to COVID-19 pandemic
- Summary of visits impacted by COVID-19 pandemic

A by-subject listing of disposition will be provided for all enrolled population.

## 9.2. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Subjects' demographics and baseline characteristics will be summarized for the safety population.

Continuous variables (e.g., age and weight) will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Qualitative variables (e.g., sex and race) will

be summarized with counts and percentages.

The demographic parameters will include age, gender race height, weight and body mass index. Age will also be presented as a categorical variable (18-29 years, 30-49 years, 50-64 years and >=65 years). The baseline characteristics include:

- Asthma history and baseline disease characteristics which includes smoking history (never, current and former), age at onset (years) asthama diagnosis, time since diagnosis, asthma duration categories (1 to <5 years, 5 to <10 years, 10 to <15 years, 15 to <20 years, 20 to <25 years and >=25 years), experienced exacerbations in the previous 12 months, optimized OCS dose, duration of OCS dose prior to screening. Baseline optimized OCS dose also presented as a categorical variable (<7.5 mg/day, 7.5 to <15 mg/day, 15 to <30 mg/day and >=30 mg/day).
- Asthma exacerbations history which includes number of exacerbations (both descriptive and categorical), exacerbation types and causes of exacerbations in the previous 12 months.
- Family history of cardiovascular risk factors
- Past and current medical conditions
- Lung function test results at screening and baseline which includes pre- and post-bronchodilator $FEV_1$ (L), pre-bronchodilator percent predicted $FEV_1$ (%), pre-bronchodilator forced vital capacity (FVC) (L), reversibility (in mL and in %) and pre-bronchodilator FEV1/FVC.

By-subject listings of demographic and baseline characteristics will be provided for the safety populations.

## 9.3. MEDICATIONS

Medications will be coded using the latest available version of the Anatomical Therapeutic Chemical (ATC) classification text from the World Health Organization Drug Dictionary (WHO DD) and summarized separately for asthma and non-asthma medications. Asthma related medications will be presented by respiratory medication class and treatment period (prior treatment, on- treatment and post-treatment) and non-asthma related medications will be reported by ATC1 class and preferred name ingredients only for on-treatment period (concomitant). A by-subject listing of asthma and non-asthma medications will be provided for the safety population.

Medication that was started in the run-in period and stopped/continued during the on-treatment (concomitant) period will be included in both pre- treatment and on-treatment (concomitant) period summaries.

# 10. STATISTICAL ANALYSIS

All analyses of safety data and efficacy data will be generated for the Safety Population. All p values and 2-sided confidence intervals will be considered nominal without multiplicity control. Additionally, separate subgroup analyses will also be generated by with/without baseline maintenance OCS use (with separate summaries in those participants receiving maintenance OCS at baseline and those not maintenance OCS at baseline).

## 10.1. EFFICACY ANALYSIS SRATEGY

### 10.1.1. SECONDARY EFFICACY ENDPOINTS

There are no primary efficacy endpoints defined for this study. The efficacy analysis is defined in terms of secondary and other efficacy endpoints as below:

### 10.1.2. Secondary Endpoints:

- Number of clinically significant exacerbations.
- Number of exacerbations requiring hospitalization or ED visits
- Number of exacerbations requiring hospitalization
- Change from baseline in clinic pre-bronchodilator FEV1 at week 24
- Change from baseline in clinic post-bronchodilator FEV1 at week 24
- Change from baseline in ACQ-5 score at week 24
- Change from baseline in morning PEF during weeks 20 – 24.

### 10.1.2. Health Outcome Endpoints:

- Clinician and Subject rated response to therapy at Week 24
- Mean change from baseline in WPAI-GH composite scores (percentage) at week 24:
    - Percent work time missed due to general health
    - Percent impairment while working due to general health
    - Percent overall work impairment due to general health
    - Percent activity impairment due to general health

### 10.1.3. Exploratory Endpoints:

CCI

[redacted]

## 10.2. STATISTICAL METHODS FOR SECONDARY EFFIACACY ENDPOINTS

### 10.2.1. Asthma Exacerbations:

The number of clinically significant asthma exacerbations (including exacerbations requiring hospitalization or ED visits) that occur while on treatment will be analyzed using Negative Binomial regression using generalized linear model with a covariate of time period (pre-, post-mepolizumab as ordinal variable) with follow-up time within each period included as an offset within the model. The exacerbation rates during the pre- and post-treatment with mepolizumab will be presented, including comparison of pre- and post-mepolizumab exacerbation rates along with the with 95% confidence limits and corresponding p-value. Exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation. The following SAS code will be used:

```
proc genmod data=modeldata plots=all;
    class period usubjid;
    model exbnum = period / dist = negbin link=log offset = logtime type3;
    repeated subject = usubjid / type=UN corrw withinsubject = period;
    lsmeans period / exp cl;
    estimate "Period ratio" period -1 1 / exp;
run;
```

where exbnum = number of clinically significant asthma exacerbations

period = pre- and post- mepolizumab treatment periods in which the exacerbation occurred

logtime = $\log_e$ (length of time in years in pre- mepolizumab and post- mepolizumab periods)

Length of time (years) in study will be calculated as length of time (days)/365.25.

An unstructured covariance structure will be used in the model. If there are any convergence issue, then an alternative exchangeable or compound symmetric, autoregressive (AR (1)), Toeplitz covariance structure will be used. The variance of the mean estimate will be corrected for within-subject correlation by using REPEATED statement for subject in the GENMOD procedure.

The period of time for which exacerbation information will be included in the post-mepolizumab period will be from the start of treatment until the week 24 visit, regardless of treatment discontinuation. For

those participants with premature study withdrawal, the time period will include from the start of treatment until the date of withdrawal. Missing data (following early withdrawal) will be assumed to be missing at random (MAR) following subject withdrawal from the study.

In addition, a similar analysis will be conducted for frequency of exacerbations requiring hospitalization or ED visits and frequency of exacerbations requiring hospitalization if there are enough subjects in the corresponding category.

Treatment policy strategy will be used for intercurrent event treatment discontinuation (for any reason). This will estimate the treatment effect at the end of the 24 week study period regardless of treatment discontinuation.

**Treatment policy strategy**: The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest. The value for the variable of interest is used regardless of whether or not the intercurrent event occurs.

Counts and percentage of subjects with any exacerbations, any clinically significant exacerbations, any exacerbations requiring hospitalization or ED visit and any exacerbations requiring hospitalization during the treatment period will be provided for the safety population. The same output will also be presented regardless of treatment discontinuation. In such case even if a patient not received the treatment but passed the screening and discontinued are also counted for the variable of interest.

The rate of exacerbations requiring hospitalization or ER visit and rate of exacerbations requiring only hospitalization during the on-treatment period will be analysed using Negative Binomial regression model similar to the analysis for the rate of clinically significant exacerbations as described above. In addition, counts and percentage of subjects with the number of exacerbations (eg. 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, >=10) during the on-treatment period will be presented.

### 10.2.2. Forced Expiratory Volume in 1 second (FEV1)

Analysis of change from baseline in clinic pre-bronchodilator FEV1 at Week 8, Week 16 and Week 24 will be performed using a mixed models repeated measures (MMRM) analysis, including visit and asthma exacerbations in the year prior to the study (as an ordinal variable – 0, 1, 2, 3+) and baseline maintenance OCS use (yes, no) (binary nominal variable) as an as covariates. Change from baseline in pre-bronchodilator FEV1 value along with a two-sided 95% confidence interval and p-value estimated from MMRM model will be presented. The following SAS code will be used:

```
proc mixed data=modeldata;
    class usubjid avisitn;
    model chg = avisitn BASEOCSD PEXACCTN / solution ddfm=kr cl htype=3;
    lsmeans avisitn / cl pdiff e;
```

```
    repeated avisitn / subject= usubjid type=un;
run;
```

Where, chg = change from baseline in clinic pre-bronchodilator FEV1 at Week 8, Week 16 and Week 24
Avisitn = Visit
BASEOCSD = baseline maintenance OCS use (Yes/No)
PEXACCTN = asthma exacerbations in the year prior to the study

An unstructured covariance structure will be used in the model. If there are any convergence issue, then an alternative compound symmetric, autoregressive (AR(1)), Toeplitz covariance structure will be used.

Treatment policy strategy will be used for treatment discontinuation (for any reason). This will estimate the treatment effect at the end of the 24 week study period regardless of treatment discontinuation.

Treatment policy strategy: The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs.

A similar analysis will be conducted for the post-bronchodilator FEV1 value at Week 24. In addition, descriptive summaries for the actual and change from baseline values for pre- and post-bronchodilator FEV1 will be presented by scheduled visits.

### 10.2.3. Asthma Control Questionnaire (ACQ-5)

The ACQ-5 questionnaire consists of the 5 symptoms questions scored on a 7-point scale from 0 = CCI to 6 = CCI. The questions are equally weighted and the ACQ-5 score will be the mean of the 5 questions. If a subject does not complete 1 of the 5 questions at a visit, then the ACQ-5 score will be the mean of the responses to the remaining 4 questions at that visit. If a subject does not complete more than 1 of the 5 questions at a visit, then their ACQ-5 score will be set to missing at that visit.

Analysis of change from baseline in ACQ score at each scheduled visit will be performed using a mixed model repeated measures (MMRM) analysis described in section 10.2.2. including visit and asthma exacerbations in the year prior to the study (as an ordinal variable – 0, 1, 2, 3+) and baseline maintenance OCS use (yes, no) (binary nominal variable) as covariates. Change from baseline in ACQ scores along with two-sided 95% confidence intervals and p-values estimated from MMRM model will be presented by visit.

In addition, descriptive summaries for the actual and change from baseline values in ACQ scores will be presented by scheduled visits.
Treatment policy strategy will be used for treatment discontinuation (for any reason). This will estimate the treatment effect at the end of the 24 week study period regardless of treatment discontinuation.

Treatment policy strategy: The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs.

### 10.2.4. Peak Expiratory Flow (PEF)

Analysis of change from baseline in morning PEF during each 4-weeks reporting period of Weeks 1-4, Weeks 5-8, Weeks 9-12, Weeks 13-16, Weeks 17-20 and Weeks 21-24 will be performed using a mixed models repeated measures (MMRM) analysis described in section 10.2.2, including reporting period and asthma exacerbations in the year prior to the study (as an ordinal variable – 0, 1, 2, 3+) and baseline maintenance OCS use (yes, no) (binary nominal variable) as covariates. Change from baseline in morning PEF along with two-sided 95% confidence intervals and p-values estimated from MMRM model will be presented.

All data will be included in the endpoint analysis will be from the start of treatment until the week 24 visit, regardless of treatment discontinuation.

Comparisons will be Weeks 20–24 vs. Baseline, and all data collected up to and including Weeks 20–24, including participants who have discontinued study treatment, will be included in the analyses. Missing data (following early withdrawal) will be assumed to be missing at random (MAR) following subject withdrawal from the study.

In addition, descriptive summaries for the actual and change from baseline values in morning PEF values will be presented by 4-weeks reporting period.
Treatment policy strategy will be used for treatment discontinuation (for any reason). This will estimate the treatment effect at the end of the 24 week study period regardless of treatment discontinuation.
Treatment policy strategy: The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs.

## 10.3. STATISTICAL METHODS FOR HEALTH OUTCOME ENDPOINTS

### 10.3.1. Clinician and Subject Rated Response to Therapy:

The clinician and subject rated overall evaluation of response to therapy at Week 8, Week 16 and Week 24 will be assessed using a 7-point scale: 1 = CCI [redacted], 2 = CCI [redacted], 3 = CCI [redacted], 4 = CCI [redacted], 5 = CCI [redacted], 6 = CCI [redacted], 7 = CCI [redacted]. Counts and percentage of subjects with each response category will be summarized separately for clinician and subject rated overall evaluation of response to therapy by scheduled visit.
Treatment policy strategy will be used for treatment discontinuation (for any reason). This will estimate the treatment effect at the end of the 24 week study period regardless of treatment discontinuation.

Treatment policy strategy: The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs.

### 10.3.2. Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH)

The WPAI-GH is a self or interviewer administered tool comprised of 6 questions which address absenteeism, presenteeism (reduced effectiveness while working), overall work productivity loss (absenteeism plus presenteeism), and activity impairment based on the data from the past 7 days. The WPAI-GH responses are scored as impairment percentages, with a higher percentage indicating greater impairment and less productivity. The following WPAI-GH composite scores will be derived:

- Percent work time missed due to health: Q2/(Q2 + Q4)
- Percent impairment while working due to health: Q5/10
- Percent overall work impairment due to health: Q2/(Q2+Q4) +[(1-Q2/(Q2+Q4)) x (Q5/10)]
- Percent activity impairment due to health: Q6/10

The above WPAI-GH composite scores and change from baseline will be summarized by visit using number of subjects, mean, SD, median, minimum and maximum values.
Treatment policy strategy will be used for treatment discontinuation (for any reason). This will estimate the treatment effect at the end of the 24 week study period regardless of treatment discontinuation.

Treatment policy strategy: The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs.

## 10.4. STATISTICAL METHODS FOR EXPLORATORY ENDPOINTS

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

**Nasal polyps assessment:**

Nasal polyps assessment will be performed at Screening (Visit 1) and at IP discontinuation/Week 24 (EOS) visits. Shift from baseline to Week 24/EOS in nasal polyps categories (Present, absent, missing/not assessed) will be presented.

**Analysis of blood eosinophilis and Serum IgE(total):**

Analysis of ratio to baseline in blood eosinophils and Serum IgE (Total) will be performed using a

mixed model repeated measures (MMRM) analysis as described in section 10.2.3 including visit, baseline maintenance OCS dose and asthma exacerbations in the year prior to the study (as an ordinal variable – 0, 1, 2, 3+) as covariates. The analysis will be conducted using $\log_e$ scale transformed values for blood eosinophils. The model will be used to estimate the ratio to baseline at each scheduled visit with 95% confidence limits and corresponding p-value.

In addition, descriptive summaries will be presented for blood eosinophils and Serum IgE (Total) at each scheduled visits using number of subjects, geometric mean, geometric SD, median, minimum and maximum values.

## 10.5. SUBGROUP ANALYSIS

Subgroup analysis will be done according to subjects received OCS at baseline (yes, no).

## 10.6. MULTIPILICTY

There will be no hypothesis test is planned. Hence, no adjustment for the multiple comparison is required.

## 10.7. IMPUTATION OF MISSING DATA

Missing values will be treated as missing unless and otherwise specified. If a subject experience a clinically significant asthma exacerbation between Weeks 20-24, then for the purpose of assessing percentage of subjects achieving at least 50% reduction in OCS dose during the weeks 20-24, the subject will be imputed into the worst-case category of ‘no reduction in OCS Dose’. For the analysis of median percent OCS reduction during weeks 20-24, the subject will be imputed using the maximum dose of OCS observed during the 4-Weekly period across all participating subjects.

# 11. SAFETY ANALYSIS STRATEGY

All analyses described in this section will be performed on the safety population. All safety analyses will be reported separately of the subjects receiving baseline OCS use (yes, no). The results will be descriptive in nature. Safety will be assessed based on the following assessments:

- Extent of Exposure
- Adverse Events

- Clinical Laboratory Evaluation
- Immunogenicity
- Vital Signs
- 12 Lead ECG
- Steroid toxicity and withdrawal

## 11.1. EXTENT OF EXPOSURE

The total exposure to mepolizumab is calculated as the date of last dose of mepolizumab minus the date of first dose of mepolizumab plus 29 minus periods of interruptions (in days). Subjects who entered into induction phase but did not report any treatment dates will be categorized as having zero days of exposure. The extent of exposure will be summarized as number of injections administered and number of days on treatment.

Interruption period is calculated as the date of dose of mepolizumab after interruption period minus the date of interruption period of mepolizumab or the date of missed dose of mepolizumab.

## 11.2. ADVERSE EVENTS

The applicable definition of an Adverse Event (AE) is in the study protocol Sections 8.3 and 10.3. All AEs occurring from when a subject sign informed consent to when a subject exits the study will be accounted for in the reporting. AEs occurring pre-treatment, on-treatment and post-treatment periods will be summarized for the safety population.

A pre-treatment AE is defined as any AE with an onset date before the date of first exposure to the study drug. An on-treatment-AE is an event does not present prior to first exposure to the study drug or any pre-existing event that worsens following exposure to study drug until the last exposure to the study drug plus 28 days inclusive. Any AE which occurs after 28 days of last exposure to the study drug will be considered as post-treatment AEs. All AEs will be coded using the MedDRA central coding dictionary (26.0) and grouped by body system and preferred term. See Appendix 1 for imputation of partial dates for AEs. Imputed dates will be used to determine on-treatment status.

The following summaries will be generated for adverse events:

- AEs by treatment period (on and post-treatment), SOC and PT
- Common (>=3%) non-serious on-treatment AEs by SOC and PT

- AE occurred on the day of dosing by SOC and PT
- On-treatment drug-related AEs by SOC and PT
- AEs leading to permanent discontinuation or withdrawal from study by SOC and PT
- Serious AEs by treatment period (pre, on and post-treatment), SOC and PT
- Non-fatal SAE by treatment period (pre, on and post-treatment), SOC and PT
- Fatal SAE by treatment period (on and post-treatment), SOC and PT

Events with missing relationship to the study drug is considered as related. In addition, a summary of overall AEs during the study duration will be presented which includes:

- Subjects with at least one AE
- Subjects with at least one drug-related AE
- Subjects with AE leading to premature discontinuation
- Subjects with at least one serious AE
- Subjects with at least one drug-related serious AE
- Subjects with at least one AE leading to death
- Any on-treatment AEs
- Any on-treatment SAEs

The following listings will be generated:

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

### 11.2.1. Adverse Events of Special Interest

Adverse events of special interest (AESIs) are adverse events associated with the identified and potential risks of mepolizumab. AESIs of systemic reactions (including systemic reactions meeting Sampson's criteria for anaphylaxis) and local injection site reactions are collected via targeted eCRF pages within the study. Events captured on the eCRF as systemic reactions will be further categorized by the investigator as 'allergic (type I hypersensitivity) reactions' or 'systemic other reactions. AESIs of opportunistic Infections, malignancies, serious cardiac, vascular and thromboembolic (CVT) events

and serious ischemic events will be identified using structured MedDRA query as defined in Appendix xx. The following AESIs will be summarized only for the on-treatment period:

- Events Reported by the Investigator as Systemic Reactions - Allergic (Type I Hypersensitivity) by PT
- Events Reported by the Investigator as Systemic Reactions – Other Reactions by PT
- Systemic Reactions Reported by the Investigator as Meeting the Criteria for Anaphylaxis by PT
- Events Reported by the Investigator as Local Injection Site Reactions by PT
- Potential Opportunistic Infections by PT
- Malignancies by PT
- Serious Cardiac, Vascular and Thromboembolic AE by PT
- Serious Ischemic AEs by PT

A subject listing will be provided for each of the AESI categories.

### 11.2.2. Cardiovascular Events

The following cardiovascular events will be captured on targeted CV event pages of the eCRF:

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

Counts and percentage of subjects with on-treatment cardiovascular events will be summarized. A subject listing will be provided.

### 11.2.3. Liver Events

A listing of all subjects with liver events will be presented with the following details:

- Time from the start of study treatment to the liver event and the time from the most recent study treatment to the liver event.
- Size, final diagnosis and abnormalities of liver biopsy.
- Alcohol intake and medical conditions at onset of liver event
- Liver imaging abnormalities

### 11.2.4. Steroid Toxicity and Withdrawal

Steroid toxicity and withdrawal will be summarized descriptively which includes:

- Prior duration of OCS use (<1 year, 1 to <5 years, 5 to <10 years, 10 to <15 years, 15 to <20 years, 20 to <25 years, >=25 years)
- Baseline optimized OCS dose both categorical (>0 - 5mg, >5 - 10mg, >10 - 15mg, >15 - 20mg, >20 - 25mg, >25 - 30mg, >30 - 35mg and >35mg).
- Baseline medical conditions specifically summarizing the status (past, current, no medical condition) of the following: hypertension, endocrine disorders, eye disorders, metabolism and nutritional disorders, nervous system disorders, and bone fractures.
- Observed and change from baseline in body weight at each visit
- Observed and change from baseline in glucose levels at each visit

### 11.2.5. Adverse Event Pertaining to COVID-19

A summary of on-treatment adverse events for subjects with COVID-19 suspected, probable and confirmed COVID-19 diagnosis by system organ class and preferred term will be presented.

## 11.3. CLINICAL LABORATORY EVALUATIONS

Clinical laboratory evaluations include hematology, clinical chemistry, and urinalysis. A list of laboratory assessments to be included in the outputs are given below:

**Hematology:** Hematocrit, Hemoglobin, Mean corpuscular hemoglobin (MCH), Mean corpuscular volume (MCV), Platelet count, Red blood cell (RBC) count, White blood cell (WBC) count, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils and Reticulocytes.

**Clinical chemistry:** ALP, ALT, AST, total bilirubin, direct bilirubin, Total Protein, Blood Urea Nitrogen, Creatinine, Glucose (non-fasting Random), Potassium, Sodium and Calcium.

**Urinalysis:** microscopy (epithelial cells, RBCs, pus cells (WBC), Dysmorphic RBC, casts, and crystals); and urine chemistry (specific gravity, pH, protein, glucose, bilirubin, urobilinogen, ketones and protein (Albumin))

**Serology:** Hepatitis B surface antigen (HBsAg) and Hepatitis C virus antibody.

The assessment timepoints for the laboratory parameters are provided in the following table.

| Laboratory Parameters | Assessment Time Points |
|---|---|
| Hematology | Screening (Visit 1), Week 0, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24 (EOS) |
| Clinical Chemistry | Screening (Visit 1), Week 0, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24 (EOS) |
| Urinalysis | Screening (Visit 1) |
| Serum IgE (total) | Pre-Screen, Screening (Visit 1) Week 0 |
| Serology | Screening (Visit 1) |
| Pregnancy Test | Screening (Visit 1), Week 0, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24 (EOS) |

If a laboratory value which is expected to have a numeric value for summary purposes, has a character value with '<x' or '>x', the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.

- Example 1: 2 Significant Digits = '<x' becomes x – 0.01
- Example 2: 1 Significant Digit = '<x' becomes x – 0.1
- Example 3: 0 Significant Digits = '<x' becomes x – 1

Actual value and change from baseline (for quantitative measurements) will be summarized for hematology and clinical chemistry parameters at each scheduled visit. Shift from baseline to Week 24/EOS visits according to normal range criteria (for quantitative measurements) will be presented for hematology and clinical chemistry parameters. No summaries will be provided for urinalysis and serology parameter results.

A by-subject listings of all laboratory parameters will be provided which includes scheduled and unscheduled visits that clearly indicate the out of normal range values (where applicable) and possible abnormal values for the safety population.

## 11.4. IMMUNOGENICITY

Immunogenicity is a measure of the immune response to a therapeutic drug (e.g. a monoclonal antibody) resulting in generation of anti-drug antibodies. Clinical samples are tested in a sequence of binding anti-drug antibody (ADA) and neutralizing antibody assays:

- Screening assay- Each sample is tested for the presence of anti-drug antibodies (ADA assay) and initially declared positive or negative according to assay cut-off criteria. Positive samples are then tested in the confirmation ADA assay. Negative samples are not tested further.
- Confirmation assay- Each positive sample from the screening assay is then confirmed positive in this assay or is declared negative. Positive samples are then tested in the neutralization (NAb) assay.
- Titration assay- Each positive sample from the confirmation assay is assessed using serial dilution to provide a titre, corresponding to the highest dilution factor that still yields a positive test result.

A table will be produced summarizing the number and percentage of confirmed positive and negative ADA samples in each treatment group in the Safety Population. The table will also be summarized the highest assay results obtained post-baseline.

A similar table will also be produced summarizing results for the neutralizing antibody assay in the Safety Population, by visit.

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

## 11.5. VITAL SIGNS

Vital Signs parameters include blood pressure (systolic and diastolic), pulse rate, respiratory rate, oral/auxiliary temperature, height and weight. Vital signs assessment will be conducted at all study visits. Vital sign parameter values and changes from baseline will be summarized using descriptive statistics by visits. A by-subject listing will be provided for all vital sign parameters which includes scheduled and unscheduled visits.

## 11.6. 12-LEAD ELECTROCARDIOGRAM

A 12-Lead ECG will be performed at Screening, Week 0, Week 8, Week 16 and Week 24 visits. The

following ECG parameters will be assessed at each scheduled study visits:

- Heart Rate (bpm)
- QRS Interval (msec)
- PR Interval (msec)
- RR Interval (msec)
- QT interval (msec)
- QTc Interval (msec)
- QTcF (msec)
- QTcB (msec)
- Overall Interpretation

Where triplicate ECG evaluations were performed, the mean value for each subject will be used for the calculation of summary statistics. The data on QTc(B) was not collected in the CRF and will be derived using the following formula.

$$QTc(B) = \frac{QT}{\sqrt{RR/1000}}$$

Descriptive summaries will be presented for the ECG parameter values and change from baseline by visit for all quantitative measurements. Overall interpretation of ECG clinical assessment will be summarized by counts and percentages. At each timepoint, QT, QTcF and QTcB will be categorized as follows, and the category based on actual value will be summarized at each visit as well as the category at each post-baseline visit based on change from baseline per the following criteria:

| Type of Value | Category 1 | Category 2 | Category 3 |
|---|---|---|---|
| Actual value | > 450 ms | > 480 ms | >500 ms |
| Change from Baseline | > 30 ms | >60 ms | |

Counts and percentages for subjects with the above categories for QT, QTcF and QTcB (>450 ms, >480 ms and >500 ms) parameter values and change from baseline (>30 ms increase, >60 ms increase and >500 ms or >60 ms increase) will be summarized at each visit. A by-subject listing of all ECG parameters will be provided which includes scheduled and unscheduled visits.

# 12 PROGRAMMING CONSIDERATIONS

All tables, figures, listings (TFLs), and statistical analyses will be generated using SAS for Windows, Release 9.4 or higher (SAS Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

- One SAS program can create several outputs.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format.
- Numbering of TFLs will follow ICH E3 guidance.
- All tables and listings will be produced in landscape orientation. Figures use the orientation that best facilitates interpretation of the data
- All TFLs will be produced using the Courier New font, size 10. The smallest acceptable point size for the Regulatory Authorities is 8.
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- TFLs will be in black and white (no color), unless otherwise specified.
- The TLFs with subgroup analysis based on OCS dose at baseline Yes/No, the each subgroup category to be printed on the left side. The overall results should be presented first, followed by Baseline OCS=Yes, Baseline OCS=No.
- Specialized text styles, such as bolding, italics, borders, shading, and color are not used in the tables and listings, unless otherwise specified. Color may be used in figures containing multiple plotted lines as long as information is not lost when the figure is reproduced in monotone.
- Mixed case will be used for titles, footnotes, column headers, and programmer-supplied formats, as appropriate.
- For categorical parameters, all categories will be presented in the table, even if n=0 for all treatment groups in a given category. For example, the frequency distribution for symptom severity would appear as:

| Severity Rating | n |
|---|---|
| Mild | 2 |
| Moderate | 5 |
| Severe | 0 |

- An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean, median, Q1 and Q3 for a set of values will be printed out to 1 more significant digit than the original values, and standard deviations and standard errors will be printed out to 2 more significant digits than the original values. The minimum and maximum will report the same significant digits as the original values.
- Confidence intervals are displayed within round brackets and separated by a comma. The lower limit is presented first, and the upper limit is presented second. The confidence interval is placed either beside or below the corresponding estimate. The estimate and the confidence limits are presented using the same degree of precision.
- P-values will be output in the format: '0.xxx', where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value is returned as >0.999, then present as >0.999.
- Percentage values will be printed to one decimal place. Unless otherwise noted, for all percentages, the number of subjects in the analysis population for the treatment group who have an observation will be the denominator. Percentages after zero counts will not be displayed and percentages equating to 100% will be presented as 100%, without decimal places.
- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data will be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (Medication class), and adverse events (by preferred term) will be displayed in decreasing order. If incidence for more than 1 term is identical, they will then be sorted alphabetically.
- Missing descriptive statistics or p-values which cannot be estimated will be reported as '-' Missing values for numeric and character variables are displayed as blanks in data listings
- The percentage of subjects will normally be calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis population presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Details will be described in footnotes or programming notes, as necessary.
- If no relevant data are available at all for a display, then present "No data to Report".

# APPENDIX 1. MISSING DATE PROCEDURE

**Prior/Concomitant Medications**

For the purpose of assessing whether a medication is prior or concomitant, if a medication has a completely missing start date it will be considered a prior medication, and if a medication has a completely missing stop date it will be considered a concomitant medication. If a partial start or stop date occurs, the following imputation process will be implemented:

| Partial Missing Start or Stop Date | Imputation for Start Date | Imputation for Stop Date |
|---|---|---|
| Day missing, month and year present | • Month and/or year different to month and year of first study drug dose: Impute day with "01"<br>• Month and/or year same as month and year of first study drug dose: Impute day with same day as first dose of study drug. | Impute day with last day of the month |
| Day and month missing, year present | • Year different to year of first study drug dose: Impute day and month with "01JAN"<br>• Year same as year of first study drug dose: Impute month and day with same month and day as first dose of study drug. | Impute day and month with "31DEC" |
| Month missing, day and year present | • Year different to year of first study drug dose: Impute month with "JAN"<br>• Year same as year of first study drug dose: Impute month with same month as first dose of study drug. | Impute with "DEC" |
| Caveats | • If any imputed start date leads to a start date that is after the stop date, then the start date will be imputed with the date of the stop of medication.<br>• No stop date will be imputed if the treatment is ongoing. | |

**Adverse Events**

For the purpose of assessing whether an AE is on on-treatment the following imputation will be used. If the last dose of study drug is missing and the AE start date is on or after the first dose of study drug then the AE will be considered as on-treatment. If the AE start date is missing or partial then the AE will be considered on-treatment unless there is evidence to the contrary (e.g. month/year of onset date is present and is earlier than the month/year of first dose of study medication).

For assessing on-treatment or for calculation of duration of AE, if a partial start or stop date occurs, the following imputation process will be implemented:

| Partial Missing Start or Stop Date | Imputation for Start Date | Imputation for Stop Date |
|---|---|---|
| Day missing, month and year present | • Month and/or year different to month and year of first study drug dose: Impute day with “01”.<br>• Month and/or year same as month and year of first study drug dose: Impute day with same day as first dose of study drug. | Impute day with last day of the month |
| Day and month missing, year present | • Year different to year of first study drug dose: Impute day and month with “01JAN”.<br>• Year same as year of first study drug dose: Impute month and day with same month and day as first dose of study drug. | Impute day and month with “31DEC” |
| Month missing, day and year present | • Year different to year of first study drug dose: Impute month with “JAN”.<br>• Year same as year of first study drug dose: Impute month with same month as first dose of study drug. | Impute with “DEC” |
| Caveats | • If any imputed start date leads to a start date that is after the stop date, then the start date will be imputed with the date of the stop of AE. | |

# APPENDIX 2. CORTICOSTEROID CONVERSION FACTORS

All corticosteroids administered via oral, IV and IM routes are to be considered when calculating a subject's daily prednisone/prednisolone dose regardless of reason for administration. All steroids administered via a sublingual route will also be considered as oral.

The following 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. If there are seen to be two corticosteroid records 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 |
| 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 |

| Standardized Medication Name | Scaling Factor |
|---|---|
| Prednisolone Sodium Succinate | 1 |
| Prednisone | 1 |
| Prednisone Acetate | 1 |
| Triamcinolone | 1.25 |
| Triamcinolone Acetonide | 1.25 |

# APPENDIX 3. ASSESSMENT VISIT WINDOWS FOR EDIRARY DEVICE VARAIBLES

The following assessments will be collected daily using an eDiary device:

- Morning peak flow
- Number of occasions of usage of rescue medication (i.e. salbutamol)
- Asthma symptom score
- Frequency of awakening due to asthma symptoms requiring use of rescue medication
- ACQ scores

To derive 4-weekly average values, the following assessment visit window will be used:

| Reporting Period | First Day Included | Last Day Included |
|---|---|---|
| Baseline | 7 days prior to Visit 2 | Day 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 | Week 24 visit date (or 168 days after day of first dose if earlier) |

The average 4-weekly values will be derived based on the non-missing values in the corresponding period 4-weekly period. At least 7 days of eDiary parameter data is required in the corresponding 4-weekly period to get the reliable estimate.

The ACQ scores, which are collected weekly using the eDiary device will be summarized in a weekly period using the following assessments:

| Reporting Period | First Day Included | Last Day Included | Multiple ACQ scores in period |
|---|---|---|---|
| Optimisation Phase | All days prior to study day -4 | | Not to be summarised |
| Baseline | Study day -7 | Study day 1 | Take score closest to day 1 |
| Week 1 | Study day 2 | Study day 12 | Take score closest to day 8 |
| Week 2 | Study day 13 | Study day 19 | Take score closest to day 15 |
| Week 3 | Study day 20 | Study day 26 | Take score closest to day 22 |
| Week 4 | Study day 27 | Study day 33 | Take score closest to day 29 |
| Week 5 | Study day 34 | Study day 40 | Take score closest to day 36 |
| Week 6 | Study day 41 | Study day 47 | Take score closest to day 43 |
| Week 7 | Study day 48 | Study day 54 | Take score closest to day 50 |

| Reporting Period | First Day Included | Last Day Included | Multiple ACQ scores in period |
|---|---|---|---|
| Week 8 | Study day 55 | Study day 61 | Take score closest to day 57 |
| Week 9 | Study day 62 | Study day 68 | Take score closest to day 64 |
| Week 10 | Study day 69 | Study day 75 | Take score closest to day 71 |
| Week 11 | Study day 76 | Study day 82 | Take score closest to day 78 |
| Week 12 | Study day 83 | Study day 89 | Take score closest to day 85 |
| Week 13 | Study day 90 | Study day 96 | Take score closest to day 92 |
| Week 14 | Study day 97 | Study day 103 | Take score closest to day 99 |
| Week 15 | Study day 104 | Study day 110 | Take score closest to day 106 |
| Week 16 | Study day 111 | Study day 117 | Take score closest to day 113 |
| Week 17 | Study day 118 | Study day 124 | Take score closest to day 120 |
| Week 18 | Study day 125 | Study day 131 | Take score closest to day 127 |
| Week 19 | Study day 132 | Study day 138 | Take score closest to day 134 |
| Week 20 | Study day 139 | Study day 145 | Take score closest to day 141 |
| Week 21 | Study day 146 | Study day 152 | Take score closest to day 148 |
| Week 22 | Study day 153 | Study day 159 | Take score closest to day 155 |
| Week 23 | Study day 160 | Study day 166 | Take score closest to day 162 |
| Week 24 | Study day 167 onwards | | Take score closest to day 169 |

# APPENDIX 4. CLINICALLY SIGNFICANT EXACERBATIONS

Clinically significant exacerbations of asthma is defined as the worsening of asthma, which requires use of systemic corticosteroids. Exacerbations will be treated per the investigator's clinical practice protocol with the use of oral or parenteral corticosteroids.

Clinically significant exacerbations recorded in the eCRF by the Investigator or designee will be verified using data from the eDiary to confirm that the exacerbation was associated with changes in peak flow, rescue medication use, nocturnal awakening due to asthma symptoms requiring rescue medication use or worsening of asthma symptom score. In the case that an event described as a clinically significant exacerbation is not associated with deterioration in at least one of these objective eDiary parameters, the investigator will be asked to provide an explanation to support the decision for defining the event as an exacerbation. In those circumstances where the event cannot be supported by any objective assessment, the case will not be included as a protocol defined exacerbation but will be included as an investigator defined exacerbation. This verification process will be overseen by GSK clinical staff to ensure consistency.

For safety reasons alerts will be programmed into the eDiary to encourage the participant to contact the investigator if their asthma worsens. However, an alert in itself will not be classified as a clinically significant exacerbation.

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