# TITLE PAGE

**Division:** Worldwide Development
**Information Type:** Protocol Amendment

| | |
|---|---|
| **Title:** | Study 201312: A Multi-Centre, Open-Label, Study of Mepolizumab in a Subset of Subjects with a History of Life Threatening/Seriously Debilitating Asthma Who Participated in the MEA115661 Trial |

**Compound Number:** SB-240563

**Development Phase:** IIIb

**Effective Date:** 06-JUL-2015

**Protocol Amendment Number:** 03

**Author (s):** PPD

**Revision Chronology**

| **GlaxoSmithKline Document Number** | **Date** | **Version** |
|---|---|---|
| 2013N187987_00 | 2014-FEB-11 | Original |
| 2013N187987_01 | 2014-JUN-27 | Amendment No. 1 |
| The primary purpose of Amendment 01 is to change three entry criteria to ensure those subjects with a history of seriously debilitating asthma and a history of improved disease control continue to receive mepolizumab in 201312. The amendment also includes a number of additional corrections and edits (Appendix 7). | | |
| 2013N187987_02 | 2014-NOV-14 | Amendment No. 2 |
| The primary reason for Amendment 2 is to insert entry criterion No. 8. There are also minor changes to clarify the subject scenarios added during Amendment 1 and an administrative change to update the Medical Monitors. | | |
| 2013N187987_03 | 2015-JUN-19 | Amendment No. 3 |
| The primary reason for Amendment 3 is to increase the treatment duration and to remove the Follow-up visit. There is also a change to the IP administration process and clarification to the IP post dose monitoring process. The amendment also includes a standardisation of the collection of concomitant medications (Appendix 9). | | |
| 2013N187987_04 | 2015-JUL-06 | Republishing Protocol Amendment 3 |
| To correct some errors in Appendix 9 to reflect the amendments made within the main protocol. | | |

**SPONSOR SIGNATORY**

PPD

July 6, 2015.

Hector Ortega MD, ScD Date

Director,
Respiratory Therapeutic Unit
Research & Development

# SPONSOR INFORMATION PAGE

**Clinical Study Identifier: 201312**

**Sponsor Legal Registered Address:**

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

**Sponsor Contact Address**

GlaxoSmithKline Research & Development Limited
Iron Bridge Road
Stockley Park West, Uxbridge, Middlesex, UB11 1BU, UK
Telephone: PPD

GlaxoSmithKline Research & Development Limited
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: PPD

**Sponsor Global Medical Monitor Contact Information**:

PPD MA MSc. MBBS FFPM (Clinical Development Physician)
Tel: PPD
Mobile: PPD

**Sponsor Global Back-up Medical Monitor Contact Information:**

PPD MD (Clinical Development Physician)
Tel: PPD
Mobile: PPD

**Sponsor Serious Adverse Events (SAE) Contact Information:**

PPD MD (Clinical Development Physician)
Tel: PPD
Mobile: PPD

**Regulatory Agency Identifying Number(s):**

IND No. 006971; EudraCT No. 2014-000314-54

# INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 201312

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

| | |
|---|---|
| Investigator Name: | |
| Investigator Address: | |
| Investigator Phone Number: | |

| | |
|---|---|
| | |
| Investigator Signature | Date |

## TABLE OF CONTENTS

**PAGE**

LIST OF ABBREVIATIONS ..... 9

PROTOCOL SUMMARY ..... 11

1. INTRODUCTION ..... 14
   - 1.1. Background ..... 14
   - 1.2. Rationale ..... 15
   - 1.3. Benefit:Risk Assessment ..... 15
     - 1.3.1. Risk Assessment ..... 16
     - 1.3.2. Benefit Assessment ..... 20
     - 1.3.3. Overall Benefit:Risk Conclusion ..... 20

2. OBJECTIVE(S) ..... 21

3. INVESTIGATIONAL PLAN ..... 21
   - 3.1. Study Design ..... 21
   - 3.2. Discussion of Design ..... 23

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA ..... 24
   - 4.1. Number of Subjects ..... 24
   - 4.2. Inclusion Criteria ..... 24
   - 4.3. Exclusion Criteria ..... 26
   - 4.4. Withdrawal Criteria ..... 27
     - 4.4.1. Subject Compliance with Visit Schedule ..... 27
     - 4.4.2. Lost To Follow-Up ..... 27
     - 4.4.3. Withdrawal By Investigator ..... 27
       - 4.4.3.1. General Withdrawal Requirements ..... 27
         - 4.4.3.1.1. ECGs ..... 28
         - 4.4.3.1.2. Other Basis for Withdrawal ..... 28
     - 4.4.4. Subject Self-Withdrawal ..... 28
     - 4.4.5. Withdrawal Documentation ..... 28

5. STUDY TREATMENTS ..... 29
   - 5.1. Investigational Product ..... 29
     - 5.1.1. Medication Preparation and Handling ..... 29
     - 5.1.2. Storage ..... 29
   - 5.2. Dosage and Administration ..... 29
   - 5.3. Treatment Assignment ..... 30
   - 5.4. Blinding ..... 30
   - 5.5. Product Accountability ..... 30
   - 5.6. Treatment Compliance ..... 30
   - 5.7. Concomitant Medications and Non-Drug Therapies ..... 30
     - 5.7.1. Permitted Medications and Non-Drug Therapies ..... 30
     - 5.7.2. Prohibited Medications ..... 31
   - 5.8. Treatment after the End of the Study ..... 31
   - 5.9. Treatment of Study Treatment Overdose ..... 31

6. STUDY ASSESSMENTS AND PROCEDURES ..... 31

6.1. Critical Baseline Assessments ..... 31
6.2. Efficacy Endpoints ..... 33
6.2.1. Efficacy Data Capture/Instruments ..... 33
6.2.1.1. Exacerbations ..... 33
6.2.1.2. Asthma Control Questionnaire-5 (ACQ-5) ..... 33
6.2.1.3. Pulmonary Function Testing ..... 33
6.3. Safety ..... 34
6.3.1. Liver Chemistry Stopping and Follow-Up Criteria ..... 34
6.3.1.1. Criteria for Liver Chemistry Stopping ..... 34
6.3.1.2. Actions ..... 35
6.3.1.3. Follow-Up Assessments ..... 36
6.3.1.4. Restarting Investigational Product ..... 38
6.3.1.4.1. Drug Restart/Rechallenge Following Liver Events that are Possibly Related to IP ..... 38
6.3.1.4.2. Drug Restart Following Transient Resolving Liver Events Not Related to IP ..... 38
6.3.2. Adverse Events ..... 39
6.3.2.1. Definition of an AE ..... 39
6.3.2.2. Definition of an SAE ..... 40
6.3.2.3. Sentinel Events ..... 41
6.3.3. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs ..... 41
6.3.4. Cardiovascular Events ..... 41
6.3.5. Death Events ..... 42
6.3.6. Pregnancy ..... 42
6.3.7. Time Period and Frequency of Detecting AEs and SAEs ..... 42
6.3.8. Method of Detecting AEs and SAEs ..... 43
6.3.9. Prompt Reporting of Serious Adverse Events and Other Events to GSK ..... 43
6.3.9.1. Regulatory Reporting Requirements for SAEs ..... 45
6.3.10. Other Safety Outcomes ..... 46
6.3.10.1. Laboratory Assessments ..... 46
6.3.10.2. Physical Examination ..... 46
6.3.10.3. Vital Signs ..... 47
6.3.10.4. Twelve-lead electrocardiogram ..... 47
6.4. Immunogenicity ..... 47

7. DATA MANAGEMENT ..... 47

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS ..... 48
8.1. Hypothesis ..... 48
8.2. Study Design Considerations ..... 48
8.2.1. Sample Size Assumptions ..... 48
8.3. Data Analysis Considerations ..... 48
8.3.1. Analysis Populations ..... 48
8.3.2. Analysis Data Sets ..... 48
8.3.3. Treatment Comparisons ..... 48
8.3.4. Interim Analysis ..... 48
8.3.5. Key Elements of Analysis Plan ..... 48
8.3.5.1. Efficacy Analyses ..... 49

8.3.5.2. Safety Analyses....49

9. STUDY CONDUCT CONSIDERATIONS....49
   9.1. Posting of Information on Publicly Available Clinical Trial Registers....49
   9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process....49
   9.3. Quality Control (Study Monitoring)....49
   9.4. Quality Assurance....50
   9.5. Study and Site Closure....50
   9.6. Records Retention....50
   9.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication....51

10. REFERENCES....52

11. APPENDICES....54
   11.1. Appendix 1: Time and Events Table....54
   11.2. Appendix 2: Acceptable Birth Control....58
   11.3. Appendix 3: Country Specific Requirements....60
   11.4. Appendix 4: Liver Chemistry Stopping and Follow-up Criteria....61
   11.5. Appendix 5: Liver Safety Drug Restart or Rechallenge Guidelines....62
   11.6. Appendix 6: Anaphylaxis Criteria....67
   11.7. Appendix 7: Protocol Amendment 01 Changes....68
   11.8. Appendix 8: Protocol Amendment 02 Changes....86
   11.9. Appendix 9: Protocol Amendment 03 Changes....91

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ACQ-5 | Asthma Control Questionnaire-5 |
| AE | Adverse Event |
| ALT | Alanine transaminase |
| AST | Aspartate transaminase |
| ATS | American Thoracic Society |
| CIB | Clinical Investigator Brochure |
| CPAP | Continuous Positive Airway Pressure |
| DNA | Deoxyribonucleic acid |
| ECG | Electrocardiogram |
| eCRF | Electronic Case report form |
| ED | Emergency Department |
| $FEV_1$ | Forced expiratory volume in 1 second |
| FVC | Forced vital capacity |
| GCP | Good clinical practice |
| GCSP | Global Clinical Safety and Pharmacovigilance |
| GINA | Global Initiative for Asthma |
| GSK | GlaxoSmithKline |
| $IC_{50}$ | Inhibitory Concentration 50% |
| ICS | Inhaled corticosteroids |
| IEC | Independent ethics committee |
| IL | Interleukin |
| IM | Intramuscular |
| IP | Investigational Product |
| IRB | Institutional review board |
| IUD | Intrauterine Device |
| IV | Intravenous |
| IVRS | Interactive voice response system |
| MedDRA | Medicinal dictionary for regulatory activities |
| mg | Milligram |
| N/A | Not applicable |
| NHLBI | National Heart Lung and Blood Institute |
| OLE | Open Label Extension Study |
| PEF | Peak expiratory flow |
| RAP | Reporting and Analysis Plan |
| SABA | Short-acting Beta Agonist |
| SAE | Serious adverse event |
| SC | Subcutaneous |
| SGRQ | St. George's Respiratory Questionnaire |
| SPM | Study procedures manual |
| ULN | Upper Limit of Normal |

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| None |

# PROTOCOL SUMMARY

## Rationale

Study 201312 is a study of subcutaneously (SC) administered mepolizumab 100mg that will enroll a subset of subjects from Study MEA115661 who have demonstrated clear benefit from therapy and who without continuation of mepolizumab therapy are individuals at greatest risk of serious deterioration of their health status. In order to target individuals at greatest risk for serious deterioration of their health status, only subjects from the MEA115661 study with a history of life-threatening or seriously debilitating asthma, as defined by this protocol, will be allowed to participate in Study 201312. Providing treatment to these subjects offers the opportunity to extend the collection of clinical data for long-term use and further assess the sustainability of efficacy in a population likely to experience significant loss of asthma control and the need for higher doses of systemic steroids if returned to standard of care (SOC) only.

## Objectives

### Primary Objective

- To provide extended treatment with mepolizumab to subjects with a history of life-threatening or seriously debilitating asthma and a history of improved disease control while receiving mepolizumab as defined by this protocol.

### Secondary Objective

- To further describe the long-term clinical experience of mepolizumab in a subset of subjects who demonstrated significant clinical benefit since receiving mepolizumab

## Study Design

This is a multi-center, open-label, long-term study of mepolizumab 100mg administered SC, in addition to standard of care (SOC), in subjects with severe eosinophilic asthma. Only subjects who complete the MEA115661 Exit Visit (Visit 14) will be offered the opportunity to consent for this study. Subjects meeting all of the eligibility criteria will be offered the opportunity to consent for this study of up to 172 weeks.

It is expected that the majority of eligible subjects will enter 201312 within 8 weeks of completing the Exit Visit (Visit 14) in MEA115661.

To reduce the burden of repeated procedures during the ending of MEA115661 and the start of 201312, subjects will start the study according to a specific “scenario”. This depends on when their Visit 1 occurs in relation to the Visit 14 of the MEA115661 study.

**Scenario 1** is when Visit 1 of 201312 is performed on the same day (or less than or equal to 8 weeks) from when Visit 14 of study MEA115661 is performed.

**Scenario 2a** is when Visit 1 of 201312 is performed greater than 8 weeks after Visit 14 of MEA115661 AND when Visit 1 of 201312 is performed on the same day as the Follow-up visit (Visit 15) of study MEA115661.

**Scenario 2b** is when Visit 1 of 201312 is performed greater than 8 weeks after Visit 14 of MEA115661 AND Visit 1 of 201312 is performed after the Follow-up visit (Visit 15) of study MEA115661 has taken place.

All applicable procedures for scenario 1, and 2a and 2b subjects are listed in Section 6.1. Critical Baseline Assessments.

All eligible subjects should be enrolled into 201312 within 4 weeks of receiving all applicable approvals.

After giving informed consent for this study, eligibility will be assessed via multiple evaluations, including physical examination, vital signs, electrocardiogram (ECG), and an updated medical history. Subjects whose health status remains appropriate for the study will then be assessed based on the inclusion and exclusion criteria. Those subjects meeting all study eligibility requirements will receive their first dose of mepolizumab at Visit 1. Mepolizumab will then be administered approximately every 4 weeks with the last dose at Week 168 (Visit 43). Forty three doses will provide therapeutic coverage for 172 weeks (4 weeks following the last dose). Subjects will continue to receive mepolizumab 100mg SC injections for up to 172 weeks or until one of the following occurs:

- the risk/benefit profile for the subject is no longer positive in the opinion of the investigator **or**
- the subject's physician withdraws the subject **or**
- the subject withdraws consent **or**
- the sponsor discontinues development of mepolizumab **or**
- the sponsor discontinues the study in the relevant participating country **or**
- mepolizumab becomes commercially available in the local country.

The study closure process will begin, on a country by country basis, as mepolizumab becomes commercially available for prescription. Some subjects will complete the original 120 week treatment period (as specified in the previous protocol) prior to mepolizumab being available for prescription. To ensure these subjects do not have a treatment gap the treatment period will be extended for an additional 52 weeks to a total of 172 weeks.

Subjects will remain on standard of care asthma therapy throughout the study. Asthma medications may be adjusted at any time during the study at the discretion of the investigator. All changes in asthma therapy will be captured in the source documents and the electronic case report form (eCRF). At each clinic visit, adverse events will be assessed and subjects will be questioned regarding the occurrence of any exacerbations since their last clinic visit. The Asthma Control Questionnaire-5 (ACQ-5) will be performed every 12 weeks during the study and at the Exit/Early Withdrawal Visit to assist the investigator in monitoring the subject's asthma status along with spirometry assessments every 6 months and at the Exit/Early Withdrawal Visit.

Safety labs (hematology, chemistry, and liver analytes) will be drawn at Visit 1 and then approximately every 6 months thereafter. Hematology and chemistry labs will also be obtained 4 weeks after the subject's last dose of mepolizumab. Serum samples for anti-mepolizumab antibody measurements will also be obtained from subjects at baseline (Visit 1), Weeks 48, 96, 144 and at the Exit Visit/Early Withdrawal Visit. Any serum sample testing positive for anti-mepolizumab antibody will also be tested for neutralizing antibody. Subjects discontinuing mepolizumab treatment will be monitored for exacerbation of their asthma during the subsequent 4 weeks after their last dose.

## Study Endpoints/Assessments

### Primary Endpoints

- Annualized rate of exacerbations
- Frequency of adverse events

### Secondary Endpoints

- Asthma Control Questionnaire-5 score
- Forced expiratory volume in 1 second ($FEV_1$)
- Number of withdrawals due to lack of efficacy
- Number of withdrawals due to adverse events
- Number of hospitalizations due to adverse events including asthma exacerbations
- Frequency of both systemic (i.e., allergic and non-allergic) and local site reactions
- 12-lead ECG parameters
- Vital signs
- Frequency of positive anti-mepolizumab binding antibodies/neutralizing antibodies
- Clinical Laboratory Parameters

# 1. INTRODUCTION

## 1.1. Background

Asthma is a disease characterised by chronic airway inflammation, bronchial hyper-reactivity and variable airflow obstruction. Eosinophils are usually prominent in the airway inflammation seen in asthma and are considered a central cause in the pathogenesis of asthma [Wardlaw, 2000]. The expression of interleukin (IL)-5 is elevated in bronchoalveolar lavage (BAL) fluid and bronchial biopsies in patients with asthma [Hamid, 1991]. Moreover, the level of IL-5 in BAL fluid and the bronchial mucosa correlates with disease severity [Robinson, 1992; Robinson, 1993; Humbert, 1997]. The cytokine IL-5 promotes eosinophil differentiation, recruitment, and survival [Clutterbuck, 1989; Wang, 1989]. Thus, a therapeutic strategy which blocks IL-5, thereby suppressing eosinophilic inflammation, may have therapeutic benefit in asthma.

Currently available therapies are highly effective at controlling asthma symptoms and airway inflammation in the majority of patients [Bateman, 2004]. Severe refractory asthma encompasses wide ranges in both clinical symptoms and in natural history. This population can be defined on the basis of medication requirements, asthma symptoms, degree of airflow limitation, and frequency of asthma exacerbations. In terms of exacerbations, three or more steroid-treated exacerbations have been considered part of the typical clinical features in this patient population [ATS, 2000].

Inhaled corticosteroids reduce airway inflammation and sputum eosinophils in most asthmatics [Kips, 2002]. However, a proportion of asthma patients remain uncontrolled despite appropriate therapy with high dose inhaled corticosteroids (ICS) or ICS with additional controller therapy [National Heart Lung and Blood Institute (NHLBI) Guidelines for the Diagnosis and Treatment of Asthma [NHLBI, 2007]; Global Initiative for Asthma guidelines [GINA, 2008]. This severe, uncontrolled, refractory population suffers from persistent symptoms and acute exacerbations of their asthma.

Patients with severe asthma have significant morbidity and mortality risk; they contribute disproportionately to health care and societal costs of the disease with particularly high costs occurring in those with frequent exacerbations. In MEA112997, subjects had features of severe, refractory asthma, as described in the American Thoracic Society (ATS) workshop on refractory asthma [ATS, 2000], and also demonstrated markers of eosinophilic inflammation [Pavord, 2012]. Together, these criteria were useful to identify a severe eosinophilic asthma population that continued to exacerbate despite maximal therapy with currently marketed asthma medications. This severe, eosinophilic population is the subset of asthmatics most likely to benefit from treatment with mepolizumab.

Subjects who are eligible for participation in 201312 will be subjects who have life-threatening or seriously debilitating asthma, who have been previously treated with mepolizumab, and who have demonstrated clear clinical benefit from the treatment. Subjects entering 201312 through MEA115588 and MEA115661 could have been treated for up to 20 months. Subjects entering the study through MEA115575 and MEA115661

could have been treated for up to 18 months. At a minimum, subjects entering the study will have already been treated for at least 12 months.

## 1.2. Rationale

Study 201312 is a study of subcutaneously (SC) administered mepolizumab 100mg that will enroll a subset of subjects from Study MEA115661 who have demonstrated clear benefit from therapy and who without continuation of mepolizumab therapy are individuals at greatest risk of serious deterioration of their health status. In order to target individuals at greatest risk for serious deterioration of their health status, only subjects from the MEA115661 study with a history of life-threatening or seriously debilitating asthma, as defined by this protocol, will be allowed to participate in Study 201312. Providing treatment to these subjects offers the opportunity to extend the collection of clinical data for long-term use and further assess the sustainability of efficacy in a population likely to experience significant loss of asthma control and the need for higher doses of systemic steroids if returned to standard of care (SOC) only.

## 1.3. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with mepolizumab (SB240563) can be found in the Investigator's Brochure.

Serious adverse events (SAEs) reported from ongoing clinical studies with mepolizumab are reviewed daily by the project Medical Monitor. Additionally, regular, systematic reviews of emerging safety data from all clinical studies are conducted by an in-house multi disciplinary Safety Review Team (SRT) which provides a central and dedicated forum for review of emerging data which could impact subject safety. The SRT, which includes the project Medical Monitor, other physicians assigned to the project, clinical scientists and a statistician reviews blinded and unblinded (i.e., from open-label trials) safety data from ongoing clinical studies with mepolizumab on a regular basis and conducts a comprehensive evaluation of the safety data upon completion of each study. Moreover, an integrated analysis of safety across the program is completed annually when additional safety data are available from completed studies. A reassessment of benefit risk and the current Developmental Core Safety Information (DCSI) is completed at each SRT meeting subsequent to review of new data.

Additionally, an adjudication committee will be utilized during the study to assess cardiovascular events. There is also a standard and comprehensive process for the reporting and management of Sentinel Events. (A Sentinel Event is an SAE that is not necessarily drug-related, but that has been associated historically with adverse reactions for other drugs, and is therefore worthy of heightened pharmacovigilance. Sentinel Events include acquired long QT syndrome, agranulocytosis, anaphylactic and anaphylactoid reactions, hepatotoxicity, renal failure, seizures, and Stevens Johnson syndrome/toxic epidermal necrolysis.) Subsequent to the reporting of a Sentinel Event, the Medical Monitor promptly notifies the SRT and the GSK Global Safety Board and leads a thorough and comprehensive follow-up of the Sentinel Event with collection of all relevant data.

The following section outlines the risk assessment and mitigation strategy for this protocol:

### 1.3.1. Risk Assessment

**Table 1 Assessment of Risk**

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Investigational Product (IP) SB 240563** | | |
| Risk of Systemic Allergic and Non-allergic Reactions, including Anaphylaxis | Reactions reported to date across the mepolizumab program are summarized in the IB; see 'Special Warnings and Special Precautions for Use' section located in Section 6 titled 'Summary of Data and Guidance for the Investigator'. | Daily monitoring of serious adverse events (SAEs) by medical monitor; regular systematic review of adverse event (AE)/SAE data from ongoing studies by a GSK safety review team.<br><br>Specific case report form (CRF) pages utilized for targeted collection of reactions data.<br><br>Use of Joint NIAID/FAAN 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (Appendix 6 Anaphylaxis Criteria).<br><br>Subjects are to be monitored based on institutional practices. |
| Risk of Immunogenicity | Biopharmaceutical products may elicit anti-drug antibody (ADA) and neutralizing antibody (NAB), which have the potential to modulate pharmacokinetic (PK), pharmacodynamic (PD) or produce adverse reactions. However, humanized and fully human antibodies are less immunogenic than mouse or chimeric monoclonal antibodies.<br><br>Immunogenicity data reported to date across the | Blood samples are collected in clinical studies for detection of both ADA and NAB.<br><br>See previous risk for mitigation strategy related to clinical safety risks. |

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | mepolizumab development program are summarized in the IB; See Section 5.4 'Clinical Immunogenicity' and a summary of immunogenicity findings in the 'Other Potentially Clinically Relevant Information for the Investigator' section located in Section 6.titled 'Summary of Data and Guidance for the Investigator's Brochure. | |
| Potential risk for adverse cardiovascular (CV) effects | Mepolizumab binding was restricted to human lymphoid tissues in an immunohistochemistry tissue binding study suggesting a low likelihood of non-pharmacologic effects on cardiovascular (CV) function.<br><br>No AEs concerning cardiac conduction or repolarization evident in cynomolgus monkeys at doses at least 10-fold in excess of humans dosed at 10 mg/kg or 750 mg.<br><br>No clinically relevant trends observed in ECG data in humans.<br><br>In one study in subjects with severe refractory asthma, cardiac events were reported in similar frequencies across treatment groups with a small numerical increase observed in serious ischemic cardiac events in the mepolizumab-treated groups. However, an integrated safety analysis of all placebo-controlled multiple dose asthma trials showed similar frequency of SAEs reported overall from the cardiac and vascular system organ class (SOC). | Daily monitoring of SAE by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team.<br><br>CV monitoring for study includes:<br><br>• ECG monitoring during the trial<br><br>• Use of standardized CRFs to collect relevant data on CV events of interest (i.e., myocardial infarction, hospitalization for unstable angina and congestive heart failure, arterial thrombosis, pulmonary embolism and deep vein thrombosis);<br><br>• Adjudication of cardiovascular events |

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | Additionally, similar findings were observed in other SOCs with thrombotic events (e.g., stroke in the Nervous System SOC). Data from 2 subsequently completed placebo-controlled severe asthma trials did not show an increased risk of serious ischemic cardiac events; there were no new reports in any treatment groups including placebo. | |
| Potential risk for increase in infections – a theoretical concern with biologics; however, the pharmacological properties of mepolizumab suggest the risk is low. | No evidence of increased incidence of infections in any preclinical studies.<br><br>Murine data demonstrate that IL-5 antagonism is unlikely to influence cellular or humoral immunity, particularly in response to parasitic infections.<br><br>No mepolizumab-related effects on lymphocyte Immunophenotyping in monkeys or humans, including T-cell activation, distribution of CD4/CD8 subtypes or Th1/Th2 cytokine patterns, B-cells, NK cells or γδ-T-cells.<br><br>An integrated safety analysis of all placebo-controlled multiple dose asthma trials showed SAEs reported in the infection and infestation SOC were 5/345 (1%) in placebo subjects and 18/754 (2%) in mepolizumab subjects.<br><br>Infections reported to date across the mepolizumab development program are summarized in the IB; see 'Special Precautions and Warnings' (for exclusion of | Daily monitoring of SAE by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team<br><br>Standard safety assessments to be conducted as outlined in protocols |

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | subjects with underlying parasitic infections) and 'Undesirable Effects' (for very common infections of nasopharyngitis, URTI, rhinitis and bronchitis reported in other patient populations) sections located in Section 6 titled 'Summary of Data and Guidance for the Investigator'. | |
| Potential risk for increase in malignancies - theoretical concern with biologics; however, blockade of IL-5 is not associated with generalized immuno-suppression or impaired host resistance. | Role of IL-5 and eosinophils in tumor surveillance is not fully characterised in the literature.<br><br>No evidence of defective tumor surveillance in IL-5 or eosinophil-deficient mice.<br><br>Direct assessment of the carcinogenic potential of long-term IL-5 blockade in rodent models not technically feasible.<br><br>Malignancies reported to date across the mepolizumab development program are summarized in the IB. | Daily monitoring of SAE by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team<br><br>Standard safety assessments to be conducted as outlined in protocols |
| Potential risk for rebound eosinophilia with associated clinical consequences | Early published data with Schering-Plough anti- IL5 mAb suggested potential for rebound eosinophilia and disease exacerbation when treatment was stopped [Kim, 2004; Gevaert, 2006]; however, no standard definition of rebound was used and criteria for reporting were variable.<br><br>There have been no verbatim reports of 'rebound' from completed clinical trials of subjects with asthma, atopic dermatitis and eosinophilic esophagitis. Furthermore, the | Daily monitoring of SAE by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team<br><br>Standard safety assessments to be conducted as outlined in protocols |

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | data do not support an exaggerated return of symptoms after cessation of treatment. | |
| **Study Procedures** | | |
| Potential risk for injury with phlebotomy | Risks with phlebotomy include bruising, bleeding, infection, nerve damage. | Procedures to be performed by trained personnel (i.e., study nurse) |

### 1.3.2. Benefit Assessment

Study 201312 will provide extended use of mepolizumab to subjects with a history of life-threatening or seriously debilitating asthma while collecting data to evaluate the long-term continuous use of mepolizumab. This population of asthma subjects has been evaluated as having received benefit from at least one year's treatment with mepolizumab (Study MEA115661) in addition to standard of care asthma treatment. This study will assess the incidence of adverse events and the rate of exacerbations to establish the long-term safety and sustained efficacy of the treatment in this population.

Exacerbations are a major concern to asthma patients and lead to a worsening of the quality of life for subjects. Interventions in at risk populations that can reduce or eliminate serious exacerbations will improve a patient's quality of life and may reduce hospitalizations. Subjects participating in this study will be required to attend visits approximately every 4 weeks and therefore may benefit from the additional monitoring to their current standard asthma care.

### 1.3.3. Overall Benefit:Risk Conclusion

Data from mepolizumab preclinical and clinical development demonstrate the ability of mepolizumab to inhibit IL-5 and, consequently, treat inflammatory conditions linked to an eosinophilic signal, such as asthma subjects predisposed to exacerbations. To date, the safety profile of mepolizumab across other mepolizumab studies has been favorable for all the patient populations studied. Adverse events (AEs) reported commonly have been manageable with minimal medical intervention. Furthermore, preclinical data and the observed safety profile to date in over 1200 clinical trial subjects, as well as the history of mepolizumab use for at least one year in this patient population already, has not identified a safety concern that would preclude continued use. Therefore, investigation of the long-term safety, efficacy, and tolerability of mepolizumab is thereby justified in Study 201312.

# 2. OBJECTIVE(S)

### Primary Objective

- To provide extended treatment with mepolizumab to subjects with a history of life-threatening or seriously debilitating asthma and a history of improved disease control while receiving mepolizumab as defined by this protocol

### Secondary Objective

- To further describe the long-term clinical experience of mepolizumab in a subset of subjects who demonstrated significant clinical benefit since receiving mepolizumab

# 3. INVESTIGATIONAL PLAN

## 3.1. Study Design

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This is a multi-center, open-label, long-term study of mepolizumab 100mg administered SC, in addition to standard of care (SOC), in subjects with severe eosinophilic asthma. Only subjects who complete the MEA115661 Exit Visit (Visit 14) will be offered the opportunity to consent for this study. Subjects meeting all of the eligibility criteria for the study will be offered the opportunity to consent for this study of up to 172 weeks in length.

It is expected that the majority of eligible subjects will enter 201312 within 8 weeks of completing the Exit Visit (Visit 14) in MEA115661.

To reduce the burden of repeated procedures during the ending of MEA115661 and the start of 201312, subjects will start the study according to a specific "scenario". This depends on when their Visit 1 occurs in relation to the Visit 14 of the MEA115661 study.

**Scenario 1** is when Visit 1 of 201312 is performed on the same day (or less than or equal to 8 weeks) from when Visit 14 of study MEA115661 is performed.

**Scenario 2a** is when Visit 1 of 201312 is performed greater than 8 weeks after Visit 14 of MEA115661 AND when Visit 1 of 201312 is performed on the same day as the Follow-up visit (Visit 15) of study MEA115661.

**Scenario 2b** is when Visit 1 of 201312 is performed greater than 8 weeks after Visit 14 of MEA115661 AND Visit 1 of 201312 is performed after the Follow-up visit (Visit 15) of study MEA115661 has taken place.

All applicable procedures for scenario 1, and 2a and 2b subjects are listed in Section 6.1. Critical Baseline Assessments.

All eligible subjects should be enrolled into 201312 within 4 weeks of receiving all applicable approvals.

After giving informed consent for this study, eligibility will be assessed via multiple evaluations, including physical examination, vital signs, electrocardiogram (ECG), and an updated medical history. Subjects whose health status remains appropriate for the study will then be assessed based on the inclusion and exclusion criteria. Those subjects meeting all of the eligibility requirements will receive their first dose of mepolizumab at Visit 1. Mepolizumab will be administered approximately every 4 weeks with the last dose at Week 168 (Visit 43). Forty three doses will provide therapeutic coverage for 172 weeks (4 weeks following the last dose). Subjects will then continue to receive mepolizumab 100mg SC injections for up to 172 weeks or until one of the following occurs:

- the risk/benefit profile for the subject is no longer positive in the opinion of the investigator **or**
- the subject's physician withdraws the subject **or**
- the subject withdraws consent **or**
- the sponsor discontinues development of mepolizumab **or**
- the sponsor discontinues the study in the relevant participating country **or**
- mepolizumab becomes commercially available in the local country.

The study closure process will begin, on a country by country basis, as mepolizumab becomes commercially available for prescription. Some subjects will complete the original 120 week treatment period (as specified in the previous protocol) prior to mepolizumab being available for prescription. To ensure these subjects do not have a treatment gap the treatment period will be extended for an additional 52 weeks to a total of 172 weeks.

Subjects will remain on standard of care asthma therapy throughout the study. Asthma medication may be adjusted at any time during the study at the discretion of the investigator. All changes in asthma therapy will be captured in the source documents and the electronic case report form (eCRF). At each clinic visit, adverse events will be assessed and subjects will be questioned regarding the occurrence of any exacerbations since their last clinic visit. The Asthma Control Questionnaire-5 (ACQ-5) will be performed every 12 weeks during the study and at the Exit/Early Withdrawal Visit to assist the investigator in monitoring the subject's asthma status along with spirometry assessments every 6 months and at the Exit/Early Withdrawal Visit.

Safety labs (hematology, chemistry, liver analytes) will be drawn at Visit 1 and then approximately every 6 months thereafter. Hematology and chemistry labs will also be obtained 4 weeks after the last dose of mepolizumab. Serum samples for anti-mepolizumab antibody measurements will also be obtained from subjects at baseline (Visit 1), Weeks 48, 96 144 and at the Exit Visit/Early Withdrawal Visit. Any serum sample testing positive for anti-mepolizumab antibody will also be tested for neutralizing antibody. Subjects discontinuing mepolizumab treatment will be monitored for exacerbation of their asthma during the subsequent 4 weeks after their last dose.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

## 3.2. Discussion of Design

The design for this study is an open-label continuation of treatment to allow and characterize longer-term experience in subjects with severe asthma who completed the MEA115661 study (through Visit 14). Subjects must have a history of life-threatening asthma and received significant clinical benefit from mepolizumab for one year or more. As mepolizumab is administered approximately every 4 weeks, this design will achieve the objectives of the study by providing appropriate monitoring and data capture at each visit.

The dose for Study 201312, mepolizumab 100mg SC, will be a continuation of the same dose administered in MEA115661. The dose rationale for the mepolizumab 100mg SC dose is based on the efficacy and safety profile observed in the MEA112997 study and is additionally supported by a PK/PD model developed for mepolizumab. The MEA112997 study investigated a 10-fold dose range with doses of 75mg, 250mg, and 750mg administered intravenously (IV) every 4 weeks. All three doses resulted in a clinically significant reduction in the frequency of severe exacerbations when compared to placebo, with a reduction of 48% occurring in the 75mg treatment arm. These three doses also produced a marked and sustained suppression of blood eosinophils throughout the dose interval with a similar safety profile across all treatment arms [Clinical Investigator's Brochure [CIB], GlaxoSmithKline Document Number CM2003/00010/07].

The mepolizumab PK/PD model, developed from 5 prior asthma studies and 1 healthy volunteer study, included 2 studies of mepolizumab administered subcutaneously. This model described the relationship between plasma mepolizumab concentrations and eosinophil counts (irrespective of the route of administration) by an $IC_{50}$ of 226ng/mL [CIB, GlaxoSmithKline Document Number CM2003/00010/07]. ($IC_{50}$ is the half-maximal inhibitory concentration or the concentration at which 50% of the eosinophil population is inhibited.) Based on prior PK studies, the bioavilability of mepolizumab has been determined to be approximately 75% and 71% when administered SC into the upper arm and thigh, respectively [GlaxoSmithKline Document Number CM2003/00010/07]. Therefore, a dose of 100mg SC is anticipated to provide similar exposure to the 75mg IV dose studied in MEA112997. Additionally, this dose will provide plasma concentrations of mepolizumab well above the $IC_{50}$ for the entire dosage interval.

Further details on the PK/PD model can be in found in the CIB [GlaxoSmithKline Document Number CM2003/00010/07].

# 4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

## 4.1. Number of Subjects

Approximately 375 subjects are estimated to be eligible to take part in this study. As the study is open-label, no randomization will occur. Attrition/withdrawal is expected to be less than 10% of enrolled subjects.

## 4.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Clinical Investigator's Brochure [GlaxoSmithKline Document Number CM2003/00010/07].

Deviations from inclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects eligible for enrolment in the study must additionally meet all of the following criteria:

1. **Informed Consent**: Prior to commencing any study related activities, subjects must be able and willing to provide written informed consent.
2. **Male or Eligible Female Subjects**:

   To be eligible for the study, females of child-bearing potential must commit to consistent and correct use of an acceptable method of birth control and for 4 months after the last study drug administration. Methods of acceptable birth control and the definitions for child-bearing and non-child bearing potential are provided in Appendix 2.

   A urine pregnancy test is required of all females of childbearing potential at the initial Baseline Visit (Visit 1).
3. **French Subjects Only:** In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.
4. **MEA115661 Participation**: Subjects must have completed Visit 14 of MEA115661.
5. **Current Anti-Asthma Therapy**: The subject's asthma has been treated with an ICS controller medication for the last 8 months with fluticasone propionate (FP) ≥500 mcg/day (or equivalent).
6. **Disease Severity**: Subjects must be assessed as having life-threatening asthma or serious debilitating asthma in order to enroll.

   Life threatening asthma is defined by the following:

   ***Subjects enrolled in MEA115588 must meet one of the following criteria:***

   a) Subject has a history of at least one intubation during their lifetime

b) ≥3 asthma exacerbations in the 12 months prior to screening for MEA115588

c) ≥1 or more hospitalization for asthma exacerbation in the 12 months prior to screening for MEA115588.

***Subjects enrolled in MEA115575 must meet one of the following criteria:***

d) Subject has a history of at least one intubation during their lifetime

e) Their optimized dose at randomization in MEA115575 was ≥10mg of prednisone

f) ≥1 or more hospitalization for asthma exacerbation in the 12 months prior to screening for MEA115575

Those subjects that do **not** meet the definition of potentially life threatening asthma must be assessed as having serious debilitating asthma.

***Subjects enrolled in MEA115588 or MEA115575 must meet the following criteria:***

At randomisation of MEA115588 or MEA115575 must have:

g) A % predicted FEV1 of ≤50% and either

h) ACQ5 score of ≥3 or

i) SGRQ score of ≥60

*7.* **Clinical Benefit**: Subjects must have experienced documented clinical benefit to enroll. Subjects must meet the following criteria demonstrating clinical benefit:

***Subjects enrolled in MEA115588 who received mepolizumab must meet all of the following criteria:***

a) Subject must have had a reduction in their exacerbation frequency by ≥50% during MEA115588. The baseline for comparison is the total number of exacerbations reported in the 12 months prior to screening for MEA115588.

b) The investigator confirms that the subject demonstrated improvement during MEA115588.

***Subjects enrolled in MEA115588 who received placebo must meet all of the following criteria:***

c) Subject must have had a reduction in their exacerbation frequency by ≥50% during the first 8 months of MEA115661. The baseline for comparison is the total number of exacerbations reported in the 12 months prior to screening for MEA115588.

d) The investigator confirms that the subject demonstrated improvement during MEA115661

***Subjects enrolled in MEA115575 who received mepolizumab must meet all of the following criteria:***

e) Subject must have reduced their oral corticosteroid dose by ≥ 50% during MEA115575. The baseline for comparison is the subject's optimized OCS dose at randomization in MEA115575

f) The investigator confirms that the subject demonstrated improvement during MEA115575.

***Subjects enrolled in MEA115575 who received placebo must meet all of the following criteria:***

g) Subject must have reduced their oral corticosteroid dose at randomization by ≥50% in the first 6 months of MEA115661. The baseline for comparison is the subject's optimized OCS dose at randomization in MEA115575.

h) The investigator confirms that the subject demonstrated improvement during MEA115661.

8. **Subjects at Significant Safety Risk:** If either criteria 6 or 7 are not met, subjects who are considered to be at risk of experiencing a life-threatening event, or whose functional health status will become significantly worse if returned to standard of care, as judged by the investigator and agreed by GSK.

## 4.3. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects meeting any of the following criteria must not be enrolled in the study:

1. **Health Status**: Clinically significant change in health status during MEA115661 which in the opinion of the investigator would make the subject unsuitable for participation in this long-term study.
2. **Pregnancy**: Subjects who are pregnant or breastfeeding. Subjects should not be enrolled if they plan to become pregnant during the time of study participation.
3. **Exacerbation History**: Subjects who received placebo in MEA115588 and had NO exacerbations during the study.
4. **Oral Corticosteroid Use**: Subjects who received placebo in MEA115575 and were able to discontinue oral corticosteroid therapy by the end of the study.
5. **Smoking Status**: Current smokers
6. **Previous Significant Protocol Deviation**: Subjects who were excluded from the per protocol analysis due to a significant protocol deviation in either study MEA115575

or MEA115588 which is deemed by the GSK Medical Monitor to put the subject at risk from further participation.

7. **ECG Assessment**: A clinically significant ECG abnormality as determined by the investigator.

## 4.4. Withdrawal Criteria

### 4.4.1. Subject Compliance with Visit Schedule

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and re-schedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study based on previous non-compliance.

### 4.4.2. Lost To Follow-Up

In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (3 telephone calls and, if necessary, a letter to the subject's last known mailing address) so that they can appropriately be withdrawn from the study. These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, then and only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up". For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the eCRF.

### 4.4.3. Withdrawal By Investigator

#### 4.4.3.1. General Withdrawal Requirements

Subjects may be withdrawn from study treatment at anytime by the investigator if it is deemed detrimental for them to continue in the study. Reasons for withdrawal can include: an adverse event, lost to follow-up, protocol violation, lack of efficacy, sponsor terminated study, non-compliance, abnormal laboratory results (Section 6.3.3), or for any other reason.

Subjects may also be withdrawn from this study if mepolizumab becomes commercially available in the respective country, if marketing of mepolizumab is no longer being sought in the respective country, or upon decision of the sponsor to discontinue further development of mepolizumab. Every effort should be made to have the subject complete the Exit/Early Withdrawal Visit.

A subject must be permanently discontinued from IP if any of the following stopping criteria are met:

- **Liver Chemistry**: Meets any of the protocol-defined liver chemistry stopping criteria (Section 11.4).

- **Pregnancy**: Positive pregnancy test

#### *4.4.3.1.1. ECGs*

Discontinuation is required if any of the following ECG criteria are met during the study:

- QTcF >500 msec
- Uncorrected QT >600 msec

These criteria should be based on the average QTc(F) value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief period, and then use the averaged QTc(F) values of the three ECGs to determine whether the patient should be discontinued from the study.

For subjects with underlying Bundle Branch Block:

| Baseline QTc(F) with Bundle Branch Block | Discontinuation QTc(F) with Bundle Branch Block |
|---|---|
| <450 msec | >500 msec |
| 450-480 msec | ≥ 530 msec |

#### *4.4.3.1.2. Other Basis for Withdrawal*

Subjects may also be withdrawn from the study if mepolizumab becomes commercially available in the respective country or upon decision of the sponsor to discontinue further development of mepolizumab in the respective country.

### 4.4.4. Subject Self-Withdrawal

Subjects are free to discontinue participation in the study at anytime. Every effort should be made to have the subject return for an Exit/Early Withdrawal visit 4 weeks post last mepolizumab injection. In those instances where the subject specifies the reason for withdrawal of consent, this information will be captured in the eCRF.

### 4.4.5. Withdrawal Documentation

The primary reason for withdrawal will be recorded in the eCRF and any data collected up until the point of withdrawal will be used in the data analyses. A subject should only be designated as lost to follow-up if the site is unable to establish contact with the subject after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc). These efforts should be documented in the clinic notes at the site. For those subjects that are lost to follow-up, every effort will be made to contact the subject to assure their safety.

# 5. STUDY TREATMENTS

## 5.1. Investigational Product

Mepolizumab (SB-240563) is a fully humanised IgG antibody (IgG1, kappa) with human heavy and light chain frameworks. Mepolizumab will be provided as a lyophilised cake in sterile vials for individual use. The contents of the label will be in accordance with all applicable regulatory requirements.

### 5.1.1. Medication Preparation and Handling

The vial will be reconstituted with Sterile Water for Injection, just prior to use. Details for dose preparation and administration of mepolizumab for injection 100mg/vial are provided in the Study Procedures Manual (SPM).

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

### 5.1.2. Storage

Mepolizumab must be stored in a refrigerator or at a temperature of 2-8°C and protected from light. Maintenance of a temperature log (manual or automated) is required.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the investigational product will be limited to the investigator and authorised site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

## 5.2. Dosage and Administration

Prior to administration, each vial of mepolizumab will need to be reconstituted and swirled gently to enable complete dissolution of the product. Detailed instructions can be found within the SPM.

Once the mepolizumab vial is reconstituted, 100mg of mepolizumab should be drawn into a polypropylene syringe and administered according to the instructions in the SPM. The dose may be given subcutaneously in the upper arm or thigh. The administration site should be documented for each dose given.

Safety monitoring of subjects will be according to local site policy. Such monitoring will include general safety monitoring including monitoring for both systemic (i.e., allergic and non-allergic) and local injection-site reactions. Trained rescue personnel and rescue medications/equipment must be available for use at all times.

## 5.3. Treatment Assignment

All subjects will receive mepolizumab 100mg administered subcutaneously into the upper arm or thigh approximately every 4 weeks.

## 5.4. Blinding

This will be an open-label study.

## 5.5. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned by study subjects (where applicable), and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

## 5.6. Treatment Compliance

All doses administered within the study will be administered under the supervision of the investigator or appropriately qualified designee (e.g., study nurse).

Drug dispensing/accountability logs will be maintained by a member of the study team designated by the Investigator.

## 5.7. Concomitant Medications and Non-Drug Therapies

### 5.7.1. Permitted Medications and Non-Drug Therapies

Subjects will be required to continue ICS controller therapy for the duration of this study. For corticosteroids, the dose must be recorded as well as any dose changes

Details of asthma-related concomitant medications administered from the first dose of mepolizumab in 201312 until the Exit/Early Withdrawal visit or last subject visit will be recorded in the electronic case report form (eCRF). In addition, any asthma-related medications started prior to first dose in 201312, but were ongoing during the first dose will also be recorded. The minimum requirement is that drug name, unit dose, and the dates of administration are to be recorded.

Details of non-asthma-related concomitant medications administered from the first dose of mepolizumab in 201312 until the Exit/Early Withdrawal visit or last subject visit will be recorded in the electronic case report form (eCRF).Additional medications to treat asthma are permitted, as are medications to treat other disease states, with the exception of those listed as prohibited in Table 2. Oxygen and Continuous Positive Airway Pressure (CPAP) are permitted for the treatment of obstructive sleep apnea.

### 5.7.2. Prohibited Medications

Table 2 lists those medications that are prohibited from use during the study.

**Table 2 Prohibited Medications**

| Medication |
|---|
| • Investigational drugs other than mepolizumab |
| • Experimental anti-inflammatory drugs (non biologicals) |
| • Immunosuppressive medications[1] |
| • Methotrexate, troleandomycin, cyclosporin, azathioprine |
| • Oral gold |
| • Chemotherapy used for conditions other than asthma |
| • Regular systemic (oral or parenteral) corticosteroids for the treatment of conditions other than asthma or for treatement of hypoadrenalism |

1. The list of immunosuppressives provided contains commonly used example medications. The list is not all-inclusive and other known immunosuppressive medications not listed are also prohibited.

## 5.8. Treatment after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition whether or not GSK is providing specific post study treatment.

## 5.9. Treatment of Study Treatment Overdose

The dose of mepolizumab considered to be an overdose has not been defined. There are no known antidotes and GSK does not recommend a specific treatment in the event of a suspected overdose. The investigator will use clinical judgement in treating the symptoms of a suspected overdose.

# 6. STUDY ASSESSMENTS AND PROCEDURES

The Time and Events Table is provided in Appendix 1.

## 6.1. Critical Baseline Assessments

Baseline assessments performed for scenario 1 subjects in study 201312:

1. Demographic information review and update for 201312

2. General medical history review and update in 201312
3. Physical examination and update in 201312
4. Assessment of Inclusion/Exclusion criteria.
5. Urine pregnancy test for females of childbearing potential (Appendix 2: Acceptable Birth Control)

Baseline assessments performed for scenario 2a subjects in study 201312:

1. Demographic information review and update for 201312
2. General medical history review and update in 201312
3. Physical examination and update in 201312
4. Pulmonary function tests and assessment
5. Assessment of Inclusion/Exclusion criteria.
6. Urine pregnancy test for females of childbearing potential (Appendix 2: Acceptable Birth Control)

For scenario 2b subjects in study 201312, the following assessments should be performed:

1. Demographic information review and update for 201312
2. General medical history review and update in 201312
3. Physical examination and update in 201312
4. Pulmonary function tests and assessment
5. Assessment of Inclusion/Exclusion criteria.
6. Asthma Control Questionnaire-5 (Section 6.2.1.2)
7. Vital signs (Section 6.3.10.3)
8. 12-lead ECG (Section 6.3.10.4)
9. Blood sampling for the following:
    - Clinical chemistry
    - Hematology
    - Liver Analytes
    - Immunogenicity
10. Urine pregnancy test for females of childbearing potential (Appendix 2: Acceptable Birth Control)

Please see the SPM for more detail around the required baseline assessments.

## 6.2. Efficacy Endpoints

- Annualized rate of exacerbations
- Asthma Control Questionnaire-5 score
- Forced expiratory volume in 1 second ($FEV_1$)

### 6.2.1. Efficacy Data Capture/Instruments

#### 6.2.1.1. Exacerbations

Subjects will be questioned at each visit regarding the occurrence of any exacerbations since their last visit. Numerical occurrences will be captured via the eCRF.

Exacerbations will be defined as worsening of asthma which requires use of systemic corticosteroids and/or hospitalisation and/or Emergency Department (ED) visits.

For all subjects, use of systemic corticosteroids is defined as IV or oral steroids (e.g., prednisone) for at least 3 days or a single intramuscular (IM) CS dose. For subjects on maintenance systemic corticosteroids, use of systemic corticosteroids is defined as at least double the existing maintenance dose for at least 3 days.

Exacerbations where the courses of systemic CS are separated by <7 days will be considered as one exacerbation for consistency across the program.

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

The ACQ-5 is a five-item questionnaire used to measures a subject's asthma control that can be quickly and easily completed [Juniper, 2005]. The questions are designed to be self-completed by the subject. The five questions enquire about the frequency and/or severity of symptoms (nocturnal awakening on waking in the morning, activity limitation, and shortness of breath, wheeze). The response options for all these questions consist of a zero (no impairment/limitation) to six (total impairment/ limitation) scale.

The ACQ-5 will be administered at Visit 1 and approximately every 12 weeks afterwards. It is recommended that the ACQ-5 be administered at the same time during each visit. To avoid biasing responses, the subjects should not be told the results of diagnostic tests prior to completing the questionnaire and should be completed before any procedures are performed on the subject to avoid influencing the subject's response. Adequate time should be allowed to complete all items on the ACQ-5. The questionnaire will be administered every 12 weeks throughout the study.

#### 6.2.1.3. Pulmonary Function Testing

Spirometry to assess subjects' $FEV_1$ will be performed approximately every 24 weeks beginning at Visit 1 using the site's own equipment (Appendix 1 Time and Events Table). The spirometer should meet American Thoracic Society standards and produce a printout of all data generated, which should be stored in the subject's notes. The spirometer should be calibrated in accordance with the manufacturer's instructions and a

calibration log maintained. Spirometry should be performed within ± 1 hour of the baseline assessment. Subjects should try to withhold short-acting beta$_2$-agonists (SABA) for ≥6 hours and LABAs for ≥12 hours prior to clinic visit, if possible. Assessments to be recorded will include $FEV_1$ and forced vital capacity (FVC).

## 6.3. Safety

- Incidence of adverse events including systemic (i.e., allergic/IgE mediated and non-allergic) and local site injection-related reactions reported throughout the treatment period**.**
  - Systemic reactions can be allergic or non-allergic in nature and are typically mild to moderate in intensity, generally develop within several hours of the injection, and are most commonly associated with a complex of symptoms including chills, fever, nausea, vomiting, asthenia, headache, skin rash, pruritus, urticaria, arthralgia/myalgia, hypotension/hypertension, dizziness, bronchospasm, dyspnea or cough.
  - Anaphylaxis, the most severe form of hypersensitivity reactions will be assessed using the diagnostic criteria outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis [Sampson, 2006; Appendix 6 Anaphylaxis Criteria].
- A 12-lead ECG will be performed to derive the following endpoints:
  - Mean change from baseline in the QTc(F) (QT interval corrected by Friderica's method)
  - Mean change from baseline in QTc(B) (QT interval corrected by Bazett's method)
  - Maximum change from baseline for QTc(F) and QTc(B)
- Clinical laboratory parameters
- Vital signs

### 6.3.1. Liver Chemistry Stopping and Follow-Up Criteria

#### 6.3.1.1. Criteria for Liver Chemistry Stopping

**Phase III-IV liver chemistry stopping and follow up criteria** have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

**Phase III-IV liver chemistry stopping criteria 1-5 are defined below and are presented in a figure in** Appendix 4**:**

**Criterion 1:** ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT ≥ 3xULN and INR>1.5, if INR measured)

**NOTE:** if serum bilirubin fractionation is not immediately available, withdraw study drug for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

**Criterion 2:** ALT ≥ 8xULN.

**Criterion 3:** ALT ≥ 5xULN but <8 xULN persists for ≥2 weeks

**Criterion 4:** ALT ≥ 3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

**Criterion 5:** ALT ≥ 5xULN but <8 xULN and cannot be monitored weekly for ≥2 weeks

#### 6.3.1.2. Actions

**When any of the liver chemistry stopping Criteria 1-5 is met, do the following:**

- **Immediately** withdraw investigational product for that subject
- Report the event to GSK **within 24 hours** of learning its occurrence
- Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN **and** INR>1.5, if INR measured); INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.

  **NOTE:** if serum bilirubin fractionation is not immediately available, withdraw study drug for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilise, or return to baseline values as described below.

- Withdraw the subject from the study (unless further safety follow-up is required) after completion of the liver chemistry monitoring as described
- Do not restart investigational product unless written approval for drug restart is granted by GSK Medical Governance (Section 6.3.1.4).

**In addition, for Criterion 1:**

- Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring
- A specialist or hepatology consultation is recommended
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilise or return to within baseline values

**For Criteria 2, 3, 4 and 5:**

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hrs** for repeat liver chemistries and liver event follow up assessments (see below)
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilise or return to within baseline values; criterion 5 subjects should be monitored as frequently as possible.

Subjects with ALT ≥ 5xULN and <8xULN which exhibit a decrease to ALT x≥ 3xULN, but <5xULN and bilirubin <2xULN without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks:

- Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss subject safety
- Can continue investigational product
- Must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline
- If at any time these subjects meet the liver chemistry stopping criteria, proceed as described above
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalise or return to within baseline values.

#### 6.3.1.3. Follow-Up Assessments

For Criteria 1-5, make every attempt to carry out the **liver event follow up assessments** described below:

- Viral hepatitis serology including:

  - Hepatitis A IgM antibody;
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
  - Hepatitis C RNA;
  - Cytomegalovirus IgM antibody;
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
  - Hepatitis E IgM antibody
- Blood sample for PK analysis, obtained within 4 weeks of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥ 2xULN.
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake case report form.

The following are required for subjects with ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies and quantitative total immunoglobulin G (IgG or gamma globulins).
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week.
- Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. **NOTE**: if hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Legal, 2005].
- Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease.

#### 6.3.1.4. Restarting Investigational Product

##### *6.3.1.4.1. Drug Restart/Rechallenge Following Liver Events that are Possibly Related to IP*

Approval by GSK for drug restart can be considered where:

- The subject is receiving compelling benefit, benefit of drug restart exceeds risk, and no effective alternative therapy is available. Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required.
- If the restart/rechallenge is approved by GSK in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the IP restart/rechallenge. Documentation of informed consent must be recorded in the study chart.
- Study drug must be administered at the dose specified by GSK.
- Subjects approved by GSK for restart/rechallenge of IP must return to the clinic twice a week for liver chemistry tests until stable, liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

##### *6.3.1.4.2. Drug Restart Following Transient Resolving Liver Events Not Related to IP*

Approval by GSK for drug restart can be considered where:

- Liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN). Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required.
- If restart of drug is approved by GSK in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study chart.
- Study drug must be administered at the dose specified by GSK.
- Subjects approved by GSK for restarting IP must return to the clinic once a week for liver chemistry tests until stable, liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.

### 6.3.2. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

#### 6.3.2.1. Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition

#### 6.3.2.2. Definition of an SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

   NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation

   NOTE: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

   Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

g. All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

   NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating

direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

#### 6.3.2.3. Sentinel Events

A Sentinel Event is a GSK-defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. Medical monitor review of all SAEs for possible Sentinel Events is mandated at GSK. The GSK medical monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current GSK-defined Sentinel Events are listed below:

- Acquired Long QT Syndrome
- Agranulocytosis/Severe Neutropenia
- Anaphylaxis & Anaphylactoid Reactions
- Hepatotoxicity
- Acute Renal Failure
- Seizure
- Stevens Johnson syndrome/Toxic epidermal necrosis

### 6.3.3. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

### 6.3.4. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- 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
- Revascularisation

This information should be recorded in the specific cardiovascular eCRF within one week of when the AE/SAE(s) is/are first reported.

### 6.3.5. Death Events

In addition, all deaths will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and noncardiovascular death.

This information should be recorded in the specific death eCRF within one week of when the death is first reported.

### 6.3.6. Pregnancy

A urine pregnancy test will be performed for all females of child bearing potential prior to enrollment, during each scheduled study visit prior to the injection of investigational product, and during the Exit/Early Withdrawal Visit.

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

### 6.3.7. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the start of study treatment and until the follow up contact.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed **as related** to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 6.3.9.

### 6.3.8. Method of Detecting AEs and SAEs

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

“How are you feeling?” or for paediatric studies, “How does your child seem to feel?”

“Have you had any (other) medical problems since your last visit/contact?” or for paediatric studies, “Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?”

“Have you taken any new medicines, other than those provided in this study, since your last visit/contact?” or for paediatric studies, ”Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?”

### 6.3.9. Prompt Reporting of Serious Adverse Events and Other Events to GSK

SAEs, pregnancies, medical device incidents, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in the following table once the investigator determines that the event meets the protocol definition for that event.

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a conclusion that a relationship to the investigational product cannot be ruled out. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the Investigator Brochure (IB) to assist in the determination of his/her assessment.

| | **Initial Reports** | | **Follow-up Information on a Previous Report** | |
|---|---|---|---|---|
| **Type of Event** | **Time Frame** | **Documents** | **Time Frame** | **Documents** |
| All SAEs | 24 hours | "SAE" data collection tool | 24 hours | Updated "SAE" data collection tool |
| Cardiovascular or death event | Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported | "CV events" and/or "death" data collection tool(s) if applicable | Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported | Updated "CV events" and/or "death" data collection tool(s) if applicable |
| Pregnancy | 2 weeks | "Pregnancy Notification Form" | 2 weeks | "Pregnancy Follow-up Form" |
| ***Liver chemistry abnormalities for Phase I to IV:*** | | | | |
| ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct) (or ALT≥3xULN **and** INR>1.5, if INR measured)[1] | 24 hours[2] | "SAE" data collection tool. "Liver Event CRF" and "Liver Imaging" and/or "Liver Biopsy" CRFs, if applicable[3] | 24 hours | Updated "SAE" data collection tool/"Liver Event" Documents[3] |
| ***Remaining liver chemistry abnormalities Phase III to IV:*** | | | | |
| ALT≥8xULN; ALT≥3xULN with hepatitis or rash or ≥3xULN and <5xULN that persists≥4 weeks | 24 hours[2] | "Liver Event" Documents (defined above) [3] | 24 hours | Updated "Liver Event" Documents[3] |

| | Initial Reports | | Follow-up Information on a Previous Report | |
|---|---|---|---|---|
| **Type of Event** | **Time Frame** | **Documents** | **Time Frame** | **Documents** |
| ALT≥5xULN plus bilirubin <2xULN | 24 hours[2] | "Liver Event" Documents (defined above) do not need completing unless elevations persist for 2 weeks or subject cannot be monitored weekly for 2 weeks[3] | 24 hours | Updated "Liver Event" Documents, if applicable[3] |
| ALT≥5xULN and bilirubin <2xULN that persists ≥2 weeks | 24 hours[2] | "Liver Event" Documents (defined above) [3] | 24 hours | Updated "Liver Event" Documents[3] |
| ALT≥3xULN and <5x ULN and bilirubin <2xULN | 24 hours[2] | "Liver Event" Documents (defined above) do not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[3] | 24 hours | Updated "Liver Event" Documents, if applicable[3] |

1. INR measurement is not required; if measured, the threshold value stated will not apply to patients receiving anticoagulants.
2. GSK must be contacted at onset of liver chemistry elevations to discuss subject safety
3. Liver Event Documents (i.e., "Liver Event CRF" and "Liver Imaging CRF" and/or "Liver Biopsy CRF", as applicable) should be completed as soon as possible.

The method of recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

#### 6.3.9.1. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

## 6.3.10. Other Safety Outcomes

### 6.3.10.1. Laboratory Assessments

All protocol required laboratory assessments, as defined in the Time and Events Table (Appendix 1 Time and Events Table), will be taken pre-dosing and will be sent to the central laboratory, Quest Diagnostics for analysis (details provided in the SPM). Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by Quest Diagnostics. Reference ranges for all safety parameters will be provided to the site by Quest Diagnostics. The central laboratory will fax laboratory results to the Investigator and will transmit the results electronically to GSK.

At the discretion of the Investigator, additional samples may be taken for safety reasons. If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in patient management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the subject's CRF. Refer to the SPM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

### 6.3.10.2. Physical Examination

A detailed physical examination including, but not limited to, an evaluation of the lungs and cardiovascular system will be conducted as outlined in Time and Events Table (Appendix 1 Time and Events Table). For the US, licensed practitioners who are listed on the Form 1572 can complete the physical examination. A licensed physician on the Form 1572 must sign off on the physical examinations completed by non-physicians. In countries outside of the US, the physical examination should be conducted by a medically qualified person; however, if the physical examination is conducted by non-physicians, a medically qualified person must sign off.

Results of the examinations will be recorded in the subject's clinic notes. The same person should perform both examinations, if possible.

#### 6.3.10.3. Vital Signs

Sitting pulse rate and blood pressure measurements will be performed by the investigator or qualified site staff as outlined in Time and Events Table (Appendix 1 Time and Events Table). Measurements will be done pre-injection with the subject sitting, having rested in this position for at least 5 minutes before each reading. They will be taken before measurement of any clinic lung function tests or ECGs at the specified time point.

At the baseline visit, height and weight will also be measured.

#### 6.3.10.4. Twelve-lead electrocardiogram

Twelve-lead ECGs will be performed at the visits specified in the Time and Events Table (Appendix 1 Time and Events Table).

Investigators will be provided with ECG machines by GSK through a designated central laboratory. Paper ECG traces will be recorded at a standard paper speed of 25mm/sec and gain of 10mm/mV, with a lead II rhythm strip. There will be electronic capture and storage of the data by a validated method, with subsequent transferral to the central laboratory for manual reading and calculation of the electrocardiographic parameters. Paper traces are required to be maintained at the site with other source documents.

Electrocardiogram measurements will be made after the subject has rested in the supine position for 5 minutes. The ECG should be obtained before lung function testing followed by other study procedures. Collection shortly after a meal or during sleep should be avoided since QT prolongation can occur at these times.

### 6.4. Immunogenicity

Blood samples will be collected for the determination of anti-mepolizumab antibodies just prior to administration of mepolizumab at the time points identified in the Time and Events Table (Appendix 1 Time and Events Table). Samples that test positive for anti-mepolizumab antibodies will be further tested for the presence of neutralizing antibody.

## 7. DATA MANAGEMENT

For this study, subject data will be entered into GSK defined electronic case report forms (eCRFs), transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, GSKDrug. An appropriate medical dictionary that covers all approved drugs in studies where Japan is participating will be referenced. eCRFs (including queries and audit trails) will be retained by GSK and copies will be sent to the investigator to maintain as the investigator copy. In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

# 8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

## 8.1. Hypothesis

Because the study has a single treatment arm, statistical analyses of treatment effect will not be performed. Therefore no hypotheses have been defined for this study.

## 8.2. Study Design Considerations

### 8.2.1. Sample Size Assumptions

There is no sample size calculation for this study. The sample size will be determined by the number of available subjects who were enrolled into study MEA115661 and are eligible for the current study based on inclusion and exclusion criteria.

## 8.3. Data Analysis Considerations

All pre-specified analyses will be described in a full Reporting and Analysis Plan (RAP) which will be finalised prior to database freeze.

### 8.3.1. Analysis Populations

The All Subjects Enrolled population will comprise all subjects for whom a record exists on the database.

The As Treated population will consist of all subjects who received at least one dose of open label mepolizumab within study 201312.

### 8.3.2. Analysis Data Sets

All analyses will be performed using all available data as outlined in the Reporting and Analysis Plan.

### 8.3.3. Treatment Comparisons

No treatment comparisons will be performed.

### 8.3.4. Interim Analysis

Interim analysis will be performed as needed in order to provide open-label safety data to inform the risk-benefit assessment of mepolizumab in severe asthma.

### 8.3.5. Key Elements of Analysis Plan

Details of the analysis plan will be fully described in the RAP.

#### 8.3.5.1. Efficacy Analyses

All efficacy endpoints will be summarized using descriptive statistics. Further details will be provided in the RAP.

#### 8.3.5.2. Safety Analyses

All safety endpoints will be summarized using descriptive statistics. Further details will be provided in the RAP.

# 9. STUDY CONDUCT CONSIDERATIONS

## 9.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

## 9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

## 9.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include

identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

## 9.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

## 9.5. Study and Site Closure

Upon completion or termination of the study, the GSK monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

## 9.6. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local

regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

## 9.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The results summary will be posted to the Clinical Study Register no later than eight months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

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# 11. APPENDICES

## 11.1. Appendix 1: Time and Events Table

| Procedures | Week 52 of MEA115661[1] | Treatment Period (Visit Window is ± 1 week) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** |
| **Week of study** | **0** | **4** | **8** | **12** | **16** | **20** | **24** | **28** | **32** | **36** | **40** | **44** | **48** | **52** | **56** | **60** |
| Written Informed Consent | X | | | | | | | | | | | | | | | |
| Medical History Changes | X | | | | | | | | | | | | | | | |
| Smoking Status | X | | | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | | | | | | | | | | |
| **Safety Assessments** | | | | | | | | | | | | | | | | |
| Concomitant Medication | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical Examination | X | | | | | | | | | | | | | | | |
| Vital Signs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG | X | | | | | | X | | | | | | X | | | |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Serious Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Laboratory Assessments**[2] | | | | | | | | | | | | | | | | |
| Immunogenicity | X | | | | | | | | | | | | X | | | |
| Hematology | X | | | | | | X | | | | | | X | | | |
| Chemistry | X | | | | | | X | | | | | | X | | | |
| Liver Analytes | X | | | | | | X | | | | | | X | | | |
| Pregnancy Test[3] | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U |
| **Efficacy Assessments** | | | | | | | | | | | | | | | | |
| Exacerbation review | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Asthma Control Questionnaire-5 | X | | | X | | | X | | | X | | | X | | | X |
| Spirometry | X | | | | | | X | | | | | | X | | | |

| **Procedures** | **Week 52 of MEA115661[1]** | **Treatment Period (Visit Window is ± 1 week)** | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** |
| **Week of study** | **0** | **4** | **8** | **12** | **16** | **20** | **24** | **28** | **32** | **36** | **40** | **44** | **48** | **52** | **56** | **60** |
| **Worksheets/IP/eCRF** | | | | | | | | | | | | | | | | |
| Administer Mepolizumab 100mg SC | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Dispense paper worksheet | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Collect paper worksheet | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Register IVRS/IWRS | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Complete eCRF | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

**1.** Before entry in to study 201312, determine which scenario the subject is best classified as and perform the relevant procedures as defined in Section 6.1 and the SPM.
**2.** All laboratory assessments to be completed prior to dosing
**3.** Pregnancy test (all females of childbearing potential) U = Urine

## 11.1 Appendix 1: Time and Events Table (Continued)

| Procedures | Treatment Period (Visit Window is ± 1 week) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** | **30** | **31** |
| **Week of study** | **64** | **68** | **72** | **76** | **80** | **84** | **88** | **92** | **96** | **100** | **104** | **108** | **112** | **116** | **120** |
| **Safety Assessments** | | | | | | | | | | | | | | | |
| Concomitant Medication | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical Examination | | | | | | | | | | | | | | | |
| Vital Signs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG | | | X | | | | | | X | | | | | | |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Serious Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Laboratory Assessments**[2] | | | | | | | | | | | | | | | |
| Immunogenicity | | | | | | | | | X | | | | | | |
| Hematology | | | X | | | | | | X | | | | | | X |
| Chemistry | | | X | | | | | | X | | | | | | X |
| Liver Analytes | | | X | | | | | | X | | | | | | X |
| Pregnancy Test[3] | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U |
| **Efficacy Assessments** | | | | | | | | | | | | | | | |
| Exacerbation review | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Asthma Control Questionnaire-5 | | | X | | | X | | | X | | | X | | | X |
| Spirometry | | | X | | | | | | X | | | | | | X |
| **Worksheets/IP/eCRF** | | | | | | | | | | | | | | | |
| Administer Mepolizumab 100mg SC | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Dispense paper worksheet | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Collect paper worksheet | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Register IVRS/IWRS | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Complete eCRF | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

**2.** All laboratory assessments to be completed prior to dosing
**3.** Pregnancy test (all females of childbearing potential) U = Urine

## 11.1 Appendix 1: Time and Events Table (Continued)

| Procedure | Treatment Period (Visit Window is ± 1 Week) | | | | | | | | | | | | Exit/ EW Visit[4] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **32** | **33** | **34** | **35** | **36** | **37** | **38** | **39** | **40** | **41** | **42** | **43** | **44** |
| **Week of study** | **124** | **128** | **132** | **136** | **140** | **144** | **148** | **152** | **156** | **160** | **164** | **168** | **172** |
| **Safety Assessments** | | | | | | | | | | | | | |
| Concomitant Medication | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical Examination | | | | | | | | | | | | | X |
| Vital Signs | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG | | | | | | X | | | | X | | | X |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Serious Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Laboratory Assessments**[2] | | | | | | | | | | | | | |
| Immunogenicity | | | | | | X | | | | | | | X |
| Hematology | | | | | | X | | | | | | X | X |
| Chemistry | | | | | | X | | | | | | X | X |
| Liver Analytes | | | | | | X | | | | | | X | X |
| Pregnancy Test[3] | U | U | U | U | U | U | U | U | U | U | U | U | U |
| **Efficacy Assessments** | | | | | | | | | | | | | |
| Exacerbation review | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Asthma Control Questionnaire-5 | | | X | | | X | | | X | | | X | X |
| Spirometry | | | | | | X | | | | | | X | X |
| **Worksheets/IP/eCRF** | | | | | | | | | | | | | |
| Administer Mepolizumab 100mg SC | X | X | X | X | X | X | X | X | X | X | X | X | |
| Dispense Paper Worksheet | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Collect Paper Worksheet | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Register IVRS/IWRS | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Complete eCRF | X | X | X | X | X | X | X | X | X | X | X | X | X |

**2.** All laboratory assessments to be completed prior to dosing

**3.** Urine pregnancy test for all females of childbearing potential, U = Urine

**4.** In the event a subject withdraws early at a scheduled visit, all study procedures scheduled for the Exit Visit (Visit 44) should be performed at this visit instead. In the event a subject withdraws between visits, the subject should be asked to return to the clinic as soon as possible to complete the Exit Visit procedures.

## 11.2. Appendix 2: Acceptable Birth Control

To be eligible for entry into the study, females of childbearing potential must commit to consistent and correct use of an acceptable method of birth control from the time of consent, for the duration of the trial, and for 4 months after the last study drug administration.

- Male partner who is sterile prior to the female subject's entry into the study and is the sole sexual partner for that female subject
- Abstinence from penile-vaginal intercourse
- Implants of levonorgestrel or etonogestrel
- Injectable progestogen
- Oral contraceptive (either combined or progestogen alone)
- Estrogenic vaginal ring
- Percutaneous contraceptive patches
- Any intrauterine device (IUD) with a documented failure rate of less than 1% per year.
- Male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository). The vaginal spermicide must be specified for use with the chosen male condom
- Male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository). The vaginal spermicide must be specified for use with the chosen male condom

Females of childbearing potential are defined as females with functioning ovaries (i.e., post-menarche, premenopausal women with no documented impairment of oviductal or uterine function that would cause sterility). This category includes females with oligomenorrhea, females who are peri-menopausal, and young females who have begun to menstruate (adolescents). The information on the lack of impairment of oviductal or uterine function that would cause sterility, can come from the site personnel's:

- Review of subject's medical records
- Medical examination of the subject
- Interview with the subject on her medical history.

Females of non-childbearing potential are defined as females with functioning ovaries and with a documented tubal ligation or hysterectomy; or females who are postmenopausal defined as 12 months of spontaneous amenorrhea with an appropriate clinical profile, e.g. age appropriate, >45 years, in the absence of hormone replacement therapy (HRT).

In questionable cases a blood sample for follicle stimulating hormone (FSH) and estradiol will be obtained and analyzed to confirm childbearing potential.

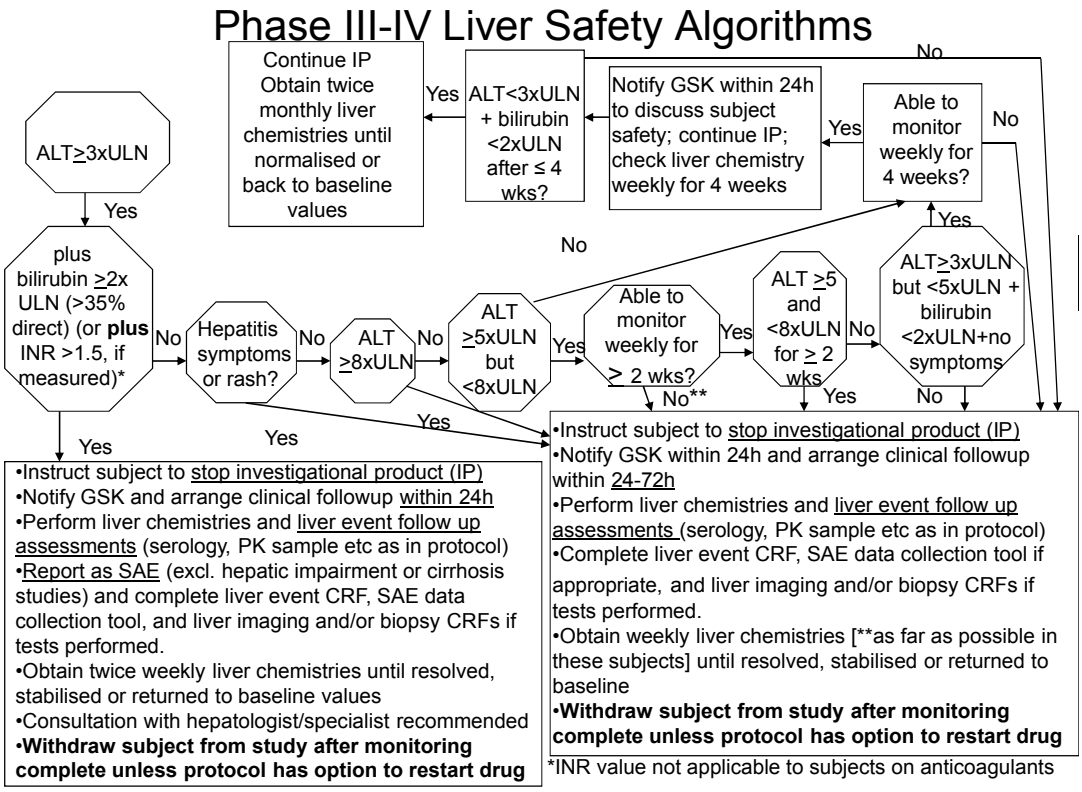
Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the contraception methods listed above for females of childbearing potential if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment. For most forms of HRT, at least 2-4 weeks should elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, they can resume use of HRT during the study without use of a contraceptive method.

Based on the absence of an identified reproductive hazard from preclinical studies, absence of a genotoxic potential, and very low levels of mepolizumab that might be present in semen, there is no recognized risk for mepolizumab to affect human sperm or the fetus if transferred to a female partner via semen. Therefore, the use of condoms or other methods of contraception in the male study subject is not required.

## 11.3. Appendix 3: Country Specific Requirements

No country-specific requirements exist.

## 11.4. Appendix 4: Liver Chemistry Stopping and Follow-up Criteria



## 11.5. Appendix 5: Liver Safety Drug Restart or Rechallenge Guidelines

1. Drug restart may be considered for a subject exhibiting compelling benefit for a critical medicine following drug-induced liver injury, if favorable benefit: risk and no alternative medicine available. It applies to Phase I-IV studies (excluding healthy volunteer studies; example of phase I studies are oncology studies).
2. In Phase III-IV, drug restart may be considered for liver safety events with a clear underlying cause (e.g. biliary, pancreatic events, hypotension, acute viral hepatitis), if not associated with drug-induced liver injury, alcoholic hepatitis, or hypersensitivity (fever, rash or eosinophilia) and drug not associated with HLA genetic marker of liver injury, when liver chemistries have improved to normal or are within 1.5x baseline and ALT<3xULN.

**Liver Events Possibly Related to IP - Drug Restart/Rechallenge Following Possible Drug-induced Liver Injury Challenge Guidelines**

Following drug-induced liver injury, **drug restart or rechallenge is associated with a 13% mortality across all drugs in prospective studies**[1] Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered in one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality. Risk factors for a fatal drug restart/rechallenge outcome include: hypersensitivity[1] with initial liver injury (e.g. fever, rash, eosinophilia), jaundice or bilirubin ≥2xULN or INR>1.5 suggesting severe liver injury, prior IP-related severe or fatal drug restart/rechallenge[2,3] or evidence of drug-related preclinical liability / mitochondrial impairment[3]

**GSK Decision Process for Drug Restart Approval or Disapproval (also see Figure 1)**

- Principal Investigator (PI) requests consideration of drug restart for a subject receiving compelling benefit from a critical or life-saving drug, who exhibits liver chemistry elevation meeting subject stopping criteria, with no alternative treatment
- GSK Medical Monitor & Clinical Safety Physician.to review the subject's restart/rechallenge risk factors & complete checklist (Table 3).

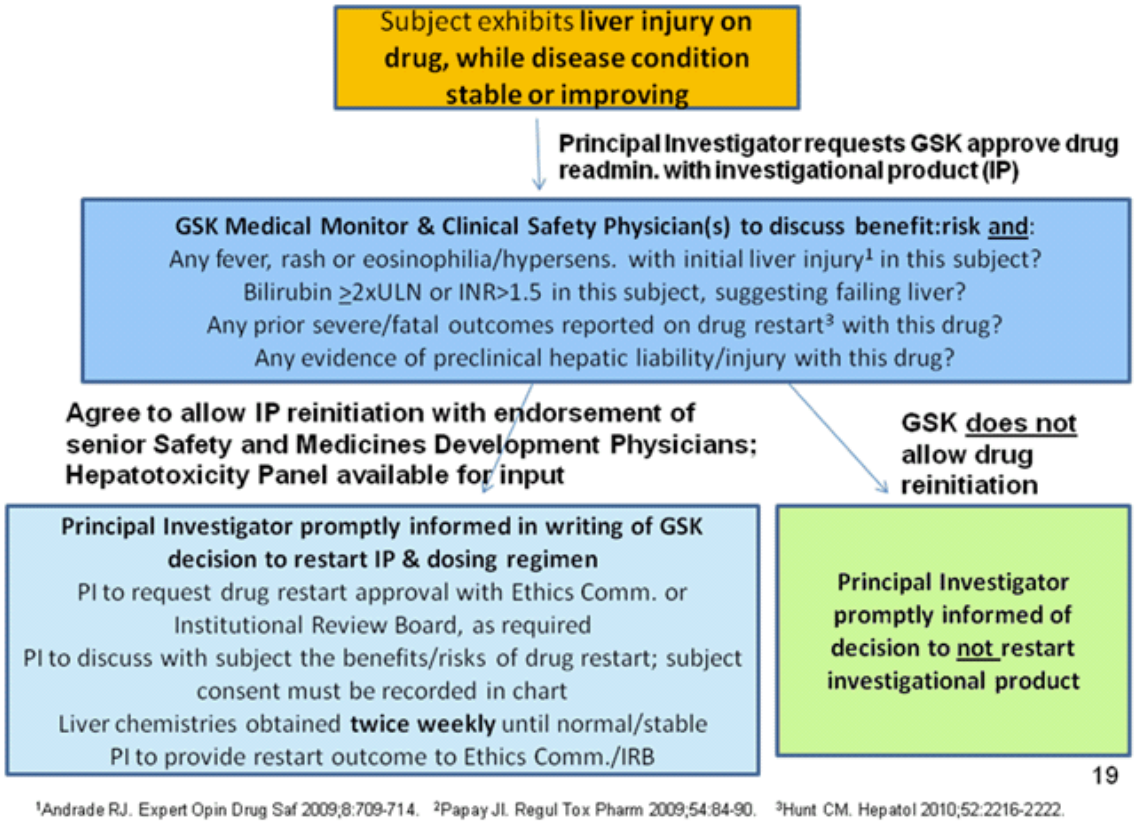
**Table 3 Checklist for drug rechallenge for critical medicine (Following drug-induced liver injury, drug rechallenge is associated with 13% mortality across all drugs in prospective studies)**

| | Yes | No |
|---|---|---|
| **Compelling benefit** of the investigational product (IP) **for this subject and no alternative therapy. Provide brief explanation:** | | |
| **Relative benefit-risk favorable for drug restart/rechallenge**, after considering the **following high risk factors**: | | |
| • Initial liver injury event included: | | |
| ○ fever, rash, eosinophilia, or hypersensitivity | | |
| ○ or bilirubin>2xULN (direct bilirubin >35% of total) | | |
| • Subject currently exhibits ALT ≥ 3xULN, bilirubin ≥ 2xULN (direct bilirubin >35% of total, if available), or INR ≥ 1.5 | | |
| • Severe or fatal restart/rechallenge has earlier been observed with IP **If yes, please provide brief explanation**: | | |
| • IP associated with known preclinical hepatic liability/ injury | | |

***Principal Investigator (PI) Actions:**

- The PI must obtain Ethics Committee or Institutional Review Board review of drug reinitiation, as required.
- PI must discuss the possible benefits and risks of drug reinitiation with the subject.
- The subject must sign informed consent with a clear description of possible benefits and risks of drug administration, including recurrent liver injury or death. Consent must be recorded in the study chart.
- The drug must be reinitiated at GSK approved dose(s).
- Liver chemistries should be followed twice weekly until stable.
- The Ethics Committee or Institutional Review Board must be informed of the subject's outcome, as required.
- GSK to be notified of any adverse events, as per Section 6.3.2-Section 6.3.3.

**Figure 1 GSK process for drug restart after possible drug-induced liver injury**




References:

**1.** Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.

2. Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010;52:2216-2222.

3. Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009;54:84-90.

## Drug Restart Guidelines

### GSK Decision Process for Drug Restart Approval or Disapproval (also see Figure 2)

- Principal Investigator (PI) requests consideration of drug reinitiation for a subject stable or improving on investigational product (IP), who exhibits liver chemistry elevation meeting subject stopping criteria, which is transient, non-drug-related, and resolves.
- GSK Medical Monitor & Clinical Safety Physician to review the subject's diagnosis, restart risk factors & complete checklist (Table 4).

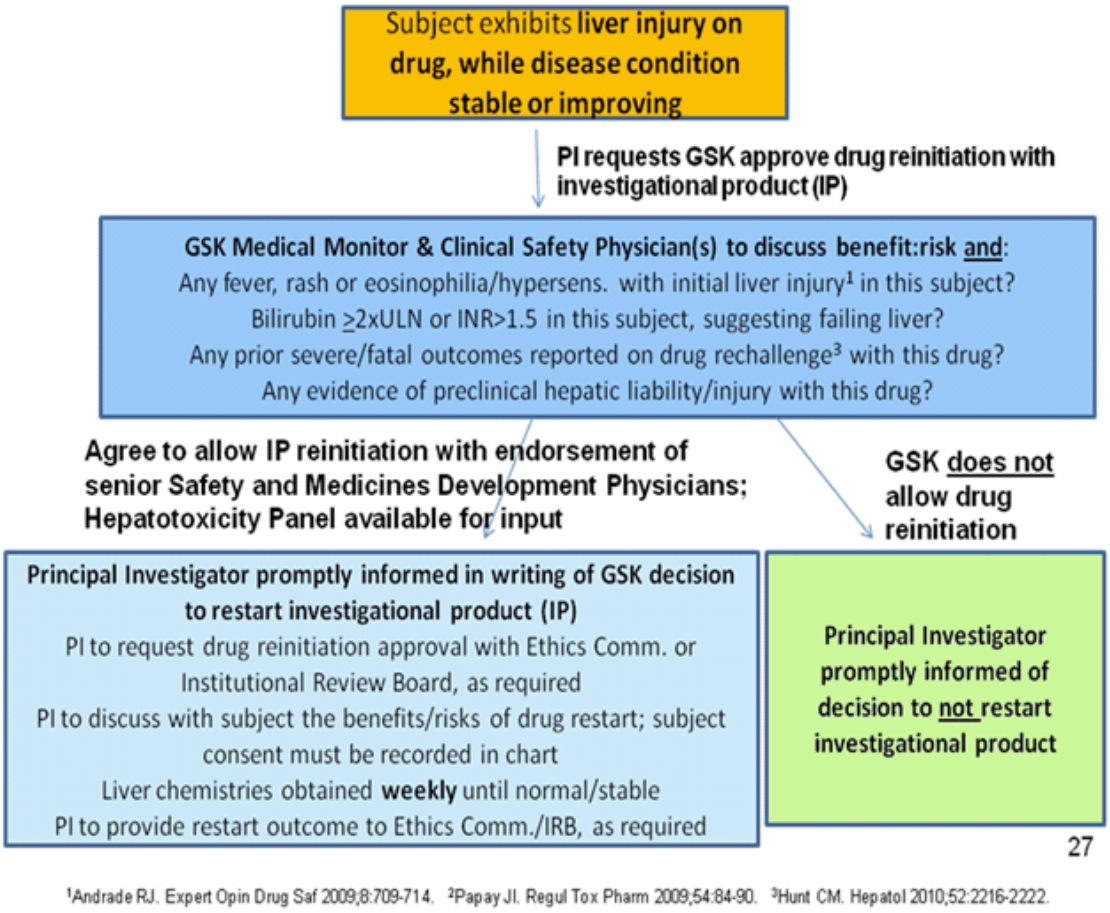
**Table 4 Checklist for Phase III drug restart after well-explained liver injury (e.g. biliary, pancreatic, hypotensive events, CHF, acute viral hepatitis), liver chemistries improving to normal, or ≤ 1.5x baseline and ALT<3xULN**

| | Yes | No |
|---|---|---|
| **Is subject stable or improving** on the investigational product (IP)? | | |
| **Do not restart** if the **following risk factors at initial liver injury:** | | |
| • fever, rash, eosinophilia, or hypersensitivity | | |
| • drug-induced liver injury | | |
| • alcoholic hepatitis (AST>ALT, typically <10xULN) | | |
| • IP associated with liver injury and an HLA genetic marker (e.g. lapatinib, abacavir, amoxicillin/clavulanate) | | |

### *Principal Investigator (PI) Actions

- The PI must obtain Ethics Comm. or Institutional Review Board review of drug reinitiation, as required.
- PI must discuss the benefits and risks of drug reinitiation with the subject.
- The subject must sign informed consent with a clear description of possible benefits and risks of drug administration, including recurrent liver injury or death. Consent must be recorded in the study chart.
- Liver chemistries should be followed weekly until stable.
- The Ethics Committee or Institutional Review Board must be informed of the patient's outcome, as required.
- GSK to be notified of any adverse or serious adverse events, as per Section 6.3.2-Section 6.3.3.

**Figure 2 GSK process for drug restart approvals**




## References


- Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.
- Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010;52:2216-2222.
- Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009;54:84-90.

## 11.6. Appendix 6: Anaphylaxis Criteria

Hypersensitivity reactions will be monitored using the diagnostic criteria for anaphylaxis as outlined by the Joint NIAID/FAAN Second Symposium on Anaphylaxis [Sampson 2006]. The criteria do not make a distinction based on underlying mechanism. These criteria are summarized as follows:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
    b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

## 11.7. Appendix 7: Protocol Amendment 01 Changes

Scope: this applies to all sites

Protocol Changes specified in Amendment No. 01 are summarised below:

**Change 1:** Study Design (Page 10) and 3.1 Study Design (page 20).

To ensure subjects are monitored according to best practice if the time between Visit 14 in MEA115661 and the start of study medication in 201312 exceeds 8 weeks.

**Original Text:**

This is a multi-center, open-label, long-term study of mepolizumab 100mg administered SC, in addition to standard of care (SOC), in subjects with severe eosinophilic asthma. Only subjects who complete the MEA115661 Exit Visit (Visit 14) will be offered the opportunity to consent for this study. Subjects meeting all of the eligibility criteria for the study will be offered the opportunity to consent for this study of up to 128 weeks in length (including the Follow-Up Visit). The Exit Visit (Visit 14) in MEA115661 will serve as the baseline visit (Visit 1) for this study (Study 201312). For sites not receiving regulatory and/or ethics approval prior to Visit 14, the window for Visit 1 can be up to 8 weeks after V14. Subjects who consent to participate in Study 201312 and who fulfill entry criteria will not perform the Follow-Up Visit for MEA115661.

**Revised Text:**

This is a multi-center, open-label, long-term study of mepolizumab 100mg administered SC, in addition to standard of care (SOC), in subjects with severe eosinophilic asthma. Only subjects who complete the MEA115661 Exit Visit (Visit 14) will be offered the opportunity to consent for this study. Subjects meeting all of the eligibility criteria for the study will be offered the opportunity to consent for this study of up to 128 weeks in length (including the Follow-Up Visit).

It is expected that the majority of eligible subjects will enter 201312 within 8 weeks of completing, the Exit Visit (Visit 14) in MEA115661. In this scenario (scenario 1), this Exit Visit will serve as the baseline visit (Visit 1) for this study (201312). The invasive procedures, e.g. blood draw, spirometry and ECG are not repeated and data from these procedures performed at the Exit Visit (Visit 14) of MEA115661 will be used for the baseline analysis. All other safety related procedures will be performed. Eligible subjects in scenario 1 will not perform the Follow-Up Visit (Visit 15) for MEA115661.

If the window between the Exit Visit (Visit 14) of MEA115661 and Visit 1 of 201312 is greater than 8 weeks, the subject should complete MEA115661 by performing the Follow-up visit (Visit 15). Once approvals for 201312 are received, eligible subject will begin study 201312 and perform all procedures listed for Visit 1. In this scenario (scenario 2), Visit 1 of 201312 will serve as the baseline visit.

All applicable procedures for scenario 1 and 2 are listed in Section 6.1. Critical Baseline Assessments.

All eligible subjects should be enrolled into 201312 within 4 weeks of receiving all applicable approvals.

**Change 2:** 4.2 Inclusion Criteria. Edit of entry criterion number 6 Disease Severity (page 23).

To introduce a definition of serious debilitating asthma.

**Original Text:**

***6.*** **Disease Severity**: Subjects must be assessed as having life-threatening /serious debilitating asthma in order to enroll, as defined by the following:

***Subjects enrolled in MEA115588 must meet one of the following criteria:***

a) Subject has a history of at least one intubation during their lifetime
b) ≥3 asthma exacerbations in the 12 months prior to screening for MEA115588
c) ≥1 or more hospitalization for asthma exacerbation in the 12 months prior to screening for MEA115588.

***Subjects enrolled in MEA115575 must meet one of the following criteria:***

d) Subject has a history of at least one intubation during their lifetime
e) Their optimized dose at randomization in MEA115575 was ≥10mg of prednisone
f) ≥1 or more hospitalization for asthma exacerbation in the 12 months prior to screening for MEA115575

**Revised Text:**

***6.*** **Disease Severity**: Subjects must be assessed as having life-threatening asthma or serious debilitating asthma in order to enroll.

Life threatening asthma is defined by the following:

***Subjects enrolled in MEA115588 must meet one of the following criteria:***

a) Subject has a history of at least one intubation during their lifetime
b) ≥3 asthma exacerbations in the 12 months prior to screening for MEA115588
c) ≥1 or more hospitalization for asthma exacerbation in the 12 months prior to screening for MEA115588.

***Subjects enrolled in MEA115575 must meet one of the following criteria:***

d) Subject has a history of at least one intubation during their lifetime
e) Their optimized dose at randomization in MEA115575 was ≥10mg of prednisone
f) ≥1 or more hospitalization for asthma exacerbation in the 12 months prior to screening for MEA115575

Those subjects that do **not** meet the definition of potentially life threatening asthma must be assessed as having serious debilitating asthma.

***Subjects enrolled in MEA115588 or MEA115575 must meet all of the following criteria:***

At randomisation of MEA115588 or MEA115575 must have:

g) A % predicted $FEV_1$ of ≤50% and **either**
h) ACQ5 score of ≥3 **or**
i) SGRQ score of ≥60

**Change 3:** 4.2 Inclusion Criteria. Edit of entry criterion number 7 Clinical Benefit (page 23).

To remove the Clinical-Rated Response to Therapy assessment and replace with an investigator confirmed demonstrated improvement whilst receiving mepolizumab.

**Original Text:**

*7.* **Clinical Benefit**: Subjects must have experienced documented clinical benefit to enroll. Subjects must meet the following criteria demonstrating clinical benefit:

***Subjects enrolled in MEA115588 who received mepolizumab must meet all of the following criteria:***

a) Subject must have had a reduction in their exacerbation frequency by ≥50% during MEA115588. The baseline for comparison is the total number of exacerbations reported in the 12 months prior to screening for MEA115588.
b) The investigator response on the "Clinician-Rated Response to Therapy" questionnaire at Visit 10 was either: mildly improved, moderately improved or significantly improved.

***Subjects enrolled in MEA115588 who received placebo must meet all of the following criteria:***

c) Subject must have had a reduction in their exacerbation frequency by ≥50% during the first 8 months of MEA115661. The baseline for comparison is the total number of exacerbations reported in the 12 months prior to screening for MEA115588.
d) The investigator confirms that the subject demonstrated improvement during MEA115661.

***Subjects enrolled in MEA115575 who received mepolizumab must meet all of the following criteria:***

e) Subject must have reduced their oral corticosteroid dose by ≥ 50% during MEA115575. The baseline for comparison is the subject's optimized OCS dose at randomization in MEA115575.
f) The investigator response on the "Clinician-Rated Response to Therapy" questionnaire at Visit 9 was either: mildly improved, moderately improved or significantly improved.

***Subjects enrolled in MEA115575 who received placebo must meet all of the following criteria:***

g) Subject must have reduced their oral corticosteroid dose at randomization by ≥50% in the first 6 months of MEA115661. The baseline for comparison is the subject's optimized OCS dose at randomization in MEA115575.
h) The investigator confirms that the subject demonstrated improvement during MEA115661.

**Revised Text:**

*7.* **Clinical Benefit**: Subjects must have experienced documented clinical benefit to enroll. Subjects must meet the following criteria demonstrating clinical benefit:

***Subjects enrolled in MEA115588 who received mepolizumab must meet all of the following criteria:***

a) Subject must have had a reduction in their exacerbation frequency by ≥50% during MEA115588. The baseline for comparison is the total number of exacerbations reported in the 12 months prior to screening for MEA115588.
b) The investigator confirms that the subject demonstrated improvement during MEA115588.

***Subjects enrolled in MEA115588 who received placebo must meet all of the following criteria:***

c) Subject must have had a reduction in their exacerbation frequency by ≥50% during the first 8 months of MEA115661. The baseline for comparison is the total number of exacerbations reported in the 12 months prior to screening for MEA115588.
d) The investigator confirms that the subject demonstrated improvement during MEA115661.

***Subjects enrolled in MEA115575 who received mepolizumab must meet all of the following criteria:***

e) Subject must have reduced their oral corticosteroid dose by ≥ 50% during MEA115575. The baseline for comparison is the subject's optimized OCS dose at randomization in MEA115575
f) The investigator confirms that the subject demonstrated improvement during MEA115575.

***Subjects enrolled in MEA115575 who received placebo must meet all of the following criteria:***

g) Subject must have reduced their oral corticosteroid dose at randomization by ≥50% in the first 6 months of MEA115661. The baseline for comparison is the subject's optimized OCS dose at randomization in MEA115575.
h) The investigator confirms that the subject demonstrated improvement during MEA115661.

**Change 4:** Section 4.3 Exclusion Criteria No. 7. (page 25) Clarification to ensure that subjects with a clinically significant abnormal ECG are not entered into 201312.

**Original Text:** 7. ECG Assessment: A clinically significant ECG abnormality at the exit visit of MEA115661, as determined by the investigator.

**Revised Text: 7.** ECG Assessment: A clinically significant ECG abnormality as determined by the investigator.

**Change 5:** 4.3 Exclusion Criteria. To clarify exclusion criterion number 6 Previous Significant Protocol Deviation (page 25).

**Original Text:**

6. **Previous Significant Protocol Deviation**: Subjects who were excluded from the per protocol analysis due to significant protocol deviations in either study MEA115575 or MEA115588.

**Revised Text:**

6. **Previous Significant Protocol Deviation**: Subjects who were excluded from the per protocol analysis due to a significant protocol deviation in either study MEA115575 or MEA115588 which is deemed by the GSK Medical Monitor to put the subject at risk from further participation.

**Change 6:** 6.3.10.2. Physical Examination (page 45). To remove the examination for nasal polyps.

**Original Text:**

A detailed physical examination including, but not limited to, an evaluation of the lungs and cardiovascular system will be conducted at Visit 1, Exit/Early Withdrawal and the Follow-Up Visit. This examination should also include observation of the nasal cavities for the presence of nasal polyps. For the US, licensed practitioners who are listed on the Form 1572 can complete the physical examination. A licensed physician on the Form 1572 must sign off on the physical examinations completed by non-physicians. In countries outside of the US, the physical examination should be conducted by a medically qualified person; however, if the physical examination is conducted by non-physicians, a medically qualified person must sign off.

**Revised Text:**

A detailed physical examination including, but not limited to, an evaluation of the lungs and cardiovascular system will be conducted at Visit 1, Exit/Early Withdrawal and the Follow-Up Visit. For the US, licensed practitioners who are listed on the Form 1572 can complete the physical examination. A licensed physician on the Form 1572 must sign off on the physical examinations completed by non-physicians. In countries outside of the US, the physical examination should be conducted by a medically

qualified person; however, if the physical examination is conducted by non-physicians, a medically qualified person must sign off.

**Change 7:** 6.1 Critical Baseline Assessments (page 31). To clarify the process and which assessments are required in 201312 if there is a delay of greater than 8 weeks between the Exit visit (Visit 14) of MEA115661 and the start of participation in 201312. Clarification of No. 5 for scenario 1 and scenario 2 by removing the bulleted sentence.

**Original Text:**

Baseline assessments at Visit 1 will be comprised of the following in the list below. Assessments performed as part of the Exit Visit for MEA115661 do not have to be repeated for Visit 1 of 201312 as results will be transferred accordingly.

1. Demographic information review
2. General medical history review and update
3. Physical examination
    - To include a nasal exam to check for nasal polyps
4. Pulmonary function tests and assessment
5. Assessment of Inclusion/Exclusion criteria.
    - Results of laboratory tests and the ECG over-read results from Visit 1 will be reviewed at Visit 2.
6. Asthma Control Questionnaire-5 (Section 6.2.1.2)
7. Vital signs (Section 6.3.10.3)
8. 12-lead ECG (Section 6.3.10.4)
9. Blood sampling for the following:
    - Clinical chemistry
    - Hematology
    - Liver Analytes
    - Immunogenicity
10. Urine pregnancy test for females of childbearing potential (Appendix 2: Acceptable Birth Control)

**Revised Text:**

For scenario 1 subjects, i.e. those that have a window of less than or equal to 8 weeks between the Exit Visit (Visit 14) of MEA115661 and the start of participation in 201312, certain assessments performed as part of the Exit Visit for MEA115661 do not have to be repeated.

For scenario 2 subjects, i.e. those that have a window of greater than 8 weeks, must perform the Follow-up visit (Visit 15) of MEA115661 and when approvals for 201312 are in place, must complete all procedures listed for Visit 1. Baseline assessments performed for scenario 1 subjects:

1. Demographic information review
2. General medical history review and update
3. Physical examination
4. Assessment of Inclusion/Exclusion criteria.
5. Asthma Control Questionnaire-5 (Section 6.2.1.2)
6. Vital signs (Section 6.3.10.3)
7. Urine pregnancy test for females of childbearing potential (Appendix 2: Acceptable Birth Control)

Baseline assessments performed for scenario 2 subjects:

1. Demographic information review
2. General medical history review and update
3. Physical examination
4. Pulmonary function tests and assessment
5. Assessment of Inclusion/Exclusion criteria.
6. Asthma Control Questionnaire-5 (Section 6.2.1.2)
7. Vital signs (Section 6.3.10.3)
8. 12-lead ECG (Section 6.3.10.4)
9. Blood sampling for the following:
    - Clinical chemistry
    - Hematology
    - Liver Analytes
    - Immunogenicity
10. Urine pregnancy test for females of childbearing potential (Appendix 2: Acceptable Birth Control)

**Change 8:** 11.1. Appendix 1: Time and Events Table, footnote no. 1 (page 53-56).

To clarify the process if the delay between MEA115661 and 201312 is greater than 8 weeks.

**Original Text:**

1. Visit 1 is the same as Visit 14 of MEA115661 however for sites not receiving regulatory and/or ethics approval prior to Visit 14, the window for Visit 1 is + 8 weeks after V14; Assessments performed as part of the exit visit for MEA115661 do not have to be repeated for Visit 1 of 201312 as results will be transferred accordingly.

**Revised Text:**

1. For scenario 1 subjects, that is when the window between Visit 14 and Visit 1 is ≤8 weeks all procedures should be performed **except** laboratory tests from blood (urine pregnancy test **must** be performed), spirometry and ECG. For scenario 2 subjects, that is when the window between Visit 14 and Visit 1 is >8 weeks, the subject should complete the Follow-up visit (Visit 15) for MEA115661. Once approvals are received the subject can only then begin 201312 and must perform **all** procedures listed for Visit 1 above.

**Change 9:** Figure 1: GSK process for drug restart after possible drug-induced liver injury (page 63): Duplicate diagram removed.

**Change 10:** Figure 2: GSK process for drug restart approvals (page 67): Duplicate diagram removed.

**Change 11:** Section 5.5 Product Accountability, (page 29). Added "where applicable" to clarify that where rescue medicine is provided to the subject, it should be accounted for.

**Original Text:**

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

**Revised Text:**

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned by study subjects (where applicable), and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

**Change 12:** Section 6.2. Efficacy Endpoints, (page 32). To add the Forced expiratory volume in 1 second (FEV1), which was missing from this section only due to an oversight.

**Orignal Text:**

- Annualized rate of exacerbations
- Asthma Control Questionnaire-5 score

**Revised Text:**

- Annualized rate of exacerbations
- Asthma Control Questionnaire-5 score
- Forced expiratory volume in 1 second (FEV1)

**Change 13:** A change of Sponsor Global Back-up Medical Monitor Contact Information page 3):

**Original Text:**

PPD MD (Director, Respiratory Medicine Development Centre)
Tel: PPD
Mobile: PPD

**Revised Text:**

PPD MD (Director, Respiratory Medicine Development Centre)
Tel: PPD
Mobile: PPD

**Change 14:** Section 11.2 Appendix 2: Acceptable Birth Control (page 57). The addition of text to ensure that the vaginal spermicide used is specified for use with the chosen male condom.

**Original Text:**

- Male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository).
- Male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).

**Revised Text:**

- Male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository). The vaginal spermicide must be specified for use with the chosen male condom,

- Male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository). The vaginal spermicide must be specified for use with the chosen male condom

**Change 15:** Section 1.3.1 Risk Assessment, (page 15, Table 1). Table updated with new information and some text reorganised.

**Original Text:**

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Investigational Product (IP) SB 240563** | | |
| Risk of Systemic Allergic and Non-allergic Reactions, including Anaphylaxis | Biopharmaceutical products may elicit anti-drug antibody (ADA) and neutralizing antibody (NAB), which have the potential to modulate pharmacokinetic (PK), pharmacodynamic (PD) or produce adverse reactions. However, humanized and fully human antibodies are less immunogenic than mouse or chimeric monoclonal antibodies.<br><br>Reactions reported to date across the mepolizumab program are summarized in the IB; see 'Special Warnings and Special Precautions for Use' section located in Section 6 titled 'Summary of Data and Guidance for the Investigator'. | Daily monitoring of serious adverse events (SAEs) by medical monitor; regular systematic review of adverse event (AE)/SAE data from ongoing studies by a GSK safety review team.<br><br>Specific case report form (CRF) pages utilized for targeted collection of reactions data.<br><br>Use of Joint NIAID/FAAN 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (Appendix 6 Anaphylaxis Criteria).<br><br>Subjects are to be monitored based on institutional practices. |
| Risk of Immunogenicity | See previous risk for background information in literature.<br><br>Immunogenicity data reported to date across the mepolizumab development program are summarized in the IB; See Section 5.4 'Clinical Immunogenicity' and a summary of immunogenicity findings in the 'Other Potentially Clinically Relevant | Blood samples are collected in clinical studies for detection of both ADA and NAB.<br><br>See previous risk for mitigation strategy related to clinical safety risks. |

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | Information for the Investigator' section located in Section 6.titled 'Summary of Data and Guidance for the Investigator's Brochure. | |
| Potential risk for adverse cardiovascular (CV) effects | Mepolizumab binding was restricted to human lymphoid tissues in an immunohistochemistry tissue binding study suggesting a low likelihood of non-pharmacologic effects on cardiovascular (CV) function.<br><br>No AEs concerning cardiac conduction or repolarization evident in cynomolgus monkeys at doses at least 10-fold in excess of humans dosed at 10 mg/kg or 750 mg.<br><br>No clinically relevant trends observed in ECG data in humans.<br><br>In one study in subjects with severe refractory asthma, cardiac events were reported in similar frequencies across treatment groups with a small numerical increase observed in serious ischemic cardiac events in the mepolizumab-treated groups. However, an integrated safety analysis of all placebo-controlled multiple dose asthma trials showed similar frequency of SAEs reported overall from the cardiac and vascular system organ class (SOC). Additionally, similar findings were observed in other SOCs with thrombotic events (e.g., stroke in the Nervous System SOC). | Daily monitoring of SAE by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team.<br><br>CV monitoring for study includes:<br><br>• ECG monitoring during the trial<br><br>• Use of standardized CRFs to collect relevant data on CV events of interest (i.e., myocardial infarction, hospitalization for unstable angina and congestive heart failure, arterial thrombosis, pulmonary embolism and deep vein thrombosis);<br><br>• Adjudication of cardiovascular events |

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| Potential risk for increase in infections – a theoretical concern with biologics; however, the pharmacological properties of mepolizumab suggest the risk is low. | No evidence of increased incidence of infections in any preclinical studies.<br><br>Murine data demonstrate that IL-5 antagonism is unlikely to influence cellular or humoral immunity, particularly in response to parasitic infections.<br><br>No mepolizumab-related effects on lymphocyte Immunophenotyping in monkeys or humans, including T-cell activation, distribution of CD4/CD8 subtypes or Th1/Th2 cytokine patterns, B-cells, NK cells or γδ-T-cells.<br><br>An integrated safety analysis of all placebo-controlled multiple dose asthma trials showed SAEs reported in the infection and infestation SOC were 5/345 (1%) in placebo subjects and 18/754 (2%) in mepolizumab subjects.<br><br>Infections reported to date across the mepolizumab development program are summarized in the IB; see 'Special Precautions and Warnings' (for exclusion of subjects with underlying parasitic infections) and 'Undesirable Effects' (for very common infections of nasopharyngitis, URTI, rhinitis and bronchitis reported in other patient populations) sections located in Section 6 titled 'Summary of Data and Guidance for the Investigator'. | Daily monitoring of SAE by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team<br><br>Standard safety assessments to be conducted as outlined in protocols |

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| Potential risk for increase in malignancies - theoretical concern with biologics; however, blockade of IL-5 is not associated with generalized immuno-suppression or impaired host resistance. | Role of IL-5 and eosinophils in tumor surveillance is not fully characterised in the literature.<br><br>No evidence of defective tumor surveillance in IL-5 or eosinophil-deficient mice.<br><br>Direct assessment of the carcinogenic potential of long-term IL-5 blockade in rodent models not technically feasible.<br><br>Malignancies reported to date across the mepolizumab development program are summarized in the IB. | Daily monitoring of SAE by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team<br><br>Standard safety assessments to be conducted as outlined in protocols |
| Potential risk for rebound eosinophilia with associated clinical consequences | Early published data with Schering-Plough anti- IL5 mAb suggested potential for rebound eosinophilia and disease exacerbation when treatment was stopped [Kim, 2004; Gevaert, 2006]; however, no standard definition of rebound was used and criteria for reporting were variable.<br><br>There have been no verbatim reports of 'rebound' from completed clinical trials of subjects with asthma, atopic dermatitis and eosinophilic esophagitis. Furthermore, the data do not support an exaggerated return of symptoms after cessation of treatment. | Daily monitoring of SAE by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team<br><br>Standard safety assessments to be conducted as outlined in protocols |
| **Study Procedures** | | |
| Potential risk for injury with phlebotomy | Risks with phlebotomy include bruising, bleeding, infection, nerve damage. | Procedures to be performed by trained personnel (i.e., study nurse) |

**Revised Text:**

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Investigational Product (IP) SB 240563** | | |
| Risk of Systemic Allergic and Non-allergic Reactions, including Anaphylaxis | Reactions reported to date across the mepolizumab program are summarized in the IB; see 'Special Warnings and Special Precautions for Use' section located in Section 6 titled 'Summary of Data and Guidance for the Investigator'. | Daily monitoring of serious adverse events (SAEs) by medical monitor; regular systematic review of adverse event (AE)/SAE data from ongoing studies by a GSK safety review team.<br><br>Specific case report form (CRF) pages utilized for targeted collection of reactions data.<br><br>Use of Joint NIAID/FAAN 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (Appendix 6 Anaphylaxis Criteria).<br><br>Subjects are to be monitored based on institutional practices. |
| Risk of Immunogenicity | Biopharmaceutical products may elicit anti-drug antibody (ADA) and neutralizing antibody (NAB), which have the potential to modulate pharmacokinetic (PK), pharmacodynamic (PD) or produce adverse reactions. However, humanized and fully human antibodies are less immunogenic than mouse or chimeric monoclonal antibodies.<br><br>Immunogenicity data reported to date across the mepolizumab development program are summarized in the IB; See Section 5.4 'Clinical Immunogenicity' and a summary of immunogenicity | Blood samples are collected in clinical studies for detection of both ADA and NAB.<br><br>See previous risk for mitigation strategy related to clinical safety risks. |

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | findings in the 'Other Potentially Clinically Relevant Information for the Investigator' section located in Section 6.titled 'Summary of Data and Guidance for the Investigator's Brochure. | |
| Potential risk for adverse cardiovascular (CV) effects | Mepolizumab binding was restricted to human lymphoid tissues in an immunohistochemistry tissue binding study suggesting a low likelihood of non-pharmacologic effects on cardiovascular (CV) function.<br><br>No AEs concerning cardiac conduction or repolarization evident in cynomolgus monkeys at doses at least 10-fold in excess of humans dosed at 10 mg/kg or 750 mg.<br><br>No clinically relevant trends observed in ECG data in humans.<br><br>In one study in subjects with severe refractory asthma, cardiac events were reported in similar frequencies across treatment groups with a small numerical increase observed in serious ischemic cardiac events in the mepolizumab-treated groups. However, an integrated safety analysis of all placebo-controlled multiple dose asthma trials showed similar frequency of SAEs reported overall from the cardiac and vascular system organ class (SOC). Additionally, similar findings were observed in other SOCs with thrombotic events (e.g., stroke in the Nervous System SOC). Data from 2 | Daily monitoring of SAE by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team.<br><br>CV monitoring for study includes:<br><br>• ECG monitoring during the trial<br><br>• Use of standardized CRFs to collect relevant data on CV events of interest (i.e., myocardial infarction, hospitalization for unstable angina and congestive heart failure, arterial thrombosis, pulmonary embolism and deep vein thrombosis);<br><br>• Adjudication of cardiovascular events |

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | subsequently completed placebo-controlled severe asthma trials did not show an increased risk of serious ischemic cardiac events; there were no new reports in any treatment groups including placebo. | |
| Potential risk for increase in infections – a theoretical concern with biologics; however, the pharmacological properties of mepolizumab suggest the risk is low. | No evidence of increased incidence of infections in any preclinical studies.<br><br>Murine data demonstrate that IL-5 antagonism is unlikely to influence cellular or humoral immunity, particularly in response to parasitic infections.<br><br>No mepolizumab-related effects on lymphocyte Immunophenotyping in monkeys or humans, including T-cell activation, distribution of CD4/CD8 subtypes or Th1/Th2 cytokine patterns, B-cells, NK cells or γδ-T-cells.<br><br>An integrated safety analysis of all placebo-controlled multiple dose asthma trials showed SAEs reported in the infection and infestation SOC were 5/345 (1%) in placebo subjects and 18/754 (2%) in mepolizumab subjects.<br><br>Infections reported to date across the mepolizumab development program are summarized in the IB; see 'Special Precautions and Warnings' (for exclusion of subjects with underlying parasitic infections) and 'Undesirable Effects' (for very common infections of nasopharyngitis, URTI, | Daily monitoring of SAE by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team<br><br>Standard safety assessments to be conducted as outlined in protocols |

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | rhinitis and bronchitis reported in other patient populations) sections located in Section 6 titled 'Summary of Data and Guidance for the Investigator'. | |
| Potential risk for increase in malignancies - theoretical concern with biologics; however, blockade of IL-5 is not associated with generalized immuno-suppression or impaired host resistance. | Role of IL-5 and eosinophils in tumor surveillance is not fully characterised in the literature.<br><br>No evidence of defective tumor surveillance in IL-5 or eosinophil-deficient mice.<br><br>Direct assessment of the carcinogenic potential of long-term IL-5 blockade in rodent models not technically feasible.<br><br>Malignancies reported to date across the mepolizumab development program are summarized in the IB. | Daily monitoring of SAE by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team<br><br>Standard safety assessments to be conducted as outlined in protocols |
| Potential risk for rebound eosinophilia with associated clinical consequences | Early published data with Schering-Plough anti- IL5 mAb suggested potential for rebound eosinophilia and disease exacerbation when treatment was stopped [Kim, 2004; Gevaert, 2006]; however, no standard definition of rebound was used and criteria for reporting were variable.<br><br>There have been no verbatim reports of 'rebound' from completed clinical trials of subjects with asthma, atopic dermatitis and eosinophilic esophagitis. Furthermore, the data do not support an exaggerated return of symptoms after cessation of treatment. | Daily monitoring of SAE by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team<br><br>Standard safety assessments to be conducted as outlined in protocols |

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Study Procedures** | | |
| Potential risk for injury with phlebotomy | Risks with phlebotomy include bruising, bleeding, infection, nerve damage. | Procedures to be performed by trained personnel (i.e., study nurse) |

## 11.8. Appendix 8: Protocol Amendment 02 Changes

**Scope**: this applies to all sites

Protocol changes specified in Amendment No. 02 are summarised below:

**Change No. 1:** The addition of an Inclusion criterion to Section 4.2 Inclusion Criteria:

**Additional Text:**

**8.** If criteria 6 and 7 are not met, subjects who are considered to be at risk of experiencing a life-threatening event or whose functional health status will become significantly worse if returned to standard of care, as judged by the investigator and agree by GSK.

**Change 2:** The addition of a third subject scenario when entering 201312 from MEA115661. Multiple sections are clarified, including the same change made to Protocol Summary, Study Design (page 11) and to Section 3.1. Study Design (page 20). Additionally, Section 6.1 Critical Baseline Assessments and Appendix 1: Time and Events Schedule, footnote 1.

**Original Text:**

**3.1 Study Design**

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This is a multi-center, open-label, long-term study of mepolizumab 100mg administered SC, in addition to standard of care (SOC), in subjects with severe eosinophilic asthma. Only subjects who complete the MEA115661 Exit Visit (Visit 14) will be offered the opportunity to consent for this study. Subjects meeting all of the eligibility criteria for the study will be offered the opportunity to consent for this study of up to 128 weeks in length (including the Follow-Up Visit).

It is expected that the majority of eligible subjects will enter 201312 within 8 weeks of completing the Exit Visit (Visit 14) in MEA115661. In this scenario (scenario 1), this Exit Visit will serve as the baseline visit (Visit 1) for this study (201312). The invasive procedures, e.g. blood draw, spirometry and ECG are not repeated and data from these procedures performed at the Exit Visit (Visit 14) of MEA115661 will be used for the baseline analysis. All other safety related procedures will be performed. Eligible subjects in scenario 1 will not perform the Follow-Up Visit (Visit 15) for MEA115661.

If the window between the Exit Visit (Visit 14) of MEA115661 and Visit 1 of 201312 is greater than 8 weeks, the subject should complete MEA115661 by performing the Follow-up visit (Visit 15). Once approvals for 201312 are received, eligible subjects will begin 201312 and perform all procedures stated for Visit 1. In this scenario (scenario 2), Visit 1 of 201312 will serve as the baseline visit.

All applicable procedures for scenario 1 and 2 are listed in Section 6.1. Critical Baseline Assessments.

**Changed To:**

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This is a multi-center, open-label, long-term study of mepolizumab 100mg administered SC, in addition to standard of care (SOC), in subjects with severe eosinophilic asthma. Only subjects who complete the MEA115661 Exit Visit (Visit 14) will be offered the opportunity to consent for this study. Subjects meeting all of the eligibility criteria for the study will be offered the opportunity to consent for this study of up to 128 weeks in length (including the Follow-Up Visit).

It is expected that the majority of eligible subjects will enter 201312 within 8 weeks of completing the Exit Visit (Visit 14) in MEA115661.

To reduce the burden of repeated procedures during the ending of MEA115661 and the start of 201312, subjects will start the study according to a specific "scenario". This depends on when their Visit 1 occurs in relation to the Visit 14 of the MEA115661 study.

**Scenario 1** is when Visit 1 of 201312 is performed on the same day (or less than or equal to 8 weeks) from when Visit 14 of study MEA115661 is performed.

**Scenario 2a** is when Visit 1 of 201312 is performed greater than 8 weeks after Visit 14 of MEA115661 AND when Visit 1 of 201312 is performed on the same day as the Follow-up visit (Visit 15) of study MEA115661.

**Scenario 2b** is when Visit 1 of 201312 is performed greater than 8 weeks after Visit 14 of MEA115661 AND Visit 1 of 201312 is performed after the Follow-up visit (Visit 15) of study MEA115661 has taken place.

All applicable procedures for scenario 1, and 2a and 2b subjects are listed in Section 6.1. Critical Baseline Assessments.

**Change 3:** Clarification of the subject scenarios in Section 6.1 Critical Baseline Assessments

**Original Text:**

For scenario 1 subjects, i.e. those that have a window of less than or equal to 8 weeks between the Exit Visit (Visit 14) of MEA115661 and the start of participation in 201312, certain assessments performed as part of the Exit Visit for MEA115661 do not have to be repeated.

For scenario 2 subjects, i.e. those that have a window of greater than 8 weeks, must perform the Follow-up visit (Visit 15) of MEA115661 and when approvals for 201312

are in place, must complete all procedures listed for Visit 1. Baseline assessments performed for scenario 1 subjects:

1. Demographic information review
2. General medical history review and update
3. Physical examination
4. Assessment of Inclusion/Exclusion criteria.
5. Asthma Control Questionnaire-5 (Section 6.2.1.2)
6. Vital signs (Section 6.3.10.3)
7. Urine pregnancy test for females of childbearing potential (Appendix 2: Acceptable Birth Control)

Baseline assessments performed for scenario 2 subjects:

1. Demographic information review
2. General medical history review and update
3. Physical examination
4. Pulmonary function tests and assessment
5. Assessment of Inclusion/Exclusion criteria.
6. Asthma Control Questionnaire-5 (Section 6.2.1.2)
7. Vital signs (Section 6.3.10.3)
8. 12-lead ECG (Section 6.3.10.4)
9. Blood sampling for the following:
    - Clinical chemistry
    - Hematology
    - Liver Analytes
    - Immunogenicity
10. Urine pregnancy test for females of childbearing potential (Appendix 2: Acceptable Birth Control)

**Amended Text:**

Baseline assessments performed for scenario 1 subjects in study 201312:

1. Demographic information review and update for 201312
2. General medical history review and update in 201312
3. Physical examination and update in 201312
4. Assessment of Inclusion/Exclusion criteria.

5. Urine pregnancy test for females of childbearing potential (Appendix 2: Acceptable Birth Control)

Baseline assessments performed for scenario 2a subjects in study 201312:

1. Demographic information review and update for 201312
2. General medical history review and update in 201312
3. Physical examination and update in 201312
4. Pulmonary function tests and assessment
5. Assessment of Inclusion/Exclusion criteria.
6. Urine pregnancy test for females of childbearing potential (Appendix 2: Acceptable Birth Control)

For scenario 2b subjects in study 201312, the following assessments should be performed:

1. Demographic information review and update for 201312
2. General medical history review and update in 201312
3. Physical examination and update in 201312
4. Pulmonary function tests and assessment
5. Assessment of Inclusion/Exclusion criteria.
6. Asthma Control Questionnaire-5 (Section 6.2.1.2)
7. Vital signs (Section 6.3.10.3)
8. 12-lead ECG (Section 6.3.10.4)
9. Blood sampling for the following:
    - Clinical chemistry
    - Hematology
    - Liver Analytes
    - Immunogenicity
10. Urine pregnancy test for females of childbearing potential (Appendix 2: Acceptable Birth Control)

Please see the SPM for more detail around the required baseline assessments.

**Change 4**: A change to footnote one of the T&E schedule (Appendix 1)

**Original Text:**

1. For scenario 1 subjects, that is when the window between Visit 14 and Visit 1 is ≤8 weeks, all procedures should be performed **except** laboratory tests from blood (urine pregnancy test **must** be performed), spirometry and ECG. For scenario 2 subjects, that is when the window between Visit 14 and Visit 1 is >8 weeks, the subject should complete

the Follow-up visit (Visit 15) for MEA115661. Once approvals are received the subject can only then begin 201312 and must perform **all** procedures listed for Visit 1 above.

**Amended Text:**

1. Before entry in to study 201312, determine which scenario the subject is best classified as and perform the relevant procedures as defined in Section 6.1 and the SPM.

**Change 5:** An administrative change of the Medical Monitors details on page 3:

**Original Text:**

**Sponsor Global Medical Monitor Contact Information**:

PPD MD (Director, Respiratory Medicine Development Centre)
Tel: PPD
Mobile: PPD

**Sponsor Global Back-up Medical Monitor Contact Information:**

PPD MD (Director, Respiratory Medicine Development Centre)
Tel: PPD
Mobile: PPD

**Sponsor Serious Adverse Events (SAE) Contact Information:**

PPD MD (Director, Respiratory Medicine Development Centre)
Tel: PPD
Mobile: PPD

**Amended Text:**

**Sponsor Global Medical Monitor Contact Information**:

PPD MA MSc. MBBS FFPM (Clinical Development Physician)
Tel: PPD
Mobile: PPD

**Sponsor Global Back-up Medical Monitor Contact Information:**

PPD MD (Clinical Development Physician)
Tel: PPD
Mobile: PPD

**Sponsor Serious Adverse Events (SAE) Contact Information:**

PPD MD (Clinical Development Physician)
Tel: PPD
Mobile: PPD

## 11.9. Appendix 9: Protocol Amendment 03 Changes

**Scope**: this applies to all sites

Protocol changes specified in Amendment No. 03 are summarised below:

**Change No. 1**: Increasing the duration of IP from 2 to 3 years. This occurs in multiple sections of the protocol listed below. The rationale is that 201312 will begin to close on a country by country basis when mepolizumab becomes commercially available. Some subjects will complete the 2 year treatment period before commercial availability and to ensure that all subjects have a seamless transition from IP to commercially available mepolizumab the study treatment duration is increased to three years.

**Change No. 2:** Removal of the Follow-up Visit. This occurs in multiple sections of the protocol listed below. The rationale is that the original reason for the Follow-up visit was to collect the final immunogenicity sample 12 weeks after the last dose of IP. The sensitivity of the immunogenicity test has since improved and the immunogenicity sample at the Exit visit is now sufficient.

**Study Design**

Original text:

Subjects meeting all of the eligibility criteria will be offered the opportunity to consent for this study of up to 128 weeks (including Follow-Up).

Changed to:

Subjects meeting all of the eligibility criteria will be offered the opportunity to consent for this study of up to 172 weeks.

**Study Design**

Original text:

Mepolizumab will then be administered approximately every 4 weeks with the last dose at Week 116 (Visit 30). Thirty doses will provide therapeutic coverage for 120 weeks (4 weeks following the last dose). ). Subjects will continue to receive mepolizumab 100mg SC injections for up to 116 weeks or until one of the following occurs:

Changed to:

Mepolizumab will then be administered approximately every 4 weeks with the last dose at Week 168 (Visit 43). Forty three doses will provide therapeutic coverage for 172 weeks (4 weeks following the last dose). Subjects will continue to receive mepolizumab 100mg SC injections for up to 172 weeks or until one of the following occurs:

**Additional paragraph added to Study Design**

The study closure process will begin, on a country by country basis, as mepolizumab becomes commercially available for prescription. Some subjects will complete the original 120 week treatment period (as specified in the previous protocol) prior to mepolizumab being available for prescription. To ensure these subjects do not have a treatment gap the treatment period will be extended for an additional 52 weeks to a total of 172 weeks.

**Study Design**

Original text:

The Asthma Control Questionnaire-5 (ACQ-5) will be performed every 12 weeks during the study, at the Exit/Early Withdrawal Visit, and Follow-Up Visit to assist the investigator in monitoring the subject's asthma status along with spirometry assessments every 6 months and at the Exit/Early Withdrawal Visit.

Safety labs (hematology, chemistry, and liver analytes) will be drawn at Visit 1 and then approximately every 6 months thereafter. Hematology and chemistry labs will also be obtained 12 weeks after the subject's last dose of mepolizumab. Serum samples for anti-mepolizumab antibody measurements will also be obtained from subjects at baseline (Visit 1), Weeks 48, 96, Exit Visit/Early Withdrawal Visit and the Follow-Up Visit. Any serum sample testing positive for anti-mepolizumab antibody will also be tested for neutralizing antibody. Subjects discontinuing mepolizumab treatment will be monitored for exacerbation of their asthma during the subsequent 12 weeks after their last dose.

Changed to:

The Asthma Control Questionnaire-5 (ACQ-5) will be performed every 12 weeks during the study and at the Exit/Early Withdrawal Visit to assist the investigator in monitoring the subject's asthma status along with spirometry assessments every 6 months and at the Exit/Early Withdrawal Visit.

Safety labs (hematology, chemistry, and liver analytes) will be drawn at Visit 1 and then approximately every 6 months thereafter. Hematology and chemistry labs will also be obtained 4 weeks after the subject's last dose of mepolizumab. Serum samples for anti-mepolizumab antibody measurements will also be obtained from subjects at baseline (Visit 1), Weeks 48, 96, 144 and at the Exit Visit/Early Withdrawal Visit. Any serum sample testing positive for anti-mepolizumab antibody will also be tested for neutralizing antibody. Subjects discontinuing mepolizumab treatment will be monitored for exacerbation of their asthma during the subsequent 4 weeks after their last dose.

**Section 3.1 Study Design**

Original text:

Subjects meeting all of the eligibility criteria will be offered the opportunity to consent for this study of up to 128 weeks in length (including the Follow-Up visit).

Changed to:

Subjects meeting all of the eligibility criteria will be offered the opportunity to consent for this study of up to 172 weeks in length.

**Section 3.1 Study Design**

Original text:

Mepolizumab will then be administered approximately every 4 weeks with the last dose at Week 116 (Visit 30). Thirty doses will provide therapeutic coverage for 120 weeks (4 weeks following the last dose). ). Subjects will continue to receive mepolizumab 100mg SC injections for up to 116 weeks or until one of the following occurs:

Changed to:

Mepolizumab will then be administered approximately every 4 weeks with the last dose at Week 168 (Visit 43). Forty three doses will provide therapeutic coverage for 172 weeks (4 weeks following the last dose). Subjects will continue to receive mepolizumab 100mg SC injections for up to 172 weeks or until one of the following occurs:

**Additional paragraph added to Section 3.1 Study Design**

The study closure process will begin, on a country by country basis, as mepolizumab becomes commercially available for prescription. Some subjects will complete the original 120 week treatment period (as specified in the previous protocol) prior to mepolizumab being available for prescription. To ensure these subjects do not have a treatment gap the treatment period will be extended for an additional 52 weeks to a total of 172 weeks.

**Section 3.1 Study Design**

Original text:

The Asthma Control Questionnaire-5 (ACQ-5) will be performed every 12 weeks during the study, at the Exit/Early Withdrawal Visit, and Follow-Up Visit to assist the investigator in monitoring the subject's asthma status along with spirometry assessments every 6 months and at the Exit/Early Withdrawal Visit.

Safety labs (hematology, chemistry, and liver analytes) will be drawn at Visit 1 and then approximately every 6 months thereafter. Hematology and chemistry labs will also be obtained 12 weeks after the subject's last dose of mepolizumab. Serum samples for anti-mepolizumab antibody measurements will also be obtained from subjects at baseline (Visit 1), Weeks 48, 96, Exit Visit/Early Withdrawal Visit and the Follow-Up Visit. Any serum sample testing positive for anti-mepolizumab antibody will also be tested for neutralizing antibody. Subjects discontinuing mepolizumab treatment will be monitored for exacerbation of their asthma during the subsequent 12 weeks after their last dose.

Changed to:

The Asthma Control Questionnaire-5 (ACQ-5) will be performed every 12 weeks during the study and at the Exit/Early Withdrawal Visit to assist the investigator in monitoring the subject's asthma status along with spirometry assessments every 6 months and at the Exit/Early Withdrawal Visit.

Safety labs (hematology, chemistry, and liver analytes) will be drawn at Visit 1 and then approximately every 6 months thereafter. Hematology and chemistry labs will also be obtained 4 weeks after the subject's last dose of mepolizumab. Serum samples for anti-mepolizumab antibody measurements will also be obtained from subjects at baseline (Visit 1), Weeks 48, 96, 144 and at the Exit Visit/Early Withdrawal Visit. Any serum sample testing positive for anti-mepolizumab antibody will also be tested for neutralizing antibody. Subjects discontinuing mepolizumab treatment will be monitored for exacerbation of their asthma during the subsequent 4 weeks after their last dose.

**Section 4.4.3.1. General Withdrawal Requirements**

Original text:

Subjects may also be withdrawn from this study if mepolizumab becomes commercially available in the respective country, if marketing of mepolizumab is no longer being sought in the respective country, or upon decision of the sponsor to discontinue further development of mepolizumab. Every effort should be made to have the subject complete the Exit/Early Withdrawal and Follow-Up Visits.

Changed to:

Subjects may also be withdrawn from this study if mepolizumab becomes commercially available in the respective country, if marketing of mepolizumab is no longer being sought in the respective country, or upon decision of the sponsor to discontinue further development of mepolizumab. Every effort should be made to have the subject complete the Exit/Early Withdrawal Visit.

**Section 4.4.4 Subject Self-Withdrawal**

Original text:

Every effort should be made to have the subject return for a follow-up visit 12 weeks post last mepolizumab injection.

Changed to:

Every effort should be made to have the subject return for an Exit/Early Withdrawal visit 4 weeks post last mepolizumab injection.

**Section 6.3.6 Pregnancy**

Original text:

A urine pregnancy test will be performed for all females of child bearing potential prior to enrollment, during each scheduled study visit prior to the injection of investigational product, and during the Follow-up Visit.

Changed to:

A urine pregnancy test will be performed for all females of child bearing potential prior to enrollment, during each scheduled study visit prior to the injection of investigational product, and during the Exit/Early Withdrawal Visit.

**Section 6.3.10.2 Physical Examination**

Original text:

A detailed physical examination including, but not limited to, an evaluation of the lungs and cardiovascular system will be conducted at Visit 1, Exit/Early Withdrawal and the Follow-Up Visit..

Changed to:

A detailed physical examination including, but not limited to, an evaluation of the lungs and cardiovascular system will be conducted outlined in Time and Events Table (Appendix 1 Time and Events Table).

**Section 11.1 Appendix 1: Time and Events Table**

Original text:

Multiple changes made. See over page.

| **Procedures** | **Week 52 of MEA115661[1]** | **Treatment Period (Visit Window is ± 1 week)** | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** |
| **Week of study** | **0** | **4** | **8** | **12** | **16** | **20** | **24** | **28** | **32** | **36** | **40** | **44** | **48** | **52** | **56** | **60** |
| Written Informed Consent | X | | | | | | | | | | | | | | | |
| Medical History Changes | X | | | | | | | | | | | | | | | |
| Smoking Status | X | | | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | | | | | | | | | | |
| **Safety Assessments** | | | | | | | | | | | | | | | | |
| Concomitant Medication | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical Examination | X | | | | | | | | | | | | | | | |
| Vital Signs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG | X | | | | | | X | | | | | | X | | | |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Serious Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Laboratory Assessments[2]** | | | | | | | | | | | | | | | | |
| Immunogenicity | X | | | | | | | | | | | | X | | | |
| Hematology | X | | | | | | X | | | | | | X | | | |
| Chemistry | X | | | | | | X | | | | | | X | | | |
| Liver Analytes | X | | | | | | X | | | | | | X | | | |
| Pregnancy Test[3] | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U |
| **Efficacy Assessments** | | | | | | | | | | | | | | | | |
| Exacerbation review | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Asthma Control Questionnaire-5 | X | | | X | | | X | | | X | | | X | | | X |
| Spirometry | X | | | | | | X | | | | | | X | | | |

| **Procedures** | **Week 52 of MEA115661[1]** | **Treatment Period (Visit Window is ± 1 week)** | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** |
| **Week of study** | **0** | **4** | **8** | **12** | **16** | **20** | **24** | **28** | **32** | **36** | **40** | **44** | **48** | **52** | **56** | **60** |
| **Worksheets/IP/eCRF** | | | | | | | | | | | | | | | | |
| Administer Mepolizumab 100mg SC | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Dispense paper worksheet | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Collect paper worksheet | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Register IVRS/IWRS | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Complete eCRF | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

**1.** Before entry in to study 201312, determine which scenario the subject is best classified as and perform the relevant procedures as defined in Section 6.1 and the SPM.
**2.** All laboratory assessments to be completed prior to dosing
**3.** Pregnancy test (all females of childbearing potential) U = Urine

| **Procedure** | **Treatment Period (Visit Window is ± 1 Week)** | | | | | | | | | | | | | | **Exit/ EW Visit[4]** | **Follow-Up Visit[5]** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** | **30** | **31** | **32** |
| **Week of study** | **64** | **68** | **72** | **76** | **80** | **84** | **88** | **92** | **96** | **100** | **104** | **108** | **112** | **116** | **120** | **128** |
| **Safety Assessments** | | | | | | | | | | | | | | | | |
| Concomitant Medication | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Physical Examination | | | | | | | | | | | | | | | X | X |
| Vital Signs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG | | | X | | | | | | X | | | | | | X | |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Serious Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Laboratory Assessments[2]** | | | | | | | | | | | | | | | | |
| Immunogenicity | | | | | | | | | X | | | | | | X | X |
| Hematology | | | X | | | | | | X | | | | | | X | X |
| Chemistry | | | X | | | | | | X | | | | | | X | X |
| Liver Analytes | | | X | | | | | | X | | | | | | X | X |

| **Procedure** | **Treatment Period (Visit Window is ± 1 Week)** | | | | | | | | | | | | | | **Exit/ EW Visit**[4] | **Follow-Up Visit**[5] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** | **30** | **31** | **32** |
| **Week of study** | **64** | **68** | **72** | **76** | **80** | **84** | **88** | **92** | **96** | **100** | **104** | **108** | **112** | **116** | **120** | **128** |
| Pregnancy Test[3] | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U |
| **Efficacy Assessments** | | | | | | | | | | | | | | | | |
| Exacerbation review | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Asthma Control Questionnaire-5 | | | X | | | X | | | X | | | X | | | X | X |
| Spirometry | | | X | | | | | | X | | | | | | X | |
| **Worksheets/IP/eCRF** | | | | | | | | | | | | | | | | |
| Administer Mepolizumab 100mg SC | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Dispense Paper Worksheet | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Collect Paper Worksheet | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Register IVRS/IWRS | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Complete eCRF | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

**1.** Before entry in to study 201312, determine which scenario the subject is best classified as and perform the relevant procedures as defined in Section 6.1 and the SPM.

**2.** All laboratory assessments to be completed prior to dosing

**3.** Urine pregnancy test for all females of childbearing potential, U = Urine

**4.** In the event a subject withdraws early at a scheduled visit, all study procedures scheduled for the Exit Visit (Visit 31) should be performed at this visit instead. In the event a subject withdraws between visits, the subject should be asked to return to the clinic as soon as possible to complete the Exit Visit procedures.

**5.** Follow-up visit is to occur approximately 12 weeks after the last injection of mepolizumab. The visit window is ±1 week.

Changed to:

| **Procedures** | **Treatment Period (Visit Window is ± 1 week)** | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** | **30** | **31** |
| **Week of study** | **64** | **68** | **72** | **76** | **80** | **84** | **88** | **92** | **96** | **100** | **104** | **108** | **112** | **116** | **120** |
| **Safety Assessments** | | | | | | | | | | | | | | | |
| Concomitant Medication | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical Examination | | | | | | | | | | | | | | | |
| Vital Signs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG | | | | | | X | | | | | | X | | | |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Serious Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Laboratory Assessments**[2] | | | | | | | | | | | | | | | |
| Immunogenicity | | | | | | | | | X | | | | | | |
| Hematology | | | X | | | | | | X | | | | | | X |
| Chemistry | | | X | | | | | | X | | | | | | X |
| Liver Analytes | | | X | | | | | | X | | | | | | X |
| Pregnancy Test[3] | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U |
| **Efficacy Assessments** | | | | | | | | | | | | | | | |
| Exacerbation review | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Asthma Control Questionnaire-5 | | | X | | | X | | | X | | | X | | | X |
| Spirometry | | | X | | | | | | X | | | | | | X |

| **Procedures** | **Treatment Period (Visit Window is ± 1 week)** | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** | **30** | **31** |
| **Week of study** | **64** | **68** | **72** | **76** | **80** | **84** | **88** | **92** | **96** | **100** | **104** | **108** | **112** | **116** | **120** |
| **Worksheets/IP/eCRF** | | | | | | | | | | | | | | | |
| Administer Mepolizumab 100mg SC | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Dispense paper worksheet | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Collect paper worksheet | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Register IVRS/IWRS | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Complete eCRF | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

**2.** All laboratory assessments to be completed prior to dosing
**3.** Pregnancy test (all females of childbearing potential) U = Urine

| **Procedure** | **Treatment Period (Visit Window is ± 1 Week)** | | | | | | | | | | | | **Exit/ EW Visit**[4] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **32** | **33** | **34** | **35** | **36** | **37** | **38** | **39** | **40** | **41** | **42** | **43** | **44** |
| **Week of study** | **124** | **128** | **132** | **136** | **140** | **144** | **148** | **152** | **156** | **160** | **164** | **168** | **172** |
| **Safety Assessments** | | | | | | | | | | | | | |
| Concomitant Medication | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical Examination | | | | | | | | | | | | | X |
| Vital Signs | X | X | X | X | X | X | X | X | X | X | X | X | X |
| 12-lead ECG | | | | | | X | | | | | | | X |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Serious Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Laboratory Assessments**[2] | | | | | | | | | | | | | |
| Immunogenicity | | | | | | X | | | | | | | X |
| Hematology | | | | | | X | | | | | | X | X |
| Chemistry | | | | | | X | | | | | | X | X |
| Liver Analytes | | | | | | X | | | | | | X | X |
| Pregnancy Test[3] | U | U | U | U | U | U | U | U | U | U | U | U | U |
| **Efficacy Assessments** | | | | | | | | | | | | | |

| **Procedure** | **Treatment Period (Visit Window is ± 1 Week)** | | | | | | | | | | | | **Exit/ EW Visit**[4] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | **32** | **33** | **34** | **35** | **36** | **37** | **38** | **39** | **40** | **41** | **42** | **43** | **44** |
| **Week of study** | **124** | **128** | **132** | **136** | **140** | **144** | **148** | **152** | **156** | **160** | **164** | **168** | **172** |
| Exacerbation review | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Asthma Control Questionnaire-5 | | | X | | | X | | | X | | | X | X |
| Spirometry | | | | | | X | | | | | | X | X |
| **Worksheets/IP/eCRF** | | | | | | | | | | | | | |
| Administer Mepolizumab 100mg SC | X | X | X | X | X | X | X | X | X | X | X | X | |
| Dispense Paper Worksheet | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Collect Paper Worksheet | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Register IVRS/IWRS | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Complete eCRF | X | X | X | X | X | X | X | X | X | X | X | X | X |

**2.** All laboratory assessments to be completed prior to dosing

**3.** Urine pregnancy test for all females of childbearing potential, U = Urine

**4.** In the event a subject withdraws early at a scheduled visit, all study procedures scheduled for the Exit Visit (Visit 44) should be performed at this visit instead. In the event a subject withdraws between visits, the subject should be asked to return to the clinic as soon as possible to complete the Exit Visit procedures.

**Change No. 3:** The following changes are regarding the change in time from reconstitution to administration and the monitoring time after administration of mepolizumab.

**Section 5.2 Dosage and Administration**

Original text:

Once the mepolizumab vial is reconstituted, 100mg of mepolizumab should be drawn into a polypropylene syringe and administered immediately

Changed to:

Once the mepolizumab vial is reconstituted, 100mg of mepolizumab should be drawn into a polypropylene syringe and administered according to the instructions in the SPM.

**Section 6.3 Safety**

Original text:

- Systemic reactions can be allergic or non-allergic in nature and are typically mild to moderate in intensity, generally develop within several hours of the injection, and are most commonly associated with a complex of symptoms including chills, fever, nausea, vomiting, asthenia, headache, skin rash, pruritus, urticaria, arthralgia/myalgia, hypotension/hypertension, dizziness, bronchospasm, dyspnea or cough. Subjects must be monitored during IP administration and for 1 hour post-administration.

Changed to:

- Systemic reactions can be allergic or non-allergic in nature and are typically mild to moderate in intensity, generally develop within several hours of the injection, and are most commonly associated with a complex of symptoms including chills, fever, nausea, vomiting, asthenia, headache, skin rash, pruritus, urticaria, arthralgia/myalgia, hypotension/hypertension, dizziness, bronchospasm, dyspnea or cough.

**Change No. 4:** The following change is to standardise the collection of concomitant medications for subjects moving from MEA115661 to 201312.

**Section 5.7.1 Permitted Medications and Non-Drug Therapies**

Original text:

Subjects will be required to continue ICS controller therapy for the duration of this study. For corticosteroids, the dose must be recorded as well as any dose changes. All other concomitant medications taken during the study will also be recorded in the electronic case report form (eCRF). The minimum requirement is that drug name and the dates of administration are to be recorded.

Additional medications to treat asthma are permitted, as are medications to treat other disease states, with the exception of those listed as prohibited in Table 2. Oxygen and Continuous Positive Airway Pressure (CPAP) are permitted for the treatment of obstructive sleep apnea.

Changed to:

Subjects will be required to continue ICS controller therapy for the duration of this study. For corticosteroids, the dose must be recorded as well as any dose changes

Details of asthma-related concomitant medications administered from the first dose of mepolizumab in 201312 until the Exit/Early Withdrawal visit or last subject visit will be recorded in the electronic case report form (eCRF). In addition, any asthma-related medications started prior to first dose in 201312, but were ongoing during the first dose will also be recorded. The minimum requirement is that drug name, unit dose, and the dates of administration are to be recorded.

Details of  non-asthma-related concomitant medications administered from the first dose of mepolizumab in 201312 until the Exit/Early Withdrawal visit or last subject visit will be recorded in the electronic case report form (eCRF).Additional medications to treat asthma are permitted, as are medications to treat other disease states, with the exception of those listed as prohibited in Table 2. Oxygen and Continuous Positive Airway Pressure (CPAP) are permitted for the treatment of obstructive sleep apnea.