TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	MEA115666: A multi-centre, open-label, long term safety study of mepolizumab in asthmatic subjects who participated in the MEA112997 trial.

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Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2012N139436_00	2012-MAY-31	Original
2012N139436_01	2012-AUG-21	Amendment No.: 1
• To clarify that the rationale and objective of the study includes long-term provision of mepolizumab therapy to subjects who have severe asthma and participated in MEA112997 • To clarify that only monoclonal antibodies are excluded, rather than all biologics • To clarify reason for more frequent safety monitoring at the start of the study • To correct Inclusion criterion 5 from Randomisation Visit to Visit 2 • To add exclusion criterion for significant cardiovascular disease • To correct inconsistencies between protocol text and the Time and Events Table • To correct bilirubin exclusion criterion at visit 2 • To expand on requirements for designating a subject as lost to follow-up • To add visit window for the follow-up visit • To move baseline spirometry from the screen visit to the baseline visit • To clarify that all subjects will have an immunogenicity test 12 weeks after last dose • To correct Section 8.3.5.2 wording “Efficacy” to “Safety” • To add reference to support Appendix 6 and remove 3 references which are not cited in the protocol. • To add Appendix 5 and Appendix 6 and amended Section 6.1 and Section 6.3.9. to support the determination of exclusion criteria 4		
2012N139436_02	2013-MAR-06	Amendment No.02
• To add two additional immunogenicity sample assessment time points when the 100mg vial is introduced. • To allow other syringe sizes for study drug administration • To allow for study drug administration in the upper thigh or the arm • To add the prohibited non-drug therapies to Section 5.7.2 • To list Adverse Events and Serious Adverse Events on the same line in Table 3 • To correct a formatting error for Section 4.6		

• To remove specific test name for confirming Hepatitis C positive sample • To delete redundant text in Section 6.3.3.1 • To remove from Section 6.3.7 the requirement to report outcome of pregnancy in female partners of male subjects • To include analyses of immunogenicity data in Section 8.3 and to clarify when interim analyses will be performed		
2012N139436_03	2015-JUN-19	Amendment No. 3
• To reduce the Follow-up visit period from 12 weeks to 4 weeks post last dose of IP • To update the time limit from reconstitution to administration of IP		

SPONSOR SIGNATORY

PPD

June 19, 2015.
Date

Director, Respiratory Therapeutic Unit

Research & Development

SPONSOR INFORMATION PAGE

Clinical Study Identifier: MEA115666

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number MEA115666

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

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LIST OF ABBREVIATIONS

ACQ	Asthma Control Questionnaire
AE	Adverse Event
ALT	Alanine transaminase
AST	Aspartate transaminase
ATS	American Thoracic Society
CIB	Clinical Investigator Brochure
CPAP	Continuous Positive Airway Pressure
CS	Corticosteroid
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case report form
ED	Emergency Department
ERS	European Respiratory Society
FEV1	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
HBsAg	Hepatitis B Surface Antigen
HIV	Human Immunodeficiency Virus
IDMC	Independent Data Monitoring Committee
IC_{50}	Inhibitory Concentration 50%
ICS	Inhaled corticosteroids
ICU	Intensive Care Unit
IEC	Independent ethics committee
Ig	Immunoglobulin
IL	Interleukin
IM	Intramuscular
IP	Investigational Product
IRB	Institutional review board
ITT	Intent to Treat
IUD	Intrauterine Device
IV	Intravenous
IVRS	Interactive voice response system
LABA	Long-acting beta-2-agonists
LTRA	Leukotriene receptor antagonist
MedDRA	Medicinal dictionary for regulatory activities
mcg	Micrograms
MDI	Metered Dose Inhaler
mg	Milligram
N/A	Not applicable
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart Lung and Blood Institute
OCS	Oral corticosteroids
OLE	Open Label Extension Study

PEF	Peak expiratory flow
RAP	Reporting and Analysis Plan
SABA	Short-acting beta-2-agonists
SAE	Serious adverse event
SC	Subcutaneous
SPM	Study procedures manual
ULN	Upper Limit of Normal

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PROTOCOL SUMMARY

RATIONALE

This study will provide long term safety and immunogenicity data when mepolizumab is administered subcutaneously (SC) in subjects with severe, refractory asthma and a history of eosinophilic inflammation. Additionally, this study will inform on the safety and immunogenicity profile when mepolizumab therapy is reinstituted in subjects following a cessation in drug therapy.

This trial also provides subjects who participated in the MEA112997 study, and meet the current trial eligibility criteria, the option of receiving treatment with mepolizumab, as an add-on to their standard of care treatment for severe asthma.

OBJECTIVE(S)

PRIMARY

The primary objective of this study is to describe the long-term safety profile of mepolizumab.

SECONDARY

To provide long-term treatment with mepolizumab to subjects who participated in MEA112997

To evaluate the effects of mepolizumab on a range of clinical markers of asthma control

STUDY DESIGN

This is a multi-centre, open-label, long term, safety study of mepolizumab100 mg administered SC in addition to standard of care in subjects with severe, refractory asthma and a history of eosinophilic inflammation. Subjects who participated in the MEA112997 trial will be offered the opportunity to consent for this study. All subjects will have experienced a gap of at least 10 months since receiving their last double-blind study medication in MEA112997.

At Visit 1, subjects will undergo an initial screening to assess their eligibility to participate in this study. This screening will include: informed consent, vital signs, update of medical history, immunogenicity status based on MEA112997 data, smoking status, prior monoclonal antibody use, and exacerbations post completion of MEA112997. Subjects meeting the Visit 1 eligibility criteria will enter the run-in period. The purpose of the run-in period is to allow for receipt and review of lab results and the ECG over-read. Visit 2, will mark the end of the run-in period.

Those subjects meeting all the inclusion criteria and none of the exclusion criteria will receive their first mepolizumab dose at Visit 2. Subjects will continue to receive mepolizumab SC injections approximately every 4 weeks until either:

- 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 relevant participating country

Subjects will remain on standard of care asthma therapy, which may be adjusted during the study, at the discretion of their physician. The use of Xolair (omalizumab) or any other monoclonal antibody will not be permitted during the course of the study.

Subjects will be monitored in the clinic approximately every 4 weeks to assess adverse events and asthma status. The Asthma Control Questionnaire-5 (ACQ) will be used to assist the investigator in assessing the subject's asthma status along with spirometry at regular intervals. As some subjects may have previously received placebo while participating in the MEA112997 study and are naive to mepolizumab, safety lab monitoring will be more frequent at the start of the study. Appropriate safety labs will be drawn prior to starting treatment and then at week 4, 8, 12, 24, 36 and 48. Thereafter, these will be collected every 24 weeks. Labs will also be obtained at 4 weeks after discontinuing mepolizumab. Subjects discontinuing mepolizumab treatment should be monitored for exacerbation of their asthma.

Serum samples for anti-mepolizumab antibody measurements will be obtained from all subjects at Weeks 0, 4, 24 and 48 of the initial year, week 24 and 48 for every additional year, as well as at the Follow-up Visit. Any anti-mepolizumab antibody positive sample will be tested for neutralization antibody.

A maximum of two additional anti-mepolizumab antibody samples will be obtained; one immediately prior to the first dose and the other prior to the second dose with the 100mg mepolizumab vial. If the first or second dose coincides with a visit where an immunogenicity sample is already required, it is not necessary to obtain an additional sample.

The number of subjects participating in this trial will be no greater than the number of subjects randomised into MEA112997 who also received 2 doses of study medication which is 608 subjects.

The study closure process will begin, on a country by country basis, as mepolizumab becomes commercially available for prescription. Please see the SPM for more details.

Study Endpoints/Assessments

Primary Endpoint

- Adverse Events

Secondary Endpoints

- Frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies
- Annualized rate of exacerbations
- Asthma Control Questionnaire score
- FEV_1 measured by clinic spirometry
- 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/IgE-mediated and non-allergic) and local site reactions
- 12 Lead ECG parameters
- Vital signs
- Clinical Laboratory Parameters

1. INTRODUCTION

1.1. Background

Asthma is a disease characterised by chronic airway inflammation, bronchial hyperreactivity 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]. Inhaled corticosteroids reduce airway inflammation and sputum eosinophils in most asthmatics [Kips, 2002]. However, a proportion of asthma patients remain uncontrolled despite appropriate therapy including high dose inhaled corticosteroids (ICS) plus additional controller therapy, i.e. treatment at Step 5/6 and Step 4/5 according to the NHLBI Guidelines for the Diagnosis and Treatment of Asthma [NHLBI, 2008] and the Global Initiative for Asthma guidelines [GINA, 2008], respectively. 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, and costs are particularly high in those with frequent exacerbations. In MEA112997 subjects had features of severe, refractory asthma as described in the ATS workshop on refractory asthma [ATS workshop, 2000] and additionally demonstrated markers of eosinophilic inflammation. 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. Mepolizumab is a humanised anti-IL-5 antibody (IgG1 kappa) currently in clinical development.

1.2. Rationale

This study will provide long term safety and immunogenicity data when mepolizumab is administered subcutaneously (SC) to subjects with severe, refractory asthma with a history of eosinophilic inflammation. Additionally, this study will inform on the safety and immunogenicity profile when mepolizumab therapy is reinstituted in subjects following a cessation in drug therapy.

This trial also provides subjects who participated in the MEA112997 study, and meet the current trial eligibility criteria, the option of receiving treatment with mepolizumab, as an add-on to their standard of care treatment for severe asthma.

2. OBJECTIVE(S)

Primary Objective

The primary objective of this study is to describe the long-term safety profile of mepolizumab.

Secondary Objectives

- To provide long-term treatment with mepolizumab to subjects who participated in MEA112997
- To evaluate the effects of mepolizumab on a range of clinical markers of asthma control

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.

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.

This is a multi-centre, open-label long term safety study of 100 mg mepolizumab administered SC in addition to standard of care in subjects with severe eosiniophilic asthma. Subjects who participated in the MEA112997 trial will be offered the opportunity to consent for this study. All subjects will have experienced a gap of at least 10 months since receiving their last double-blind study medication in MEA112997.

At Visit 1, subjects will undergo an initial screening to assess their eligibility to participate in this study. This screening will include: informed consent, vital signs, update of medical history, immunogenicity status based on MEA112997 data, smoking status, prior monoclonal antibody use, and exacerbations post completion of MEA112997. Subjects meeting the Visit 1 eligibility criteria will enter the run-in period. The purpose of the run-in period is to allow for receipt and review of lab results and the ECG over-read. Visit 2 will mark the end of the run-in period.

Those subjects meeting all the inclusion criteria and none of the exclusion criteria will receive their first mepolizumab dose at Visit 2. Subjects will continue to receive mepolizumab SC injections approximately every 4 weeks until either:

- 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 relevant participating country

All subjects will be dosed with the 250mg vial up until such time that the 100mg vial is available at the site. Once the 100mg vial is available at the site, all subjects will switch to dosing with the 100mg vial at the next treatment visit and will be dosed with the100mg vial for the remainder of the study.

Subjects will remain on standard of care asthma therapy, which may be adjusted during the study, at the discretion of their physician. The use of Xolair (omalizumab) or any other monoclonal antibody will not be permitted during the course of the study.

At each clinic visit, adverse events will be assessed, and appropriate safety labs will be obtained as per the Time and Events schedule (see Table 2 and Table 3). As some subjects will be naive to mepolizumab, safety lab monitoring will be more frequent at the start of the study. Exacerbations will also be reviewed at each clinic visit.

The study closure process will begin, on a country by country basis, as mepolizumab becomes commercially available for prescription. Please see the SPM for more details.

3.2. Discussion of Design

This study will allow subjects that were randomised into MEA112997 study to reinstitute (or initiate treatment if a placebo subject) mepolizumab as adjunctive therapy. Subjects in MEA112997 could have received mepolizumab or placebo. Thus, the Investigator will need to review the randomization code to aid their assessment of whether a subject may receive benefit from study participation in MEA115666. For example, subjects receiving placebo during MEA112997 may not have demonstrated a positive clinical response, nonetheless, may be considered appropriate for the current study as all subjects will receive mepolizumab. Investigators should continue subjects on their baseline asthma therapy and adjust this therapy as needed in response to improving or worsening asthma. All changes in asthma therapy will be captured in the source and eCRF.

Subjects will be evaluated in the clinic approximately every 4 weeks, to assess adverse events and asthma status. The Asthma Control Questionnaire (ACQ-5) will be used to assist the investigator in assessing the subject's asthma status along with spirometry.

At a minimum, each subject should have a yearly assessment of risk/benefit of mepolizumab therapy performed by the investigator. The investigator should review the frequency of exacerbations, blood eosinophil suppression, and the occurrence of treatment related adverse events, and any other relevant assessments for each subject. Those subjects with an unfavourable risk: benefit ratio, in the opinion of the investigator, should be withdrawn from the study.

The dose selected for the current study is based on the results of the MEA112997 study, which investigated a 10-fold dose range from 75mg to 750mg administered IV every 4 weeks. All 3 doses investigated (75mg, 250mg and 750mg) 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. All 3 doses produced a marked and sustained suppression of blood eosinophils throughout the dose interval. The safety profile was similar across all treatment arms and was similar to placebo. Further details are available in the Clinical Investigator's Brochure (CIB). [GlaxoSmithKline Document Number CM2003/00010/07]. As the SC route is generally preferred by patients and a SC route of administration is easy to administer and cost-effective, a SC route of administration has been chosen for this study.

A PK/PD model has been developed for mepolizumab with data obtained from 5 prior asthma studies and 1 healthy volunteer study. Two of these 5 studies, administered mepolizumab via the SC route. The model well describes the relationship between plasma mepolizumab concentration and eosinophil counts (irrespective of the route of administration), with an IC_{50} (the concentration at which 50% of the maximum reduction of eosinophils) of 226ng/ml [GlaxoSmithKline Document Number CM2003/00010/07]. Based on prior PK studies, the bioavilability of mepolizumab administered SC into the the upper arm is approximately 75% [GlaxoSmithKline Document Number CM2003/00010/07], and therefore a dose of 100mg SC is anticipated to provide similar exposure to the 75mg IV effective dose from 112997. Additionally, a dose of 100mg SC will provide plasma concentrations of mepolizumab well above the IC_{50} for the entire dosage interval. In summary, the 100 mg dose via the SC route has been selected for this study based primarily on the efficacy and safety profile observed in the MEA112997 study, and is additionally supported by the previously developed PK/PD model.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

In order to qualify for this study, subjects must have been randomised and received at least 2 doses of investigational product (IP) in the MEA112997 study. Therefore, the number of subjects in this study will be no greater than 608.

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 [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 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. **MEA112997 Study Participation:** Received at least 2 doses of double-blind investigational product during the MEA112997 trial.
3. **MEA112997 Treatment Assignment:** If the subject received mepolizumab, they must have had a positive risk: benefit ratio in the opinion of the investigator.
4. **Current Anti-Asthma Therapy:** Asthma is currently being treated with a controller medication and the subject has been on a controller medication for the past 12 weeks. Subjects will be expected to continue controller therapy for the duration of the study.
5. **Male or Eligible Female Subjects:**

   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 (Appendix 2) for the duration of the trial and for 4 months after the last study drug administration.

   A serum pregnancy test is required of **all** females. at the initial Screening Visit (Visit 1). In addition, a urine pregnancy test will be performed for **all** females prior to Visit 2, during each scheduled study visit prior to the injection of investigational product, and during the Follow-up Visit.

French subjects: 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.

4.3. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize 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. **Immunogenicity:** Positive neutralizing antibody status based on the last sample obtained during the MEA112997 study.
2. **Hypersensitivity:** Report of a hypersensitivity reaction assessed as related to mepolizumab that led to patient withdrawal. Subjects who experienced a localized injection-site reaction do not need to be excluded.
3. **Health Status:** Clinically significant change in health status since completing participation in the MEA112997 trial which in the opinion of the investigator would make the subject unsuitable for participation in this long term study.

4. **Cardiovascular:** Subjects who have severe or clinically significant cardiovascular disease uncontrolled with standard treatment. Including but not limited to:
   - known ejection fraction of <30% **OR**
   - severe heart failure meeting New York Heart Association Class IV (see Appendix 6) classification **OR**
   - hospitalised in the 12 months prior to Visit 1 for severe heart failure meeting New York Heart Association Class III (see Appendix 6) **OR**
   - angina diagnosed less than 3 months prior to Visit 1 or at Visit 1
5. **Malignancy:** A current malignancy or previous history of cancer in remission for less than 12 months prior to screening (Subjects that had localized carcinoma of the skin which was resected for cure will not be excluded). [**Note for South Korea:** Korean subjects with a diagnosis of malignancy within **5** years are excluded]
6. **Prior SAE:** For those subjects who had a a SAE in MEA112997 that was assessed as possibly related to mepolizumab by the investigator
7. **Pregnancy:** Subjects who are pregnant or breastfeeding. Subjects should not be enrolled if they plan to become pregnant during the time of study participation.
8. **ECG:** Screening ECG which has a clinically significant abnormality or which shows QTcF > 450msec or QTcF >480msec for subjects with Bundle Branch Block.
9. **Xolair:** Received Xolair (omalizumab) within the past 130 days
10. **Clinical trial:** Participated in a clinical trial within the past 30 days or have received investigational medication within five terminal half-lives of Screen Visit, whichever is longer.
11. **Smoking status**: Current smokers

4.4. Visit 2 Criteria

Subjects should be excluded if any of the following are met:

1. **Liver Function:** Liver Function Tests at screening that meet any of the following:
   - ALT ≥2 x ULN (upper limit of normal)
   - AST ≥2 x ULN
   - Alk Phos ≥2 x ULN
   - Bilirubin >1.5 x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)
2. **Hepatitis Status:** Positive Hepatitis B Surface Antigen (HBsAg) screen at Visit 1
3. **ECG Over-read:** Clinically significant abnormality identified during the central over-read
4. **Parasitic Infection:** Subjects with a known parasitic infection within 6 months of Visit 2.

4.5. Withdrawal Criteria

Subjects may be withdrawn from study treatment at anytime by the Investigator if it is considered to be 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, pregnancy, abnormal liver function test, abnormal laboratory results, or for any other reason. Liver chemistry stopping criteria are detailed in Section 6.3.2. In addition, QTc discontinuation criteria are listed below:

- QTc(F)>500 msec or uncorrected QT>600 msec
- Bundle branch block: QTc(F)>530 msec (**Note:** QTc(F)>500 msec for Korean subjects)
- Change from baseline: QTc > 60msec

[Based on average QTc(F) value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period, and then use the averaged QTc(F)values of the 3 ECGs to determine whether the patients should be discontinued from the study].

Subjects are free to discontinue participation in the study at anytime. Every effort should be made to have the subject return for a Follow-up 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.

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.

Subjects may also be withdrawn from this study if mepolizumab becomes commercially available in the respective country, marketing of mepolizumab is no longer being sought in the respective country, or upon decision of the sponsor to discontinue further development of mepolizumab.

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.

4.6. Screening/Run-in Failures

Subjects will be assigned a study number at the time of signing the Informed Consent Form. Those subjects that complete at least one additional Visit 1 (Screen Visit) procedure, but do not enter the run-in period will be designated as screen failures.

Those subjects that enter the Run-in period, but do not receive a dose of mepolizumab, will be designated as run-in failures.

Information to be collected for screen failure and run-in failures will be detailed in the eCRF completion guidelines.

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 vial will be reconstituted with Sterile Water for Injection, just prior to use. Further details of dose preparation and administration can be found in the Clinical Investigator's Brochure (CIB), and the Study Procedures Manual (SPM).

The contents of the label will be in accordance with all applicable regulatory requirements.

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.

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's authorized site staff. Mepolizumab must be stored under the appropriate physical conditions which includes storage 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 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, 100 mg of mepolizumab should be drawn into a polypropylene syringe, and administered according to the instructions in the SPM.

Safety monitoring of subjects will occur during the SC administration and for one hour after the injection for the first 3 doses. After the first 3 doses, safety monitoring will be according to local site policy. Such monitoring will include general safety monitoring including monitoring for both systemic (ie, allergic/IgE-mediated and non-allergic) and local injection-site reactions. Trained rescue personnel and rescue medications/equipment must be available for use at all times. (See Section 6.3.1)

5.3. Treatment Assignment

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

5.4. Blinding

This study is open label.

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 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 unit will be administered under the supervision of the Investigator, designee or study nurses.

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

All concomitant medications taken during the study will 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. However, for corticosteroids, the dose must be recorded as well as well as any dose changes.

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

5.7.2. Prohibited Medications and Non-Drug Therapies

The following medications are not allowed prior to screening according to the following schedule or during the study:

Table 1 Medications not allowed prior to the screening visit and throughout the study

Medication	Washout Time Prior to Screening Visit
Investigational drugs	1 month or 5 half-lives whichever is longer
Omalizumab [Xolair]	130 days
Other monoclonal antibodies	5 half-lives
Experimental anti-inflammatory drugs (non biologicals)	3 months
Immunosuppressive medications such as those listed below (not all inclusive)	
• Corticosteroids intramuscular, long-acting depot if used to treat a condition other than asthma	3 months
• Methotrexate, troleandomycin, cyclosporin, azathioprine	1 month
• Oral gold	3 months
• Chemotherapy used for conditions other than asthma	12 months
• Regular systemic (oral or parenteral) corticosteroids for the treatment of conditions other than asthma	3 months

Additionally, Bronchial Thermoplasty and Radiotherapy are excluded for 12 months prior to Visit 1 and for the duration of the study. Neither CPAP nor oxygen therapy may be initiated after Visit 1.

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 subject's medical condition whether or not GSK is providing specific post study treatment. At the end of the study, subjects should be prescribed appropriate alternative asthma therapy if needed and as determined by the study Investigator.

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

Table 2 Time and Events Table for the First Year

Procedures	Screen	Baseline	Treatment (window is ± 1 week)												Follow-up 4 weeks post last injection[6]
visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Week of study	-4 to -1	0	4	8	12	16	20	24	28	32	36	40	44	48	
Written Informed Consent	X														
Medical History changes	X														
Assess cardiac risk factors	X														
Immunogenicity status	X														
Smoking status	X														
Prior monoclonal antibody use	X														
Parasite screening[3]	X														
Exacerbations post completion of MEA 112997	X														
Inclusion/Exclusion Criteria	X	X													
Safety Assessments															
Concomitant Medication	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
12-lead ECG	X							X						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[4]															
Haematology	X		X		X			X			X			X	X
Chemistry plus lipoproteins[5]		X												X	
Chemistry	X		X	X	X			X			X				X
Pregnancy Test [1]	S	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Immunogenicity		X	X				*	X	*	*	*	*	*	X	X
HbsAg and hepatitis C antibody[2]	X														
Efficacy Assessments															

Procedures	**Screen**	**Baseline**	**Treatment (window is ± 1 week)**												**Follow-up 4 weeks post last injection[6]**
visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Week of study	**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	
Exacerbation review		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						X	
Worksheets/IP/eCRF															
Administer Investigational Product.		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	
Collect paper worksheet		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone IVRS	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

1. Pregnancy test (all females) U = Urine, S= Serum
2. Hepatitis B Surface Antigen and Hepatitis C antibody (if Hepatitis C antibody positive, a hepatitis C confirmatory test should be automatically performed to confirm the result)
3. Parasitic screening only in countries with a high-risk or for subjects who have visited high-risk countries in the past 6 months. Sites should utilise local laboratories.
4. All laboratory assessments to be completed prior to dosing
5. Subject must be in the fasting state. If subject has not fasted, may return the next business day to obtain this sample
6. Follow-up visit window is ± 1 week

* Take additional immunogenicity sample immediately prior to first dose with 100mg vial and prior to the second dose with the 100mg vial. Maximum of 2 additional samples

Table 3 Time and Events Table for Additional Years

Procedures	Treatment subsequent years (repeat 48 week cycle for each subsequent year)													Follow-up 4 weeks
visit	15	16	17	18	19	20	21	22	23	24	25	26	27	post last
Week of study (± 1 week)	52	56	60	64	68	72	76	80	84	88	92	96	100	injection[4]
Safety Assessments														
Assess Risk: Benefit ratio	X													
Concomitant Medication	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
12-lead ECG						X						X		X
Adverse Events/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[2]														
Haematology						X						X		X
Chemistry plus lipoproteins[3]												X		
Chemistry						X								X
Pregnancy Test[1]	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Immunogenicity	*	*	*	*	*	X	*	*	*	*	*	X		X
Efficacy Assessments														
Exacerbation review (worksheet)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Asthma Control Questionnaire			X			X			X			X		X
Spirometry-						X						X		
IP/eCRF/Worksheets														
Administer IP	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense paper diary card	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect paper diary card	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Phone IVRS	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

1. Pregnancy test (all females) U = Urine
2. All laboratory tests are to be completed prior to dosing
3. Subject must be in the fasting state. If subject has not fasted, may return the next business day to obtain this sample
4. Follow-up visit window is ± 1 weeks

* Take additional immunogenicity sample immediately prior to first dose with 100mg vial and prior to the second dose with the 100mg vial. Maximum of 2 additional samples

6.1. Critical Baseline Assessments

Screening and baseline assessments at Visit 1 or Visit 2 (Week 0) will comprise the following:

- Demographic information including date of birth
- Update medical history
- Cardiovascular medical history/risk factors will be assessed at screening. This assessment must include a review of the subject responses to the cardiovascular assessment questions (See Appendix 5) and height, weight, blood pressure, medical conditions, and family history of premature cardiovascular disease.
- Therapy history, including review of use of biologics.
- Review of immunogenicity status from MEA112997.
- Physical examination (including nasal exam to check for the presence or absence of nasal polyps.)
- Pulmonary function tests and assessment.
- Assessment of Inclusion/Exclusion criteria. (At Visit 2, will need to review the results of laboratory tests from Visit 1 and the ECG over-read results)
- Asthma Control Questionnaire (ACQ-5). Further details are provided in Section 6.2.1.3
- Vital signs (further details are provided in Section 6.3.10.1)
- 12-lead ECG (further details are provided in Section 6.3.10.2)
- Blood sampling for the following:
    - Clinical chemistry
    - Clinical chemistry plus lipoproteins at Visit 2 (subject must fast)
    - Haematology
    - Immunogenicity
    - Pregnancy test (all females)
    - HbsAg and hepatitis C antibody
- Parasitic screening (only in countries with a high-risk or in subjects who have visited a country with a high-risk)

6.2. Efficacy

6.2.1. Efficacy Endpoints

- Annualized rate of exacerbations
- Asthma Control Questionnaire score
- FEV_1 measured by clinic spirometry

6.2.1.1. Exacerbations

Exacerbations will be defined as worsening of asthma which requires use of systemic corticosteroids[1] and/or hospitalisation and/or Emergency Department (ED) visits.

[1]For all subjects, IV. or oral steroid (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For subjects on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days is required.

6.2.1.2. Pulmonary Function Testing

Spirometry will be conducted, using the site's own equipment at the visits specified in the Time and Events schedule (Table 2 and Table 3). 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 (SABAs) for ≥6 hours and LABAs for ≥12 hours prior to clinic visit, if possible. Assessments to be recorded will include FEV_1 and FVC.

6.2.1.3. Asthma Control Questionnaire-5 (ACQ)

The ACQ-5 is a five-item questionnaire, which has been developed as a measure of subject' 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 subject should be given a quiet area in which to complete the paper questionnaire. The investigator should ask the subject to complete the questions as accurately as possible. If the subject requests help or clarification with any of the questions, he/she will be asked to re-read the instructions and give the answer that best reflects how he/she felt over the previous week. The subject should be reassured that there are no right or wrong answers. The investigator should not provide the subject with any answer or attempt to interpret any portion of a question. The site-staff will transfer the subject responses on paper into the eCRF.

It is recommended that the ACQ 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.

6.3. Safety

6.3.1. Safety Endpoints

- Adverse Events, including both systemic (ie, allergic/IgE-mediated and non-allergic) and local site reactions.

  NOTE: Hypersensitivity reactions (ie, allergic or IgE-mediated reactions) will be monitored using the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis [Sampson, 2006] (Appendix 4). Information will be also collected to assess localised site reactions.

- 12-lead ECG to derive the following endpoints:
  - Mean change from baseline in the QTc(F) (QT interval corrected by Fridericia'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

6.3.2. Liver chemistry stopping and follow up criteria

Phase III-IV liver chemistry stopping criteria 1-5 are defined below and in Appendix 3:

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.

2. ALT ≥ 8xULN.
3. ALT ≥ 5xULN but <8 xULN persists for ≥2 weeks
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).
5. ALT ≥ 5xULN but <8 xULN and cannot be monitored weekly for ≥2 weeks

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, stabilize, or return to baseline values as described below.
- Withdraw the subject from the study after completion of the liver chemistry monitoring (unless further safety follow up is required)
- Do not re-challenge with investigational product.

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, stabilize 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, stabilize 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, stabilize 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 normalize or return to within baseline values.

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.
- 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) – as outlined in: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1153793/
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

6.3.3. Adverse Events

Subject will be issued a paper worksheet to record adverse events during the study

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

6.3.3.1. 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 fulfill 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

6.3.3.2. Definition of a 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 hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization 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 hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

   Hospitalization 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 hospitalization but may jeopardize 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 hospitalization, 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.

6.3.4. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (haematology, 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.

6.3.5. Cardiovascular Events

Investigators will be required to fill out event specific pages in the eCRF 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 thrombosis
- Deep Venous Thrombosis
- Revascularization

Cardiovascular events information should be recorded on the corresponding eCRF pages within one week of when the AE/SAE(s) are first reported. Please refer to Section 6.3.9 for timelines for reporting AE/SAEs.

6.3.6. Death Events

In addition, all deaths will require completion of a specific death data collection page in the eCRF. The death data collection page in the eCRF includes questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

Death information should be recorded on the death eCRF page within one week of when the death is first reported.

Please refer to Section 6.3.9 for timelines for reporting SAEs.

6.3.7. Pregnancy

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.

6.3.8. 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 investigational product (Visit 2) and until the follow up visit (4 weeks after the last injection).

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.

6.3.9. 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.

	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 "CV events" and/or "death" data collection tool(
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]
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 detecting, 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.

Procedures for documenting, transmitting and follow-up of medical device incidents along with the regulatory reporting requirements for medical devices 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. 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 (see Table 2 and Table 3). 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 Screen visit, height and weight will also be measured.

6.3.10.2. Twelve-lead electrocardiogram

Twelve-lead ECGs will be performed at the visits specified in the Time and Events Table (see Table 2 and Table 3).

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.

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.

ECGs will also be taken at the end of the Follow-up period.

Paper traces are required to be maintained at the site with other source documents.

6.3.10.3. Clinical Laboratory Parameters

Clinical laboratory tests will be conducted at the visits specified in the Time and Events Table (see Table 2 and Table 3). At the discretion of the Investigator, additional samples may be taken for safety reasons.

All blood samples, which will be taken pre-dosing will be sent to a central laboratory for analysis (details provided in the Study Procedures Manual). Standard reference ranges will be used. Full details of the collection and shipping requirements for the central laboratory are provided in the Central Laboratory Investigator Manual. The central laboratory will fax laboratory results to the Investigator and will transmit the results electronically to GSK.

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 (see Table 2 and Table 3). Samples that test positive for anti-mepolizumab antibodies will be further tested for the presence of neutralising antibody.

A maximum of two additional anti-mepolizumab antibody samples will be obtained; one immediately prior to the first dose and the other prior to the second dose with the 100mg mepolizumab vial. If the first or second dose coincides with a visit where an immunogenicity sample is already required, it is not necessary to obtain an additional sample.

For all subjects, immunogenicity testing will occur at 4 weeks after the last dose.

7. DATA MANAGEMENT

For this study subject data will be entered into GSK defined electronic case report forms (eCRFs), transmitted electronically to GSK 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. 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. Hypotheses

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 randomised into study MEA112997 and are eligible for the current study based on inclusion and exclusion criteria.

8.2.2. Sample Size Sensitivity

Not applicable.

8.2.3. Sample Size Re-estimation

Not applicable.

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.

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.

8.3.3.1. Primary Comparisons of Interest

Not applicable.

8.3.3.2. Other Comparisons of Interest

Not applicable.

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

Further detail will be fully described in the RAP.

8.3.5.1. Efficacy Analyses

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

8.3.5.2. Safety Analyses

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

8.3.5.3. Immunogenicity Analyses

All immunogenicity endpoints will be summarised using descriptive statistics. The number and percentage of subjects with positive neutralizing antibodies before and after the introduction of the 100mg mepolizumab vial will be tabulated. 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

The study will be considered complete when the last subject completes the last visit. 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.

GSK aims to post a results summary to the GSK Clinical Study Register and other publicly available registers no later than 8 months after the last subject's last visit (LSLV) [this applies to each data analysis phase for studies with multiple phases, e.g., primary analysis, follow up analysis etc]. In addition, the aim is to submit a manuscript to a peer-reviewed journal for publication within 18 months of LSLV. GSK also aims to publish the full study protocol on the GSK Clinical Study Register at the time the results of the study are published as a manuscript in the scientific literature.

When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

9.8. Independent Data Monitoring Committee (IDMC)

An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter, which is available upon request.

10. REFERENCES

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11. APPENDICES

11.1. Appendix 1: Country Specific Requirements

Country-Specific Requirements

No country-specific requirements exist.

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

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.

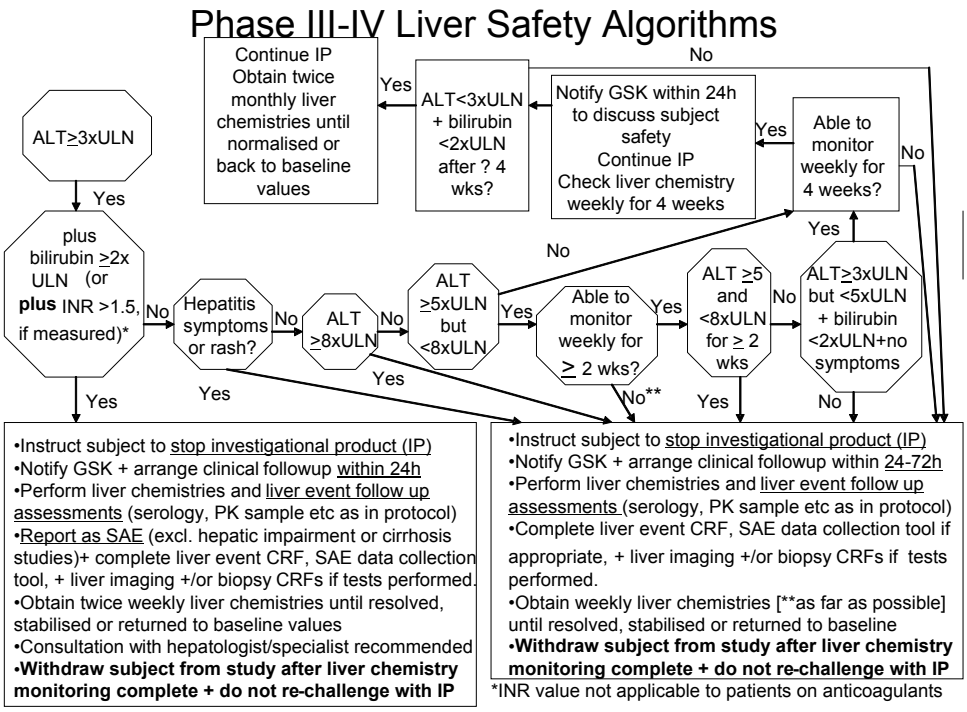
Females of non-childbearing potential are defined as females with functioning ovaries and with a documented tubal ligation or hysterectomy; or females who are postmenopausal defined as 12 months of spontaneous amenorrhea with an appropriate clinical profile, e.g. age appropriate, >45 years, in the absence 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: Liver Chemistry Stopping and Followup Criteria



11.4. Appendix 4: Anaphylaxis Criteria

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:
    - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    - 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):
    - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    - Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    - Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
    - Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

11.5. Appendix 5: Cardiovascular Screening Questions

At screening each subject should be asked the following:

Unrelated to the symptoms you experience with your asthma:

1. **Do you have any pain or discomfort (such as pressure) in your chest?**
   h. If yes, does this pain/discomfort/pressure go to other areas of your body such as neck, jaw, throat, or down your arms (including a numbness feeling in your arm) when it occurs?
2. **When you walk at an ordinary pace on a level surface does this produce chest pain?** If yes, respond to a and b:
   a. Does this chest pain or discomfort occur when you are not doing any activities such as resting in bed or sitting in a chair?
   b. Has this chest pain/discomfort been more frequent or more intense or last longer or come on with less exertion lately?
3. **When you walk uphill or hurry does this produce chest pain/discomfort?**
4. **Do you use or have you been previously prescribed nitroglycerine to relieve the discomfort?**
   - If yes, have you needed to increase the number of pills or frequency of using the pills recently?

i. **If the subject responds "yes" to any of the above questions a study physician should further assess for the presence of undiagnosed or unrecognized angina when evaluating Exclusion Criterion 4.**

Subject responses will be entered into the eCRF.

11.6. Appendix 6: New York Heart Association Functional Classification of Congestive Heart Failure

CLASS	PATIENT SYMPTOMS
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases

Adapted from American Heart Association, 2012

11.7. Appendix 7: Protocol Changes

Scope

This amendment applies to all sites

Protocol changes specified in Amendment No. 1 are summarized below:

- To clarify that the rationale and objective of the study includes long-term provision of mepolizumab therapy to subjects who have severe asthma and participated in MEA112997
- To clarify that only monoclonal antibodies are excluded, rather than all biologics
- To clarify reason for more frequent safety monitoring at the start of the study
- To correct Inclusion criterion 5 from Randomisation Visit to Visit 2
- To add exclusion criterion for significant cardiovascular disease
- To correct inconsistencies between protocol text and the Time and Events Table
- To correct bilirubin exclusion criterion at visit 2
- To expand on requirements for designating a subject as lost to follow-up
- To add visit window for the follow-up visit
- To move baseline spirometry from the screen visit to the baseline visit
- To clarify that all subjects will have an immunogenicity test 12 weeks after last dose
- To correct Section 8.3.5.2 wording “Efficacy” to “Safety”
- To add reference to support Appendix 6 and remove 3 references which are not cited in the protocol.
- To add Appendix 5 and Appendix 6 and amended Section 6.1 and Section 6.3.9. to support the determination of exclusion criteria 4

Protocol Changes Amendment 1:

Section RATIONALE

Additional Text:

This trial also provides subjects who participated in the MEA112997 study, and meet the current trial eligibility criteria, the option of receiving treatment with mepolizumab, as an add-on to their standard of care treatment for severe asthma.

Section OBJECTIVES

Additional Text:

To provide long-term treatment with mepolizumab to subjects who participated in MEA112997

Section STUDY DESIGN

Original Text:

Subjects will remain on standard of care asthma therapy, which may be adjusted during the study, at the discretion of their physician. The use of Xolair (omalizumab) or any other **biologic** will not be permitted during the course of the study.

Subjects will be monitored in the clinic approximately every 4 weeks to assess adverse events and asthma status. The Asthma Control Questionnaire-5 (ACQ) will be used to assist the investigator in assessing the subject's asthma status along with spirometry at regular intervals. As some subjects may have previously received placebo while participating in the MEA112997 study and are naive to mepolizumab, safety lab monitoring will be more frequent at the start of the study. Appropriate safety labs will be drawn prior to starting treatment and then at week 4, 8, 12, 24, 36 and 48. Thereafter, these will be collected every 24 weeks. Labs will also be obtained at 12 weeks after discontinuing mepolizumab. Subjects discontinuing mepolizumab treatment should be monitored for exacerbation of their asthma.

Serum samples for anti-mepolizumab antibody measurements will be obtained from all subjects at **screen, week** 4, 24 and 48 of the initial year, week 24 and 48 for every additional year, as well as at the Follow-up Visit. Any anti-mepolizumab antibody positive sample will be tested for neutralization antibody.

Revised Text

Subjects will remain on standard of care asthma therapy, which may be adjusted during the study, at the discretion of their physician. The use of Xolair (omalizumab) or any other **monoclonal antibody** will not be permitted during the course of the study.

Subjects will be monitored in the clinic approximately every 4 weeks to assess adverse events and asthma status. The Asthma Control Questionnaire-5 (ACQ) will be used to assist the investigator in assessing the subject's asthma status along with spirometry at regular intervals. As some subjects may have previously received placebo while participating in the MEA112997 study and are naive to mepolizumab, safety lab monitoring will be more frequent at the start of the study. Appropriate safety labs will be drawn prior to starting treatment and then at week 4, 8, 12, 24, 36 and 48. Thereafter, these will be collected every 24 weeks. Labs will also be obtained at 12 weeks after discontinuing mepolizumab. Subjects discontinuing mepolizumab treatment should be monitored for exacerbation of their asthma.

Serum samples for anti-mepolizumab antibody measurements will be obtained from all subjects at **Weeks 0,4**, 24 and 48 of the initial year, week 24 and 48 for every additional year, as well as at the Follow-up Visit. Any anti-mepolizumab antibody positive sample will be tested for neutralization antibody.

Section 1.2 Rationale

Added text:

This trial also provides subjects who participated in the MEA112997 study, and meet the current trial eligibility criteria, the option of receiving treatment with mepolizumab, as an add-on to their standard of care treatment for severe asthma.

Section 2 Objectives:

Added Text:

- To provide long-term treatment with mepolizumab to subjects who participated in MEA112997

Section 3.1 Study Design:

Original Text:

Subjects will remain on standard of care asthma therapy, which may be adjusted during the study, at the discretion of their physician. The use of Xolair (omalizumab) or any other **biologic** will not be permitted during the course of the study.

Revised Text:

Subjects will remain on standard of care asthma therapy, which may be adjusted during the study, at the discretion of their physician. The use of Xolair (omalizumab) or any other **monoclonal antibody** will not be permitted during the course of the study.

Original Text:

At each clinic visit, adverse events will be assessed, and appropriate safety labs will be obtained as per the Time and Events schedule (see Table 2 and Table 3). As laboratory results have not been characterized when subjects reinstitute treatment with mepolizumab, safety lab monitoring will be more frequent at the start of the study. Exacerbations will also be reviewed at each clinic visit.

Revised Text

At each clinic visit, adverse events will be assessed, and appropriate safety labs will be obtained as per the Time and Events schedule (see Table 2 and Table 3). **As some subjects will be naive to mepolizumab**, safety lab monitoring will be more frequent at the start of the study. Exacerbations will also be reviewed at each clinic visit.

Section 4.2 Inclusion Criteria:

Original Text:

> A serum pregnancy test is required of **all** females. at the initial Screening Visit (Visit 1). In addition, a urine pregnancy test will be performed for **all** females prior to randomisation, during each scheduled study visit prior to the injection of investigational product, and during the Follow-up Visit.

Revised Text:

> A serum pregnancy test is required of **all** females. at the initial Screening Visit (Visit 1). In addition, a urine pregnancy test will be performed for **all** females prior toVisit 2, during each scheduled study visit prior to the injection of investigational product, and during the Follow-up Visit.

Section 4.3 Exclusion Criteria:

Added Text:

4. **Cardiovascular:** Subjects who have severe or clinically significant cardiovascular disease uncontrolled with standard treatment. Including but not limited to:
    a. known ejection fraction of <30% **OR**
    b. severe heart failure meeting New York Heart Association Class IV (see Appendix 6 classification **OR**
    c. hospitalised in the 12 months prior to Visit 1 for severe heart failure meeting New York Heart Association Class III (see Appendix 6) **OR**
    d. angina diagnosed less than 3 months prior to Visit 1 or at Visit 1

Section 4.5 Withdrawal Criteria:

Original Text:

Subjects are free to discontinue participation in the study at anytime. Every effort should be made to have the subject return for a Follow-up visit 12 weeks post last mepolizumab injection.

Subjects may also be withdrawn from this study if mepolizumab becomes commercially available in the respective country, marketing of mepolizumab is no longer being sought in the respective country, or upon decision of the sponsor to discontinue further development of mepolizumab.

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. For those subjects that are lost to follow-up, every effort will be made to contact the subject to assure their safety. These efforts should be documented in the clinic notes at the site.

Revised Text:

Subjects are free to discontinue participation in the study at anytime. Every effort should be made to have the subject return for a Follow-up visit 12 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.**

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.

Subjects may also be withdrawn from this study if mepolizumab becomes commercially available in the respective country, marketing of mepolizumab is no longer being sought in the respective country, or upon decision of the sponsor to discontinue further development of mepolizumab.

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.

Section 5.7.2 Prohibited Medications:

Original Text:

Medication	**Washout Time Prior to Screening Visit**
Investigational drugs	1 month or 5 half-lives whichever is longer
Omalizumab [Xolair]	130 days
Other **biologicals**	5 half-lives
Experimental anti-inflammatory drugs (non biologicals)	3 months

Revised Text:

Medication	**Washout Time Prior to Screening Visit**
Investigational drugs	1 month or 5 half-lives whichever is longer
Omalizumab [Xolair]	130 days
Other monoclonal antibodies	5 half-lives
Experimental anti-inflammatory drugs (non biologicals)	3 months

Section 6 Study Assessments and Procedures:

Added Footnote:

6. Follow-up visit window is ± 2 weeks

Moved initial sprirometry from screen visit to Visit 2 (Baseline)

Section 6.1 Critical Baseline Assessments:

Original Text:

- Cardiovascular medical history/risk factors will be assessed at **baseline.**

Revised Text:

- Cardiovascular medical history/risk factors will be assessed at **screening. This assessment must include a review of the subject responses to the cardiovascular assessment questions (See Appendix 5) and height, weight, blood pressure, medical conditions, and family history of premature cardiovascular disease.**

Section 6.3.5: Cardiovascular Events

Added Text:

Investigators will be required to fill out event specific pages in the eCRF 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 thrombosis
- Deep Venous Thrombosis
- Revascularization

Cardiovascular events information should be recorded on the corresponding eCRF pages within one week of when the AE/SAE(s) are first reported. Please refer to Section 6.3.9 for timelines for reporting AE/SAEs.

Section 6.3.6: Death Events

In addition, all deaths will require completion of a specific death data collection page in the eCRF. The death data collection page in the eCRF includes questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

Death information should be recorded on the death eCRF page within one week of when the death is first reported.

Please refer to Section 6.3.9 for timelines for reporting SAEs.

Section 6.3.9 Prompt Reporting of Serious Adverse Events and Other Events to GSK

Original Text:

	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

Revised Text:

	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 "***CV events" and/or "death" data collection tool(s***)

Section 6.4 Immunogenicity:

Original Text:

For subjects who prematurely withdraw from the study, immunogenicity testing will occur at 12 weeks after the last dose.

Revised Text:

For **all** ~~who prematurely withdraw from the study~~ subjects, immunogenicity testing will occur at 12 weeks after the last dose.

Section 8.3.5.2 Safety Analyses:

Original Text:

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

Revised Text:

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

Section 10 References:

Added text:

American Heart Association. Classes of Heart Failure. Available at: http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp. Accessed 14 August 2012.

Deleted text:

~~Dolan P, Cookson R. A qualitative study of the extent to which health gain matters when choosing between groups of patients. *Health Policy* 2000;51:19-30.~~

~~Flood-Page P, Swenson C, Faiferman I, Matthews J, Williams M, Brannick L, Robinson D, Wenzel S, Busse W, Hansel T and Barnes N. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Resp Crit Care 2007*;176:1062-1071.~~

~~Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, Marshall RP, Bradding P, Green RH, Wardlaw AJ, Pavord ID. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;360:973-984.~~

Section 11.5 Appendix 5

Added text:

Appendix 5 Cardiovascular Screening Questions

At screening each subject should be asked the following:

Unrelated to the symptoms you experience with your asthma:

1. **Do you have any pain or discomfort (such as pressure) in your chest?**
    a. If yes, does this pain/discomfort/pressure go to other areas of your body such as neck, jaw, throat, or down your arms (including a numbness feeling in your arm) when it occurs?
2. **When you walk at an ordinary pace on a level surface does this produce chest pain?** If yes, respond to a and b:
        a. Does this chest pain or discomfort occur when you are not doing any activities such as resting in bed or sitting in a chair?
        b. Has this chest pain/discomfort been more frequent or more intense or last longer or come on with less exertion lately?
3. **When you walk uphill or hurry does this produce chest pain/discomfort?**
4. **Do you use or have you been previously prescribed nitroglycerine to relieve the discomfort?**
    - If yes, have you needed to increase the number of pills or frequency of using the pills recently?

b. **If the subject responds "yes" to any of the above questions a study physician should further assess for the presence of undiagnosed or unrecognized angina when evaluating Exclusion Criterion 4.**

Subject responses will be entered into the eCRF.

Section 11.6 Appendix 6

Added Text:

Appendix 6 New York Heart Association Functional Classification of Congestive Heart Failure

CLASS	PATIENT SYMPTOMS
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases

Adapted from American Heart Association, 2012.

Appendix 7

Original Text:

1. **Liver Function:** Liver Function Tests at screening that meet any of the following:
    - ALT ≥2 x ULN (upper limit of normal)
    - AST ≥2 x ULN
    - Alk Phos ≥2 x ULN
    - Bilirubin ≥2 x ULN (isolated bilirubin ≥2 x ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%

Revised Text:

5. **Liver Function:** Liver Function Tests at screening that meet any of the following:
    - ALT ≥2 x ULN (upper limit of normal)
    - AST ≥2 x ULN
    - Alk Phos ≥2 x ULN
    - Bilirubin >1.5 x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)

Protocol Amendment Number 02

Scope: This amendment applies to all sites.

Protocol Changes specified in Amendment No. 2 are summarised below:

- To add two additional immunogenicity sample assessment time points when the 100mg vial is introduced.
- To allow other syringe sizes for study drug administration
- To allow for study drug administration in the upper thigh or the arm
- To add the prohibited non-drug therapies to Section 5.7.2
- To list Adverse Events and Serious Adverse Events on the same line in Table 3
- To correct a formatting error for Section 4.6
- To remove specific test name for confirming Hepatitis C positive sample
- To delete redundant text in Section 6.3.3.1
- To remove from Section 6.3.7 the requirement to report outcome of pregnancy in female partners of male subjects
- To include analyses of immunogenicity data in Section 8.3 and to clarify when interim analyses will be performed

Study Design:

Added Text:

A maximum of two additional anti-mepolizumab antibody samples will be obtained; one immediately prior to the first dose and the other prior to the second dose with the 100mg mepolizumab vial. If the first or second dose coincides with a visit where an immunogenicity sample is already required, it is not necessary to obtain an additional sample.

Added Text:

All subjects will be dosed with the 250mg vial up until such time that the 100mg vial is available at the site and all regulatory/ethics approvals have been received. Once the 100mg vial is available at the site, all subjects will switch to dosing with 100mg vial. Subjects will then be dosed with the 100mg vial for the duration of the study.

Section 4.6

Corrected formatting to add the Section number.

Section 5.2 Dosage and Administration:

Original Text

Once the mepolizumab vial is reconstituted, 100 mg of mepolizumab should be drawn into a 1ml polypropylene syringe, and administered right away.

Revised Text:

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

Section 5.3 Treatment Assignment:

Original Text:

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

Revised Text:

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

Section 5.7.2 Prohibited Medications and Non-Drug Therapies

Added Text:

Additionally, Bronchial Thermoplasty and Radiotherapy are excluded for 12 months prior to Visit 1 and for the duration of the study. Neither CPAP nor oxygen therapy may be initiated after Visit 1.

Time and Events For First Year Table 2:

Original Text:

Hepatitis B Surface Antigen and Hepatitis C antibody (if Hepatitis C antibody positive, a hepatitis C RIBA should be automatically performed on the same sample to confirm the result)

Revised Text:

Hepatitis B Surface Antigen and Hepatitis C antibody (if Hepatitis C antibody positive, a hepatitis C confirmatory test should be automatically performed to confirm the result)

Added Text:

* Take additional immunogenicity sample prior to first dose with 100mg vial and prior to the second dose with the 100mg vial

Table 3 Time and Events Table for Additional Years:

Original Text:

Adverse Events

Revised Text:

Adverse Events/SAEs

Added Text:

* Take additional immunogenicity sample prior to first dose with 100mg vial and prior to the second dose with the 100mg vial. Maximum of 2 additional samples

Section 6.3.3.1 Definition of an AE

Deleted Text:

The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Deleted Text:

Section 6.3.7 Pregnancy:

In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to GSK as described above.

Section 6.4 Immunogenicity

Added Text:

Two additional anti-mepolizumab antibody samples will be obtained; One prior to the first dose and the other prior to the second dose with the 100mg mepolizumab vial.

Original Text:

Section 8.3.4 Interim Analysis

Interim analysis will be performed on an annual basis and at other times as needed in order to provide open-label safety data to inform the risk-benefit assessment of mepolizumab in severe asthma.

Revised Text:

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.

Original Text:

Section 8.3.5.3 Health Outcome Analyses

No health outcomes endpoints are defined for this study.

Revised Text:

Section 8.3.5.3 Immunogenicity Analyses

All immunogenicity endpoints will be summarised using descriptive statistics. The number and percentage of subjects with positive neutralizing antibodies before and after the introduction of the 100mg mepolizumab vial will be tabulated. Further details will be provided in the RAP.

Deleted Text:

Section 8.3.5.4 Pharmacodynamic Analyses

No pharmacodynamic endpoints are defined for this study.

Appendix 7 Amendment 01

Added Text:

Appendix 7

Original Text:

2. **Liver Function:** Liver Function Tests at screening that meet any of the following:
    - ALT ≥2 x ULN (upper limit of normal)
    - AST ≥2 x ULN
    - Alk Phos ≥2 x ULN
    - Bilirubin ≥2 x ULN (isolated bilirubin ≥2 x ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%

Revised Text:

2. **Liver Function:** Liver Function Tests at screening that meet any of the following:
    - ALT ≥2 x ULN (upper limit of normal)
    - AST ≥2 x ULN
    - Alk Phos ≥2 x ULN
    - Bilirubin >1.5 x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%)

Protocol Amendment Number 03 Changes

Scope: This amendment applies to all sites.

Protocol Changes specified in Amendment No. 3 are summarised below:

Change No. 1: To change the Follow-up visit from 12 weeks to 4 weeks post last dose of IP. 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:

Labs will also be obtained at 12 weeks after discontinuing mepolizumab.

Changed to:

Labs will also be obtained at 4 weeks after discontinuing mepolizumab.

Additional paragraph added to Study Design and 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. Please see the SPM for more details.

Section 4.5 Withdrawal Criteria

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 a Follow-up visit 4 weeks post last mepolizumab injection.

Section 6 Table 2 Study Assessments and Procedures, column header

Original text:

Follow-up 12 weeks post last injection

Changed to:

Follow-up 4 weeks post last injection

Section 6 Study Assessments and Procedures (Footnote No. 6)

Original text:

6. Follow-up visit window is ± 2 weeks

Changed to:

6. Follow-up visit window is ± 1 weeks

Section 6 Table 3 Study Assessments and Procedures, column header

Original text:

Follow-up 12 weeks post last injection

Changed to:

Follow-up 4 weeks post last injection

Section 6 Table 3 Study Assessments and Procedures (Footnote No. 4)

Original text:

4. Follow-up visit window is ± 2 weeks

Changed to:

4. Follow-up visit window is ± 1 weeks

Section 6.3.8 Time Period and Frequency of Detecting AEs and SAEs

Original text:

AEs will be collected from the start of investigational product (Visit 2) and until the follow up visit (12 weeks after the last injection).

Changed to:

AEs will be collected from the start of investigational product (Visit 2) and until the follow up visit (4 weeks after the last injection).

Section 6.4 Immunogenicity

Original text:

For all subjects, immunogenicity testing will occur at 12 weeks after the last dose.

Changed to:

For all subjects, immunogenicity testing will occur at 4 weeks after the last dose.

Change No. 2: To update the time limit from reconstitution to administration of IP

Section 5.2 Dosage and Administration

Original text:

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

Changed to:

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