TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	An open-label, single arm, repeat dose, multi-centre study to evaluate the use of a safety syringe for the subcutaneous administration of mepolizumab in subjects with severe eosinophilic asthma (Study 205667)

Compound Number: SB-240563

Development Phase: IIIA

Effective Date: 06-OCT-2016

Protocol Amendment Number: 01

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2016N275349_00	2016-AUG-12	Original
2016N275349_01	2016-AUG-18	Republishing
To add serious systemic reactions including anaphylaxis to the risk assessment section To remove GCSP as a contributory author as per GUI_264305 (3.0) To clarify the wording around assessing eosinophilia from blood counts collected following a Liver Stopping Event		
2016N275349_02	2016-OCT-06	Amendment No. 1
To refine the criteria for a successful injection following a use-related risk review To amend Exclusion Criterion 7 to allow either Fridericia's or Bazett's to be used as the correction formula for heart rate when measuring the QT interval To remove Exclusion Criterion 15 as the exclusion of pregnant or lactating females is covered in Inclusion Criterion 9 To correct the EudraCT No. To correct minor typographical errors		

SPONSOR SIGNATORY

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10/6/14

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): IND No 006971, EudraCT No: 2016-001831-10

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 205667

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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1. PROTOCOL SYNOPSIS FOR STUDY 205667

Rationale

Mepolizumab (SB-240563) is a humanised monoclonal antibody (IgG1, kappa, mAb) that blocks human interleukin-5 (hIL-5) from binding to the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibits signalling; neutralisation of IL-5 with mepolizumab reduces blood, sputum and tissue eosinophils.

Mepolizumab for Injection is supplied as a sterile, single-use, preservative-free, lyophilised powder formulation (herein referred to as lyophilised drug product). This is the form that was used in the clinical development programmes and is the current marketed presentation for asthma (NUCALA™). Before use, a healthcare provider must reconstitute each vial of lyophilised drug product with water for injection using aseptic techniques. As part of the life-cycle of mepolizumab, a liquid drug product provided as a ready-to-use pre-filled syringe assembled into either a safety syringe or an autoinjector, Mepolizumab Injection, has been developed. Administration of Mepolizumab Injection (herein referred to as liquid drug product in safety syringe) will improve patient/physician convenience and enable home/self injection via caregivers and/or patients.

Objective(s)/Endpoint(s)

The aim of this study is to assess the correct real-world use of a safety syringe for the repeat self-administration of mepolizumab subcutaneously by determining the proportion of subjects with severe eosinophilic asthma who are successfully able to self-administer a dose of mepolizumab. For the purposes of this study, 'self-administration' is defined as either the administration of mepolizumab liquid drug product in safety syringe by the subject themselves or by their caregiver.

The primary and secondary objectives and associated endpoints are outlined below:

Objectives	Endpoints
Primary	
• To assess the use of the combination product, mepolizumab liquid drug product in safety syringe for the subcutaneous self-administration of mepolizumab by subjects with severe eosinophilic asthma	• Proportion of subjects successfully able to self-administer their observed third dose at Week 8
Secondary	
• To assess the use of mepolizumab liquid drug product in safety syringe outside the clinic setting	• Proportion of subjects successfully able to self-administer their unobserved second dose outside the clinic setting at Week 4

Overall Design

This Phase III study will be an open-label, single-arm, repeat-dose, multi-centre study of mepolizumab liquid drug product in a safety syringe (100 mg) administered subcutaneously (SC) every 4 weeks in subjects with severe eosinophilic asthma. Subjects will receive 100 mg mepolizumab SC as a single injection that is self-administered in the thigh, abdomen or administered in the upper arm (caregiver only). The site of administration will be recorded.

Subjects (and/or their caregiver, if applicable) will self-administer mepolizumab liquid drug product in safety syringe for the first time immediately after being trained in its use at Visit 2 (i.e. the Start of Study Visit). The training is designed to be representative of the instruction and training materials that will be provided once the device is commercially available.

Three doses of mepolizumab drug product in the safety syringe will be self-administered by the subject/caregiver at 4-weekly intervals; 2 doses will be administered under observation in the clinic (at Visits 2 and 4). The second in clinic administration (Visit 4) will not include any onsite training or other support, other than the Instructions for Use (IFU), which could assist the subject. One dose will be administered outside the clinic and without observation (within 24 hours after attending the clinic for Visit 3). Following each injection, subjects will complete a patient diary immediately following, 1- and 24-hours after administration indicating the pain experienced and, for the unobserved dose administered at home following Visit 3, subjects/caregivers will complete a checklist of the steps required to successfully administer the injection. At the End of Study Visit (Visit 5), subjects will be asked about their overall experience with the liquid drug product in safety syringe, including device performance and ease of use.

Treatment Arms and Duration

The study is single arm in which all subjects will receive mepolizumab 100 mg SC from the liquid drug product in safety syringe presentation. Each subject will participate in the study for up to 18 weeks and will have a Pre-screening visit (Visit 0), a Screening visit (Visit 1) and a 12-week Treatment Period (Visits 2 through 4) which concludes with End of Study assessments (Visit 5) 4 weeks after the last dose of mepolizumab at Visit 4.

Type and Number of Subjects

Male or female subjects aged 12 years or older with severe eosinophilic asthma. Subjects must either have been receiving mepolizumab administered SC for the treatment of severe eosinophilic asthma every 4 weeks for at least 12 weeks prior to Visit 1 or, if not previously using mepolizumab, must be using high dose inhaled corticosteroids plus an additional controller with a history of 1 or more exacerbations requiring systemic corticosteroids in the 12 months prior to Visit 1.

Approximately 75 subjects will be screened to achieve 55 enrolled subjects with the aim of achieving 50 completed/evaluable subjects.

Sample Size Calculations and Statistical Analyses

No formal sample size calculations were performed. Assuming a ~30% dropout rate during screening, approximately 75 subjects will be screened in order to enrol 55 subjects (attempting at least one self-administration of mepolizumab). Assuming a dropout rate of up to 10% during the study, 55 enrolled subjects should provide at least 50 subjects with complete study data.

The number and percentage of subjects successfully able to self-administer their doses will be presented together with 95% confidence intervals. No hypothesis testing will be performed.

2. INTRODUCTION

Mepolizumab (SB-240563) is a humanised monoclonal antibody (IgG1, kappa, mAb) that blocks human interleukin-5 (hIL-5) from binding to the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibits signalling; neutralisation of IL-5 with mepolizumab reduces blood, sputum and eosinophils.

Mepolizumab has recently been approved in a number of markets including the United States (US), European Union (EU), Canada, Australia, Japan, South Korea, Switzerland and Taiwan for the treatment of severe eosinophilic asthma. Mepolizumab is also under development for other indications, including the treatment of Chronic Obstructive Pulmonary Disease (COPD), FIP1L1/PDGFRα-negative hypereosinophilic syndrome (HES) and eosinophilic granulomatosis with polyangiitis (EGPA) (i.e., Churg Strauss syndrome).

2.1. Study Rationale

Mepolizumab for Injection is supplied as a sterile, single-use, preservative-free, lyophilised formulation (herein referred to as lyophilised drug product). This is the form that was used in the clinical development programmes and is the current marketed presentation for asthma (NUCALA™). Before use, a healthcare provider must reconstitute each vial of lyophilised drug product with water for injection (WFI) using aseptic techniques. As part of the life cycle of mepolizumab, a liquid drug product (provided as a ready-to-use pre-filled syringe assembled into either a safety syringe or an autoinjector), Mepolizumab Injection, is being developed. Administration of Mepolizumab Injection (herein referred to as liquid drug product in safety syringe) is intended to improve patient/physician convenience and enable home/self injection via caregivers and/or patients.

The changes to the liquid drug product site of manufacture, processing and formulation have been minimised. The liquid drug product has been assessed against the lyophilised drug product, prior to clinical evaluation, using comprehensive biochemical/biophysical comparability evaluations with comparability between the two products being demonstrated. The likelihood of clinically significant differences in the systemic exposure, efficacy, safety and/or immunogenicity of the liquid drug product in autoinjector or safety syringe as compared with the reconstituted lyophilised drug product is considered to be low. To provide further assurance of comparable exposure from the liquid drug products and the lyophilised drug product, a single-dose pharmacokinetic (PK) comparability study in healthy subjects will be performed in parallel with this trial (Study 204958).

2.2. Brief Background

Mepolizumab binds with high affinity to human IL-5 and blocks its binding to and the activation of the IL-5 receptor (CD125).

Randomised, multi-centre, placebo-controlled exacerbation studies (MEA112997, MEA115588) and an Oral Corticosteroid (OCS) Reduction Study (MEA115575) have

demonstrated the efficacy of mepolizumab and support the use of mepolizumab 100 mg subcutaneous (SC) every 4 weeks as an add-on therapy for the treatment of severe eosinophilic asthma. Compared with placebo, mepolizumab has been shown to:

- Reduce the rate of clinically significant exacerbations by approximately 50%. These results were replicated in studies MEA112997 and MEA115588.
- Reduce the rate of exacerbations requiring hospitalisations and/or Emergency Department (ED) visits, with mean reductions ranging from 32% to 61%.
- Produce statistically significant and/or clinically relevant improvements in lung function based on forced expiratory volume in one second (FEV_1), asthma control based on Asthma Control Questionnaire (ACQ-5), quality of life based on St. George's Respiratory Questionnaire (SGRQ) and clinician and subject-rated overall response to therapy in the target population.
- Produce consistent reductions in blood eosinophil levels detected at Week 4 which were sustained for the duration of treatment.

Additional details of the pharmacology, efficacy and safety can be found in the Investigator Brochure (IB) [GSK Document Number CM2003/00010/10].

3. OBJECTIVE(S) AND ENDPOINT(S)

The aim of this study is to assess the correct real-world use of the mepolizumab liquid drug product in safety syringe for the repeat self-administration of mepolizumab subcutaneously by determining the proportion of subjects with severe eosinophilic asthma who are successfully able to self-administer a dose of mepolizumab. For the purposes of this study, 'self-administration' is defined as either the administration of mepolizumab liquid drug product in safety syringe by the subject themselves or by their caregiver.

The objectives and endpoints associated with these objectives are outlined below:

Objectives	Endpoints
Primary	
• To assess the use of the combination product, mepolizumab liquid drug product in safety syringe for the subcutaneous self-administration of mepolizumab by subjects with severe eosinophilic asthma	• Proportion of subjects successfully able to self-administer their observed third dose at Week 8
Secondary	
• To assess the use of mepolizumab liquid drug product in safety syringe outside the clinic setting	• Proportion of subjects successfully able to self-administer their unobserved second dose outside the clinic setting at Week 4

Objectives	Endpoints
Other	
• To assess the use of mepolizumab liquid drug product in safety syringe both inside and outside of the clinic setting	• Proportion of subjects successfully able to self-administer their observed first dose at Week 0 • Proportion of subjects successfully able to self-administer both their unobserved second dose and observed third observed dose at Weeks 4 and 8 • Proportion of subjects successfully able to self-administer all three doses at Weeks 0, 4 and 8
• To evaluate safety syringe use & functionality	• Device usability/functionality questionnaire completed at the End of Study/Early Withdrawal Visit
• To evaluate any safety syringe injection errors/failures related to use or device performance	• Investigator evaluation of user/device errors • Root cause analysis of each unsuccessful injection
• To characterise the subject experience of using the mepolizumab liquid drug product in safety syringe	• Subject Exit Interviews completed over the telephone after the End of Study/Early Withdrawal Visit
• To assess mepolizumab plasma trough concentrations following the SC administration of mepolizumab liquid drug product in safety syringe	• Mepolizumab plasma trough concentrations (Ctrough) at Weeks 4, 8 and 12
• To assess the pharmacodynamic effect following the SC administration of mepolizumab liquid drug product in safety syringe	• Ratio to baseline of blood eosinophils at Weeks 4, 8 and 12

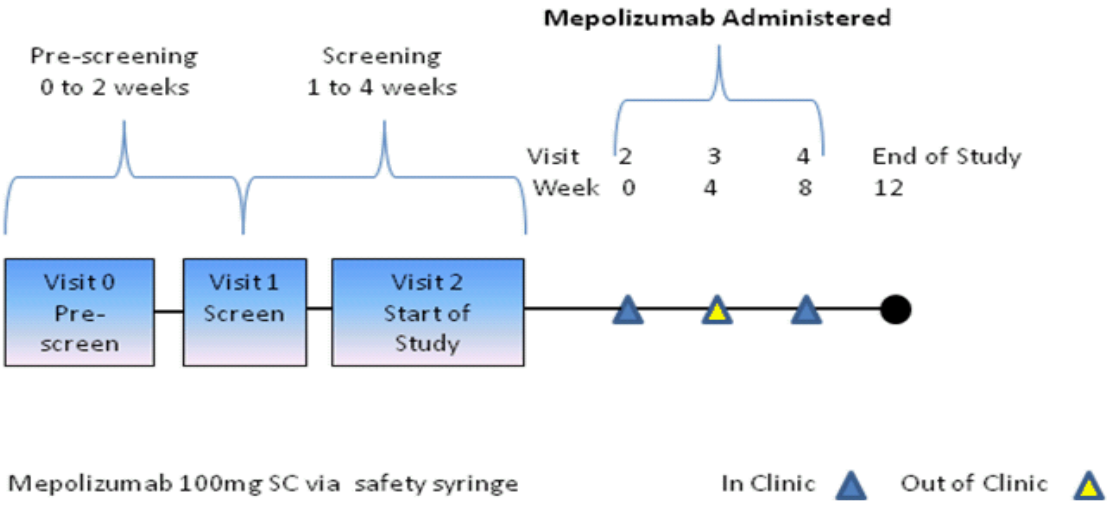
Objectives	Endpoints
Safety	
To evaluate the safety and tolerability of mepolizumab liquid drug product in safety syringe	• Incidence and frequency of Adverse Events / Serious Adverse Events including systemic reactions and injection site reactions • Incidence of asthma exacerbations • Clinically significant change in haematological and/or clinical chemistry parameters. • Vital signs • 12-lead electrocardiogram (ECG) • Incidence of immunogenicity • Level of self-reported pain immediately following,1- and 24-hours following each injection (patient diary)

4. STUDY DESIGN

4.1. Overall Design

This Phase III study will be an open-label, single arm, repeat-dose, multi-centre study of mepolizumab liquid drug product in safety syringe (100 mg) administered SC every 4 weeks in subjects with severe eosinophilic asthma. The study is designed to evaluate the use of the safety syringe liquid drug product presentation by severe eosinophilic asthma subjects (or their caregivers) for the SC administration of mepolizumab (Figure 1).

Figure 1 Study Schematic



For the purposes of this study, 'self-administration' is defined as either the administration of mepolizumab liquid drug product in safety syringe by the subject themselves or by their caregiver. If applicable, only one caregiver per subject will be permitted.

Subjects will receive 100 mg mepolizumab SC as a single injection that is self-administered in the thigh, abdomen or administered in the upper arm (caregiver only), using the liquid drug product in safety syringe presentation. The site of administration will be recorded.

Subjects (and/or their caregiver, if applicable) will self-administer mepolizumab liquid drug product in safety syringe for the first time immediately after being trained in its use at Visit 2 (i.e. the Start of Study Visit). The training is designed to be representative of the instruction and training materials, including the Instructions for Use (IFU) that will be provided once the device is commercially available.

Three doses of mepolizumab liquid drug product in safety syringe will be self-administered by the subject/caregiver at 4-weekly intervals; 2 doses will be administered under observation in the clinic (at Visits 2 and 4). The second in clinic administration (Visit 4) will not include any onsite training or support, other than the IFU, which could assist the subject. One dose will be administered outside the clinic and without observation (within 24 hours after attending the clinic for Visit 3). Following each injection, subjects will complete a patient diary, included in the Study Reference Manual (SRM), and report the pain experienced immediately following, 1- and 24-hours post injection. Observations about the injection will be recorded by the investigators for the doses administered in the clinic using an observer checklist. For the unobserved dose administered at home, a similar checklist detailing the steps required to successfully administer the injection will be completed by the subject/caregiver. All injections will be assessed by the investigator for success based on:

- Direct observation of the self-administration using the investigator Observer Checklist if the mepolizumab dose was administered in the clinic, and inspection of the safety syringe

- Subject/caregiver completed checklist and inspection by the investigator of the returned safety syringe if the mepolizumab dose was administered outside the clinic

A self-administered injection is considered successful if the following criteria are met:

- Use of a correct injection site (abdomen/thigh or upper arm [caregiver only])

- Full dose administered: subject fully inserts the needle, slowly depresses the plunger until the stopper reaches the bottom of the syringe and activates the needle guard by moving the thumb up

- No observations are made with respect to the safety syringe, following inspection by the investigator, which indicates the full dose has not been dispensed

If the above criteria are met, the investigator will confirm the injection was successfully delivered.

Any unsuccessful injection will undergo a root-cause investigation, following a scripted approach, and evaluation to assess whether the unsuccessful injection was associated with the instructions / use of the device or whether it was associated with a device failure using the Safety Syringe Error/Failure Reporting Form, further details of which can be found in the SRM. All devices associated with an unsuccessful injection, will be evaluated by Device Engineering at GlaxoSmithKline (GSK), post-use, to assess overall performance and robustness of the device.

At the End of Study Visit, subjects will be asked to record their overall experience with the safety syringe including device performance.

In all subjects, blood samples for both PK, haematology assessment (which will include blood eosinophil count for the pharmacodynamic effect assessment) and clinical chemistry assessment will be collected at the time points indicated in the Time and Events Table (Section 7.1).

4.2. Treatment Arms and Duration

This is a single arm study in which all subjects will receive mepolizumab 100 mg SC every 4 weeks, using the liquid drug product in safety syringe presentation, for 12 weeks. Each subject will participate in the study for up to 18 weeks (Visit 0 to the End of Study Visit (Visit 5) as described in Table 1.

Table 1 Study Phases

Phase	Phase Title	Duration	Description
1	Pre-screening	0 to 2 weeks	At the Pre-screening Visit, details about the study and procedures will be explained through the informed consent process. The Pre-screening Visit (Visit 0) can occur on the same day as the Screening Visit (Visit 1) but must be completed prior to initiating any Visit 1 procedures.
2	Screening	1 to 4 weeks	Subjects will be assessed for eligibility at the Screening Visit (Visit 1). Blood draws will be taken for assessments of liver function and to determine blood eosinophil levels in subjects not previously using mepolizumab and who do not meet the historical blood eosinophil criterion.
3	Treatment	12 weeks	At Visit 2 (Week 0) those subjects who continue to meet the eligibility criteria and the continuation to treatment criteria (see Section 5.3) will receive mepolizumab 100 mg SC every 4 weeks for a total of 3 doses. The treatment period will conclude with subjects completing End of Study Visit (Visit 5) assessments approximately 4 weeks after the subject was administered their last dose of study treatment at Visit 4.

A subject who adheres to the study treatment and assessment schedule (as detailed in Time and Events Table, Section 7.1) will be considered to have completed the study if they complete all of the assessments at the End of Study visit (Visit 5). A subject who permanently discontinues study treatment early will be withdrawn from the study after completing the Early Withdrawal visit (see Time and Events Table, Section 7.1).

Subjects receiving mepolizumab prior to the study will be advised to continue with their pre-study mepolizumab treatment following completion of the assessments at the End of Study/Early Withdrawal visit. Subjects not receiving mepolizumab prior to the start of the study will have mepolizumab treatment stopped at the End of Study/Early Withdrawal visit and will receive appropriate care and treatment as determined by their treating physician.

4.3. Type and Number of Subjects

Approximately 75 subjects with severe eosinophilic asthma will be screened in order to achieve 55 enrolled subjects (attempting at least one self-administration of mepolizumab) and 50 subjects with complete study data.

4.4. Design Justification

An open-label, repeat-dose, single arm, multi-centre study design is deemed appropriate to evaluate self-administration of mepolizumab liquid drug product in safety syringe in subjects with severe eosinophilic asthma. A population of subjects with severe eosinophilic asthma either currently receiving or not currently receiving commercially available mepolizumab SC at study entry (Visit 1) was selected to reflect the intended population in "real world" conditions. Subjects not currently receiving mepolizumab will be required to have severe eosinophilic asthma and be using high dose inhaled corticosteroids (ICS) plus a second controller, with a history of ≥1 exacerbations requiring treatment with systemic corticosteroids in the previous 12 months. The standardised training provided in this study will be representative of the instruction and training materials that will be given once the device is commercially available for use. Subjects will be instructed to use the safety syringe at the clinic immediately after being trained in its use at Visit 2 (Week 0) and thereafter at 4-weekly intervals either at the clinic or outside of the clinic (Time and Events Table, Section 7.1). The primary endpoint of the study will be assessed under observation at Visit 4, 8 weeks after the subject received training in the use of the safety syringe.

With regards to the pharmacokinetic and pharmacodynamic assessments, it is acknowledged that mepolizumab exposure will not be at steady-state after the first and second SC doses (administered at Visits 2 and at home following Visit 3, respectively) in those subjects not previously receiving mepolizumab treatment at Visit 1; however, mepolizumab plasma concentration at the end of the dosing interval (Ctrough) measurements can be compared with historical data. Likewise data from the Phase III study MEA115588 showed that in subjects previously not treated with mepolizumab, the reduction in blood eosinophil count at the end of the dosing interval following the first SC dose of mepolizumab (i.e. pre-steady-state) was close to the reduction observed at the end of the dosing interval following the eighth SC dose of mepolizumab (i.e. at steady-state). Therefore, in those subjects not receiving mepolizumab treatment at Visit 1, assessing the pharmacodynamic effect of mepolizumab is still of interest.

4.5. Dose Justification

The 100 mg dose of mepolizumab liquid drug product in safety syringe will match the dose of reconstituted lyophilised drug product (the currently marketed form).

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with mepolizumab (SB-240563) lyophilised drug product can be found in the Investigator's Brochure [GSK Document Number CM2003/00010/10]. The following section outlines

the key risks, risk assessment and mitigation strategy for this protocol based on mepolizumab lyophilised formulation. The safety profile of the mepolizumab liquid formulation is anticipated to be similar to the lyophilized formulation.

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP)		
Risk of Systemic Reactions including allergic reactions	Biopharmaceutical products administered subcutaneously may elicit systemic (e.g. hypersensitivity) and local site reactions. In the placebo controlled severe asthma studies both acute and delayed systemic reactions including hypersensitivity have been reported following administration of mepolizumab with incidence rates similar between mepolizumab and placebo-treated subjects: • 54/915 subjects or 6% in the mepolizumab [all doses combined] group • 7/263 subjects or 3% in the mepolizumab 100 mg SC group • 12/344 subjects or 3% in the mepolizumab 75 mg intravenous (IV) group • 20/412 subjects or 5% in the placebo group. The most common symptoms reported with any systemic reaction included headache, rash, pruritus, fatigue, and dizziness. While rare, serious systemic reactions including anaphylaxis have been reported. Systemic reactions reported to date across the mepolizumab programme are summarised in the	Daily monitoring of serious adverse events (SAEs) by medical monitor; regular systematic review of adverse event (AE)/SAE data from ongoing studies by the GSK study team and/or safety review team. Customised AE and SAE case report form (CRF) utilised for targeted collection of information for systemic reaction adverse events. Use of Joint National Institute of Allergy and Infectious Diseases (NIAID)/Food Allergy and Anaphylaxis Network (FAAN) 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (see Appendix 2). Subjects are monitored in clinic for at least 1 hour following self-administration of mepolizumab at the clinic. For administration at home, subjects will be instructed to call the investigator and/or go to an Emergency Department for any unusual symptoms (e.g. symptoms concerning for hypersensitivity include skin rash [hives] or redness, swelling of the face or mouth, becoming wheezy, coughing or having difficulty in breathing and/or feeling

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	IB "Adverse events of special interest" section; see also 'Special Warnings and Special Precautions for Use' section located in Section 6 titled 'Summary of Data and Guidance for the Investigator' [GSK Document Number CM2003/00010/10]	weak or light headed).
Injection site reactions	In the placebo controlled severe asthma (PCSA) studies the incidence of local site reactions with SC administration of mepolizumab was higher on mepolizumab 100 mg SC group (21/263 or 8%) compared to mepolizumab 75mg IV (10/344 or 3%) or placebo (13/412 or 3%). Symptoms included pain, erythema, swelling, itching, and burning sensation. Local injection site reactions reported to date across the mepolizumab program are summarized in the IB "Adverse events of special interest" section; see also Section 6 titled 'Summary of Data and Guidance for the Investigator' [GSK Document Number CM2003/00010/10].	Daily monitoring of serious adverse events (SAEs) by medical monitor; regular systematic review of adverse event (AE)/SAE data from ongoing studies by GSK study team and/or safety review team. Customised AE and SAE case report form (CRF) utilised for targeted collection of information for local injection site reaction adverse events. Pain assessment will also be done utilizing visual analog scale, in the patient diary, immediately after injection, 1 hour after injection and 24 hours (±4 hours) after injection.
Potential risk of immunogenicity	Biopharmaceutical products may elicit anti-drug antibody (ADA) and neutralising antibody (NAb), which have the potential to modulate pharmacokinetic (PK), pharmacodynamic (PD) or produce adverse reactions. Mepolizumab has low immunogenic potential. Both incidence and titer data from completed	Blood samples will be collected for detection of both ADA and NAb.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	studies demonstrate a low risk for loss of efficacy associated with AEs and/or altered PK/PD. Immunogenicity data reported to date across the mepolizumab development program are summarized in the IB; See Section 5.4 'Clinical Immunogenicity' and a summary of immunogenicity findings in Section 6 'Other Potentially Clinically Relevant Information for the Investigator' [GSK Document Number CM2003/00010/10].	
Study Procedures		
Injuries due to accidental needle sticks	The safety syringe has been designed and verified to comply with ISO23908 'Sharps injury protection – Requirements and test methods – Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling'	The subject will be educated by the staff prior to self-administration and their first scheduled dose will be supervised in the clinic by the staff. Additionally, the IFU will instruct the subject on the safe use of the device. A plastic / rubber needle shield protects the needle before injection to minimise the potential for needle stick injuries. The needle automatically retracts into the syringe body after the injection.

4.6.2. Benefit Assessment

Data from earlier studies [Haldar, 2009; Nair, 2009; Pavord, 2012] attest to the clinical utility of mepolizumab in the treatment of severe eosinophilic asthma which was confirmed in the Phase III studies MEA115575 and MEA115588 [Bel, 2014; Ortega, 2014]. The safety syringe provides a more convenient mode of delivery from previous mepolizumab administration and potentially provides patients an option to self-administer mepolizumab at home.

4.6.3. Overall Benefit:Risk Conclusion

Current data from mepolizumab preclinical and clinical development indicate the ability of mepolizumab to inhibit IL-5 leading to consistent reduction in blood eosinophils, with demonstration of clinical benefit in the treatment of conditions associated with eosinophilic inflammation, such as asthma. Data from the Phase III asthma programme with mepolizumab demonstrates, compared to placebo, a reduction in asthma exacerbations, improvements in asthma control and quality of life (as measured by the ACQ and SGRQ, respectively), improvements in lung function and a reduction in oral corticosteroid use in those subjects on chronic OCS treatment. To date, the safety profile of mepolizumab has been favourable and the benefit/risk profile remains positive in patients with severe asthma. The change in drug product presentation from a lyophilised drug product to a liquid drug product in an safety syringe is not anticipated to alter the overall benefit:risk. The ability of subjects to self-administer treatment will be closely observed in the clinic and subjects will be instructed to seek medical attention if they experience any abnormal symptoms following administration at home, away from the clinic.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB/IB supplement(s).

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

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
1. **Age:** At least 12 years of age inclusive, at the time of signing the informed consent. [For those countries where local regulations permit enrolment of adults only, subject recruitment will be restricted to those who are ≥18 years of age]

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. **Asthma:** A physician diagnosis of asthma for ≥2 years that meets the National Heart, Lung and Blood Institute guidelines [National heart, lung and blood institute (NIH), 2007] or Global Initiative for Asthma (GINA) guidelines [GINA, 2015] 3. **Mepolizumab treatment**: a. Not receiving mepolizumab treatment at Visit 1 (NB: these subjects must also meet inclusion criteria 4, 5, 6 and 7). **OR** b. Receiving 100 mg SC mepolizumab administered for the treatment of severe eosinophilic asthma every 4 weeks for at least 12 weeks prior to Visit 1. **The following inclusion criteria are only applicable to those subjects NOT receiving mepolizumab treatment at Visit 1:** 4. **Eosinophilic asthma**: A high likelihood of eosinophilic asthma as per the required 'Continuation to Treatment' - Criterion 2. 5. **Inhaled Corticosteroid:** A well-documented requirement for regular treatment with high dose inhaled corticosteroid (ICS) in the 12 months prior to Visit 1 with or without maintenance oral corticosteroids (OCS). • For subjects ≥18 years old: • ICS dose must be ≥880 mcg/day fluticasone propionate (FP) (ex-actuator) or equivalent daily. • For ICS/long-acting-beta-2-agonist (LABA) combination preparations, the highest approved maintenance dose in the local country will meet this ICS criterion. • For subjects ≥12 to ≤17 years old: • ICS dose must be ≥440 µg/day FP (ex-actuator) or equivalent daily. • For ICS/LABA combination preparations, the mid-strength approved maintenance dose in the local country will meet this ICS criterion.

6. **Controller Medication:** Current treatment with an additional controller medication, besides ICS, for at least 3 months or a documented failure in the past 12 months of an additional controller medication [e.g., long-acting beta-2-agonist (LABA), leukotriene receptor antagonist (LTRA), or theophylline] for at least 3 successive months.

7. **Exacerbation history:** Previously confirmed history of one or more exacerbations requiring treatment with systemic corticosteroid (CS) [intramuscular (IM), intravenous, or oral] in the 12 months prior to Visit 1, despite the use of high-dose ICS. For subjects receiving maintenance CS, the CS treatment for an exacerbation must have been a two-fold dose increase or greater.

WEIGHT
8. **Body weight**: A minimum ≥40 kg at Visit 1

SEX
9. **Gender:** Male or Female

Females:

A female subject is eligible to participate if she is not pregnant (as confirmed by a negative urine human chorionic gonadotrophin (hCG) test), planning to become pregnant during the time of study participation (and up to 16 weeks after the last dose), not lactating, and at least one of the following conditions applies:

a. Non-reproductive potential defined as:
   - Pre-menopausal females with one of the following:
     - Documented tubal ligation
     - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
     - Hysterectomy
     - Documented Bilateral Oophorectomy
   - Postmenopausal female (see Appendix 3 for specific criteria).

b. Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 3) from 30 days prior to the first dose of study medication and until 16 weeks after the last dose of study medication and completion of the End of Study/Early Withdrawal visit.

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

INFORMED CONSENT
10. **Informed Consent:** Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. **Concurrent Respiratory Disease:** Presence of a known pre-existing, clinically important lung condition other than asthma. This includes current infection, bronchiectasis, pulmonary fibrosis, bronchopulmonary aspergillosis, or diagnoses of emphysema or chronic bronchitis (chronic obstructive pulmonary disease other than asthma) or a history of lung cancer. 2. **Eosinophilic Diseases:** Subjects with other conditions that could lead to elevated eosinophils such as Hypereosinophilic Syndromes, including Churg-Strauss Syndrome, or Eosinophilic Esophagitis. Subjects with a known, pre-existing parasitic infestation within 6 months prior to Visit 1 are also to be excluded. 3. **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). 4. **Immunodeficiency:** A known immunodeficiency (e.g. human immunodeficiency virus – HIV), other than that explained by the use of corticosteroids taken as therapy for asthma. 5. **Other Concurrent Medical Conditions:** Subjects who have known, pre-existing, clinically significant cardiovascular, endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, haematological or any other system abnormalities that are uncontrolled with standard treatment. 6. **Liver Disease:** Known, pre-existing, unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices or persistent jaundice), cirrhosis, and known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). 7. **ECG Assessment:** QT interval corrected for heart rate by either Fridericia's or Bazett's formula QTc(F)/QTc(B) ≥450msec or QTc(F)/QTc(B) ≥480 msec for subjects with Bundle Branch Block at Visit 1.

CONCOMITANT MEDICATIONS
8. **Xolair:** Subjects who have received omalizumab within 130 days of Visit 1. 9. **Other Monoclonal Antibodies not including mepolizumab:** Subjects who have received any monoclonal antibody (other than Xolair) to treat inflammatory disease within 5 half-lives of Visit 1.

10. **Investigational Medications:** Subjects who have received treatment with an investigational drug, other than mepolizumab within the past 30 days or five terminal phase half-lives of the drug whichever is longer, prior to visit 1 (this also includes investigational formulations of marketed products) or experimental anti-inflammatory drugs (non biologicals) in the past 3 months.
11. **Chemotherapy:** Subjects who have received chemotherapy within 12 months prior to Visit 1.

RELEVANT HABITS
12. **Alcohol/Substance Abuse:** A history (or suspected history) of alcohol misuse or substance abuse within 2 years prior to Visit 1.

CONTRAINDICATIONS
13. **Hypersensitivity:** Subjects with hypersensitivity to mepolizumab or to any of the excipients (sodium phosphate, citric acid, sucrose, EDTA, polysorbate 80).

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
14. **Adherence:** Subjects who have known evidence of lack of adherence to controller medications and/or ability to follow physician's recommendations.

5.3. Continuation to Treatment Criteria

At Visit 2, those subjects who continue to meet the inclusion/exclusion criteria and who meet the continuation to treatment criteria will commence the study treatment phase until the target of approximately 55 enrolled subjects is reached.

In order to receive study treatment subjects must have fulfilled all inclusion and exclusion criteria described in Section 5.1 and Section 5.2. In addition to the following:

REQUIRED CRITERIA TO START TREATMENT

1. **Liver Function:** At Visit 2, ALL study subjects must fulfil the following additional criteria in order to be eligible for study treatment:
    - **Liver Function Tests**: obtained at Visit 1:
        - Alanine aminotransferase (ALT)≤2x ULN (upper limit of normal)
        - Bilirubin ≤1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
2. **Eosinophilic Phenotype**: At Visit 2, study subjects that were **NOT** receiving mepolizumab treatment at Visit 1 must fulfil the following additional criteria in order to be eligible for study treatment:

- Airway inflammation characterised as eosinophilic in nature as indicated by one of the following:

  a) A peripheral blood eosinophil count of ≥300 cells/μL that is related to asthma demonstrated in the past 12 months prior to Visit 1.

  OR

  b) A peripheral blood eosinophil count of ≥150 cells/μL at Visit 1 that is related to asthma.

5.4. Pre-Screening/Screening Failures

A subject will be assigned a subject number at the time the informed consent is signed.

A subject who is assigned a subject number at Visit 0 but does not have any screening Visit 1 procedures will be considered a pre-screen failure.

Screen failures will be defined as those subjects who complete at least one Visit 1 (Screening) procedure but do not attempt to self-administer a dose of mepolizumab.

The following information will be collected in the electronic case report form (eCRF) for subjects who are pre-screen and screen failures:

- Date of Informed Consent Form (ICF) signature
- Demographic information including race, age and gender
- Child bearing status assessment for all female subjects of reproductive potential
- Subject number
- Details of asthma medications within 3 months of the pre-screening Visit 0
- Details of asthma exacerbations during the pre-screening period
- Serious Adverse Event information only for any SAE considered as related to study participation (e.g. protocol mandated procedures, invasive tests or change in existing therapy) or related to a GSK concomitant medication
- Investigator signature page

In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.7.1).

5.5. Withdrawal/Stopping Criteria

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or

administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records. As the aim of this study is to evaluate the use of the mepolizumab liquid drug product, in safety syringe presentation, for delivery of mepolizumab, subjects who permanently withdraw from study treatment will also be withdrawn from the study (see Section 5.5.1). Reasons for premature discontinuation of study treatment will be captured in the CRF.

5.5.1. Withdrawal from the Study

Subjects who have withdrawn from the study should complete assessments for the Early Withdrawal Visit, 4 weeks after the last dose of mepolizumab (see Time and Events Table, Section 7.1).

A reason for the withdrawal from the study must be captured in the eCRF.

A subject must be discontinued if any of the following criteria are met:

- Withdrawal of consent
- Lost to follow-up

A subject will also be withdrawn from the study, in consultation with the medical monitor and principal investigator, if any of the following stopping criteria are met:

- Laboratory parameters: Clinically important changes in laboratory parameters identified.
- ECG: Clinically significant abnormality identified during the study that meet the QTc stopping criteria described in Section 5.5.3.
- Liver Chemistry: Meets any of the Liver chemistry stopping criteria (See Section 5.5.2 and Appendix 4.
- Pregnancy: Positive pregnancy test (see Appendix 3). Pregnancy and pregnancy outcomes of subjects exposed to mepolizumab will be followed.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

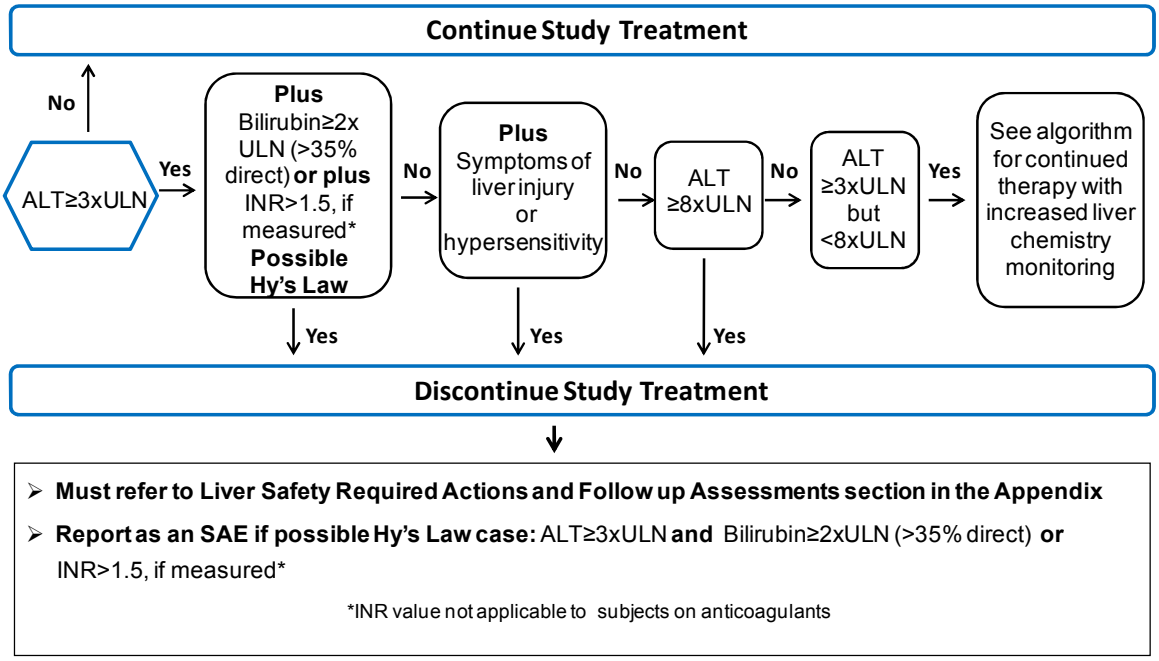
- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed ‘lost to follow up’, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject’s last known mailing address or local equivalent methods). These contact attempts should be documented in the subject’s medical record.

- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

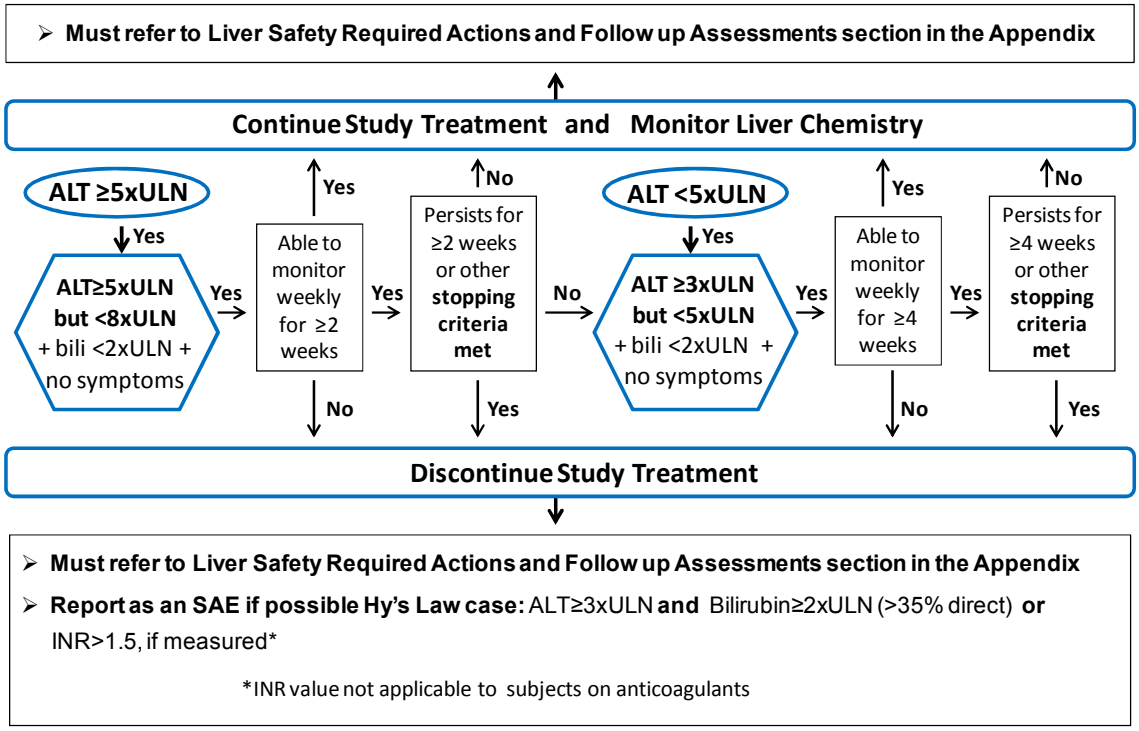
5.5.2. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the Food and Drug Administration [FDA] premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3xULN but <8xULN



Required actions and follow-up assessment for all subjects who meet liver chemistry stopping or monitoring criteria are defined in Appendix 4.

5.5.2.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met, by any subject participating in this study, is not allowed.

5.5.3. QTc Stopping Criteria

- The *same* QT correction formula *must* be used for *each individual subject* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled. For example, if a subject is eligible for the protocol based on QT interval corrected for heart rate by Bazett's formula (QTcB), then QTcB must be used for discontinuation of this individual subject as well.
- Once the QT correction formula has been chosen for a subject's eligibility, the *same formula* must continue to be used for that subject *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period. For example if a routine ECG demonstrates a prolonged QT, obtain 2 more ECGs

over a brief period and then use the averaged QTc values of the 3 ECGs to determine whether patient should be withdrawn from the study.

A subject who meets either of the bulleted criteria below will be withdrawn from the study:

- QTc >500 msec OR Uncorrected QT >600 msec
- Change from baseline (Visit 2) of QTc >60 msec

For patients with underlying **bundle branch block**, follow the discontinuation criteria listed below:

Baseline (Visit 2) QTc with Bundle Branch Block	**Discontinuation QTc with Bundle Branch Block**
<450 msec	>500 msec
450 – 480 msec	≥530 msec

5.6. Subject and Study Completion

A completed subject is one who has completed the End of Study (Week 12) visit.

The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe the mepolizumab drug product in safety syringe received by the subject as per the protocol design.

Mepolizumab liquid drug product will be supplied by GSK in Type I glass syringes with staked needles (1/2 inch x 29 gauge thin wall), sealed with latex-free rubber plungers. These will be assembled in single use, disposable safety syringes to enable delivery of the drug product. Each device will deliver 100mg mepolizumab in 1.0mL. The formulation contains sodium phosphate, citric acid, sucrose, EDTA and polysorbate 80.

	Study Treatment
Product name:	Mepolizumab (NUCALA) (SB240563)
Device:	Pre-filled syringe contained within a safety syringe
Formulation description:	100 mg/mL mepolizumab with sodium phosphate, citric acid, sucrose EDTA and polysorbate 80
Dosage form:	Sterile, liquid formulation
Unit dose strength(s)/Dosage level(s):	100 mg/mL; 1.0mL (deliverable)
Route of Administration	SC injection
Dosing instructions:	SC dose in thigh, abdomen or upper arm every 4 weeks
Physical description: mepolizumab	Clear to opalescent, colourless to pale yellow sterile solution for SC injection in a single-use, pre-filled syringe contained within safety syringe
Physical description of injection device:	Single use, disposable safety syringe assembled with the pre-filled syringe containing the drug product. The safety syringe enables delivery of the drug product by the subject/caregiver. A plastic needle cover shields the needle after injection to minimise the potential for needle stick injuries.
Manufacturer/source of procurement:	**Pre-filled syringe**: Pre-filled syringe components are procured from Becton Dickinson. Prefilled syringe is filled with drug product and assembled at GSK, Barnard Castle, UK. **Safety syringe:** The safety syringe components are manufactured by Becton Dickinson and assembled with the prefilled syringe at GSK, Barnard Castle, UK.

6.2. Medical Devices

The GSK manufactured medical devices (or devices manufactured for GSK by a third party) provided for use in this study are injection devices: a prefilled syringe contained within a safety syringe. The devices used in the study are representative of the devices planned to be marketed for the product.

The components that comprise the prefilled syringe, including glass barrel with prestaked needle and plunger are sourced from Becton Dickinson. The prefilled syringe is filled and assembled at GSK, Barnard Castle.

The safety syringe components are manufactured by Becton Dickinson. The safety syringe components are assembled with the prefilled syringe at GSK, Barnard Castle.

The IFU of these injection devices are provided in the SRM. The instructions were developed and optimised as a result of formative human factors studies and are representative of those that are planned for the product.

GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study – see Section 7.7.3.

6.3. Treatment Assignment

All subjects will be assigned to the same treatment at Visit 2 (Week 0).

6.4. Blinding

This will be an open-label, single arm study.

6.5. Packaging and Labeling

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

6.6. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

Study treatment must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive study treatment. Only authorised site staff may supply study treatment. All study treatment must be stored in a secure area with access limited to the investigator and authorised site staff.

Mepolizumab will be supplied in a single-use safety syringe and should be stored in a refrigerator at 2 to 8°C with protection from light. Each injection device will contain 100 mg mepolizumab as a single 1.0 mL injection of the liquid drug product (100 mg/mL). Maintenance of a temperature log at the clinical dispensing sites (manual or automated) is required.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only the subject or previously identified caregiver may administer the study treatment. Whilst on site, all study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.

- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.
- Subjects will be provided a safety syringe for home use at Visit 3 and asked to follow the information on the IFU with regards to the storage and use of the device. Cool bags and cold packs will be provided to transport the safety syringe from site to home. Subjects will be asked to return the used safety syringe at Visit 4. A record of the dispensing of the safety syringe given to the subject at Visit 3 and collection of the safety syringe returned at Visit 4 will be maintained by the Investigator or designee. The Investigator or designee will also inspect the returned safety syringe to determine if the dose has been dispensed correctly.

6.7. Training Session

Training of study treatment, handling and administration techniques by qualified study site personnel will be provided to the study participants at Visit 2 prior to self-administration. The training is designed to be representative of the instruction and training materials that will be used in the post-marketing setting. The training will consist of a walk-through of the IFU for the injection devices by the site personnel. Finally, the first actual injection will then be supervised by site personnel including feedback to the subject as needed.

6.8. Compliance with Study Treatment Administration

A record of the number of safety syringes dispensed and returned by each subject must be maintained and reconciled with study treatment and compliance records.

6.8.1. Self-Administration at the Clinic

Following the training (see Section 6.7) at Visit 2 (Week 0), the subject (and/or caregiver, if applicable) will self-administer the first dose of study treatment by SC injection under medical supervision of the investigator or designee at the study site. The subject/caregiver will also administer the dose of study treatment at the clinic under medical supervision, but without further training, at Visit 4 (Week 8). Observations about the injection will be recorded by the investigator using a checklist for the doses administered in the clinic. Details of the Observer Checklist can be found in the SRM. The subject will complete a patient diary with a visual analogue scale (VAS) indicating the pain experience immediately following, 1- and 24-hours after the dose.

The date, time of the dose, person administering the dose (subject/caregiver) and site of administration (thigh, abdomen or upper arm [caregiver only]) of each dose administered in the clinic will be recorded on the Observer Checklist and in the source documents.

Subjects will be monitored for 1 hour after mepolizumab self-administrations in the clinic at Visit 2 and Visit 4. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study treatment, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the

subject including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the patient to another facility for additional care if appropriate.

6.8.2. Self-Administration Outside the Clinic

The subject (or caregiver) will self-administer the dose of study treatment outside the clinic and without observation during Week 4, up to 24 hours after attending clinic Visit 3. The subject/caregiver will complete a checklist of the steps required to use the safety syringe, which will also include the date and time of dose, site of injection, person administering the dose (subject/caregiver) and the ease with which the subject/caregiver was able to complete each of the critical steps required to administer the dose from the safety syringe. In addition, the subject will complete the patient diary capturing the pain experienced by the subject immediately following, 1- and 24-hours after the dose.

Subjects will be instructed to contact clinical study staff if they have concerns or questions regarding self-administration. They will have the option of returning to the clinical site for further training or assistance with self-administration. Requirement for additional training will be documented.

Compliance with the safety syringe will be assessed through reviewing the subject completed checklist, inspection of the returned safety syringe and querying the subject during the next site visit (Visit 4) and documented in the source documents.

For self-administration of mepolizumab outside of the clinic (at home), subjects should be instructed to call the investigator and/or go to an Emergency Department for any unusual symptoms (e.g. skin rash [hives] or redness, swelling of the face or mouth, becoming wheezy, coughing or having difficulty in breathing and/or feeling weak or light headed).

6.9. 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 judgment in treating the symptoms of a suspected overdose.

6.10. 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.

There are no plans to provide mepolizumab following study completion.

6.11. Concomitant Medications and Non-Drug Therapies

6.11.1. Permitted Medications and Non-Drug Therapies

Throughout the study, subjects are to be maintained on their baseline standard of care asthma treatment.

For subjects previously receiving mepolizumab, additional asthma medications such as theophyllines or anti-leukotrienes will be permitted provided that they have been taken regularly in the 3 months prior to first dose of mepolizumab treatment (Visit 2, Week 0).

For subjects who have not previously received mepolizumab, subjects must have a well-documented requirement for regular treatment with high dose inhaled corticosteroid (ICS) in the 12 months prior to Visit 1 with or without maintenance oral corticosteroids (OCS).

- Subjects ≥18 years old:
  - ICS dose must be ≥880 mcg/day fluticasone propionate (FP) (ex-actuator) or equivalent daily.
  - For ICS/LABA combination preparations, the highest approved maintenance dose in the local country will meet this ICS criterion.
- Subjects ≥12 to ≤17 years old:
  - ICS dose must be ≥440 µg/day FP (ex-actuator) or equivalent daily.
  - For ICS/LABA combination preparations, the mid-strength approved maintenance dose in the local country will meet this ICS criterion.

Subject not previously receiving mepolizumab must also be receiving current treatment with an additional controller medication, besides ICS, for at least 3 months or a documented failure in the past 12 months of an additional controller medication [e.g., LABA, LTRA, or theophylline] for at least 3 successive months.

All concomitant medications taken during the study will be recorded in the eCRF. In addition, all medications taken by the patient for the treatment of asthma including asthma exacerbations in the 12 months prior to Visit 1 must also be recorded in the eCRF. The minimum requirement is that the drug name and the dates of administration are recorded.

6.11.2. Prohibited Medications and Non-Drug Therapies

The following medications (Table 2) are not allowed prior to screening (Visit 1) according to the following schedule, or during the study:

Table 2 Medications not allowed prior to the Screening Visit 1 and throughout the study

Medication	**Washout Time Prior to Screening Visit 1**
Omalizumab (Xolair)	Within 130 days
Other monoclonal antibodies (other than Xolair or mepolizumab) to treat inflammatory disease	5 half-lives
Investigational drugs (excluding mepolizumab)	30 days or 5 half-lives whichever is longer
Chemotherapy	12 months

Recreational drug use is not allowed during the study.

7. STUDY ASSESSMENTS AND PROCEDURES

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

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1

7.1. Time and Events Table

	Pre-screening Week -6 to Week -5[a]	Screening Week -4 to Week -1	Week 0 (Day 1)	Week 4 (±7 days)	Week 8 (±7 days)	Week 12 (±7 days) End of Study/ Early Withdrawal[b]
Procedures Visit number	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**
Informed consent	X					
Demography/child bearing status assessment	X					
Medical history		X				
Asthma and Exacerbation history	X					
Asthma Therapy history	X					
Smoking history		X				
Parasitic screening[c]		X				
Prior needle use / self-administration assessment		X				
Inclusion/Exclusion criteria		X				
Training session			X[d]			
Safety syringe self-administration in clinic			X		X	
Safety syringe self-administration outside of clinic				X[e, f]		
Laboratory:						
Urine pregnancy test		X	X[d]	X[d]	X[d]	X
Hematology (including eosinophils)[g] / Clinical Chemistry		X	X[d]	X[d]	X[d]	X[d]
Urinalysis		X				
Immunogenicity			X[d]			X[d]
PK			X[d]	X[d]	X[d]	X[d]
Pharmacogenetics[h]			X			
Physical/Clinical:						
Vital signs[i]		X	X[d]	X[d]	X[d]	X
12-lead ECG		X				X
Physical examination		X				X
Weight		X				
Concomitant Medication	X	X	X	X	X	X
Serious Adverse Events[j,k,l]	X	X	X	X	X	X
Adverse Events[j,k,l]			X	X	X	X

	Pre-screening Week -6 to Week -5	Screening Week -4 to Week -1	Week 0 (Day 1)	Week 4 (±7 days)	Week 8 (±7 days)	Week 12 (±7 days) End of Study/ Early Withdrawal[b]
Procedures Visit number	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**
Dispense patient diary			X[m]	X	X	
Return/review patient diary				X	X	X[n]
Dispense safety syringe for self-administration outside of clinic				X		
Return/ inspect safety syringe following self-administration outside of clinic					X	X[n,o]
Subject completed pain assessment diary (0, 1- and 24-hours post dose)			X	X[f]	X	
Safety syringe observer assessment checklist			X		X	
Subject/caregiver completed safety syringe checklist				X[f]		
Assessment of injection success			X		X[p]	
Device usability/functionality questionnaire						X
Exit Interview[Q]						(X)

a. Pre-screening Visit can occur on the same day as the Screening Visit but must be completed prior to initiating any Visit 1 procedures; The Pre-screening Visit can be conducted up to a maximum of 2 weeks prior to the Screening Visit.
b. The Early Withdrawal Visit will occur 4 weeks (±7 days) after last dose of mepolizumab for any subject who withdraws prior to Week 12
c. Parasitic screening is only required in countries with high-risk or for subjects who have visited high-risk countries in the past 6 months. Sites should use local laboratories.
d. Perform prior to mepolizumab administration during the study and prior to restarting pre-study mepolizumab treatment on study completion/early withdrawal.
e. Subjects will be instructed to contact clinical study staff at any time if they have concerns or questions regarding self-administration. They will have the option of returning to the clinical site for further training or assistance with self-administration. Requirement for additional training or assistance will be documented.
f. Self-administration of mepolizumab using the safety syringe should occur within 24 hours following the clinic visit.
g. Includes measurement of eosinophil levels for pharmacodynamic analysis at Visits 2, 3, 4 and 5
h. Pharmacogenetic sample may be drawn any time after the respective informed consent form is signed and the subject is enrolled.
i. Vital signs include temperature, sitting blood pressure, respiratory rate and pulse.
j. 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 other AEs/SAEs are recorded from the start of study treatment until the End of Study / Early Withdrawal visit.
k. Injection site reactions (e.g., induration, erythema, edema, rash, pruritus, pain) are to be recorded on both AE and SAE CRF forms.
l. Information on systemic reactions and events that meet the anaphylaxis criteria is collected on both AE and SAE CRF forms.
m. Patient diary should be dispensed prior to administration of injection

n. For any subject who withdraws prior to Week 12, patient diary and study drug for self-administration outside of clinic will be returned at the Early Withdrawal visit (if applicable).
o. Assessment to be completed at the Early Withdrawal visit only if the dose of mepolizumab immediately prior to withdrawal was administered outside of the clinic.
p. Includes both the injection outside the clinic from Week 4 and the injection in clinic at Week 8
q. In a subset of subjects only. Completed over the telephone after the End of Study/Early Withdrawal Visit

7.2. Screening and Critical Baseline Assessments

Subjects can perform the Pre-screening Visit (Visit 0) up to 2 weeks prior to or on the same day as the Screening Visit (Visit 1). A subject number will be assigned at the time the informed consent form (ICF) is signed. During the Pre-screening Visit, study designated personnel must provide informed consent (including informed consent for the optional pharmacogenetics part of the study, as applicable) to study participants.

Once the informed consent document has been signed, pre-screening assessments can be conducted. The following demographic parameters will be captured: year of birth, sex, race and ethnicity. In addition, Asthma Therapy, Asthma and Exacerbation history and concomitant medications will be assessed. From the pre-screening visit onwards concomitant medications, exacerbations and SAEs (considered as related to study participation) must be reported.

7.2.1. Critical procedures performed at Screening (Visit 1)

- Medical history including smoking status, history of sinusitis, nasal polyposis, aspirin sensitivity, current treatment, duration of asthma, courses of rescue corticosteroids in the past 12 months, history of previous intubations, asthma exacerbation history in the previous 12 months, asthma triggers and smoking history
- Prior experience of needle use including any history of self-administration using an safety syringe device
- Therapy history, including use of mepolizumab, omalizumab or previous biologics in the past 12 months (see Section 6.11.2). For subjects currently receiving mepolizumab, data will be collected on whether mepolizumab treatment was initiated based on an eosinophil count within 6 weeks of starting treatment or a historical measurement collected in the 12 months prior to initiating mepolizumab. The blood eosinophil count closest to the initiation of mepolizumab treatment, if available, should be recorded.
- Cardiovascular medical history/risk factors (as detailed in the eCRF). This assessment must include a review of the subject responses to the cardiovascular assessment questions and height, weight, blood pressure, smoking history, medical conditions, and family history of premature cardiovascular disease
- Physical exam (see Section 7.7.4)
- Vital signs (see Section 7.7.5)
- Resting 12-lead ECG (see Section 7.7.6)
- Laboratory tests (see Section 7.7.7). This should include:
    - Chemistry
    - Haematology with differential count
    - Urinalysis
    - Urine pregnancy test- for all women of child bearing potential

  - Follicle stimulating hormone (FSH) will be assessed to confirm child-bearing status (if applicable)
  - Parasitic screening (only in countries with a high-risk or in subjects who have visited a high-risk country)
- Review of Inclusion/Exclusion criteria
- Review of exacerbations, SAEs

Procedures conducted as part of the subject's routine clinical management [e.g. blood eosinophil counts] and obtained prior to signing of informed consent may be utilised for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Time and Events Schedule.

7.2.2. Critical procedures performed at first treatment Visit (Baseline Visit 2)

- Vital signs (see Section 7.7.5)
- Laboratory tests (see Section 7.7.7). This should include
  - Clinical Chemistry
  - Haematology with differential
  - Blood for baseline immunogenicity
  - Blood for PK assessment
  - Urine pregnancy test for all females of childbearing potential
- Review of exacerbations, concomitant medications, AEs, SAEs
- Review of Continuation to Treatment criteria (see Section 5.3).
- Training of the subject or caregiver as to the correct use of the safety syringe

7.3. Assessment of Safety Syringe Use

At Visit 2 (Week 0), and at Visit 4 (Week 8), the investigator or designee will observe, using a checklist based on the safety syringe IFU, the ability of the subject/caregiver to (self)-administer the injection. The Observer Checklist (see SRM) will be used to determine if each step, according to the IFU, was completed easily, with some difficulty or not completed/intervention required. Failure to perform one of the critical steps, i.e., correct choice of injection site and a full dose administered (determined by the subject fully inserting the needle, slowly depressing the plunger until the stopper reaches the bottom of the syringe and activating the needle guard by moving the thumb up) will be deemed to be a failure to successfully administer the injection. In addition, the investigator will be asked to inspect the safety syringe, following each injection, to confirm that the white plunger has been pushed all the way down and the needle has retracted up into the syringe body, as well as noting any additional observations which indicate the full dose has not been dispensed.

Any user errors or device malfunctions will be recorded and reported using the Safety Syringe Error/Failure Reporting Form (see SRM). Malfunction or failure of the safety syringe meeting the definition of a Medical Device Incident (see Appendix 5), will also require a Medical Device Incident form to be completed and must be reported as described in Section 7.7.3.

Subjects will complete a patient diary at Week 0, 4 and 8 recording the pain experienced immediately following, 1- and 24-hour after the injection (see SRM). At Week 4, when self-administration is performed outside the clinic (within 24-hours of attending the Visit 3 clinic visit), the subject/caregiver will also record the date and time of injection, site of injection, who administered the injection (subject or caregiver) and complete a checklist similar to the Observer Checklist outlining the various steps in the IFU and whether each step was completed easily, with some difficulty, or not completed (see SRM). The responses on the checklist will be checked by the Investigator or designee at the next clinic visit (Visit 4). Failure to perform one of the critical steps will deemed to be a failure to successfully administer the injection.

All devices utilised as part of the study will be returned to the clinic where they will be assessed to confirm that the device has been successfully actuated. Any unsuccessful injection will undergo a root-cause investigation, following a scripted approach, and evaluation to assess whether the unsuccessful injection was associated with the instructions / use of the device or whether it was associated with a device failure using the Safety Syringe Error/Failure Reporting Form, further details of which can be found in the SRM. All devices associated with an unsuccessful injection, will be evaluated by Device Engineering, post-use, to assess overall performance and robustness of the device.

7.4. Pain Assessment

Following each injection, any pain at the injection site will be assessed by the subject using a visual analog scale, in the patient diary, immediately after injection, 1 hour after injection and 24 hours (±4 hours) after injection. The results will be recorded in the patient diary. All measurement timings are detailed in the Time and Events Table (Section 7.1) and further details regarding the pain assessment are found in the SRM.

7.5. Device Usability/Functionality Question

A short survey will be administered to all subjects at the End of Study/Early Withdrawal Visit. This survey (see SRM) will collect quantitative data on patient views of treatment and the use of the safety syringe.

7.6. Exit Interviews

Exit interviews will be conducted after the End of Study/Early Withdrawal Visit over the telephone, in a subset of subjects only, to explore subjects' experience with study treatment and device usage. Exit interviews are qualitative interviews conducted with study subjects to capture subject experiences in drug development on completion of participation in a clinical study. Interview questions are designed to fully assess a subject's experience with a study medication and safety syringe and are administered in a

semi-structured format over the telephone by a trained interviewer. Subject feedback will be captured in a data collection sheet as well as being audio-taped for subsequent transcription and qualitative analysis. The Exit interview technique and questions will be described in the SRM.

7.7. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1).

7.7.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 6.

The following adverse events of special interest will have customized AE and SAE pages in the eCRF:

- Local injection site reactions
- Systemic reactions

In addition, the information whether an event met the diagnostic criteria for anaphylaxis as outlined by the Second Symposium on Anaphylaxis [Sampson, 2006] and in Appendix 2 will be collected on the AE and SAE CRF pages.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.7.1.1. Time period and Frequency for collecting AE and SAE information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment (Visit 2) until the End of Study/Early Withdrawal Visit at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 6.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 6.

7.7.1.2. Method of Detecting AEs and SAEs

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

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.7.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.5). Further information on follow-up procedures is given in Appendix 6.

7.7.1.4. Cardiovascular and Death Events

7.7.1.4.1. Cardiovascular events

Cardiovascular-related AEs and SAEs that will require the investigator to complete event specific pages in the eCRF are listed in Section 12.6.3, Appendix 6.

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 Appendix 6 for timelines for reporting AE/SAEs.

7.7.1.4.2. Deaths

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 12.6.6, Appendix 6 for timelines for reporting SAEs.

7.7.1.5. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation 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.

7.7.2. Pregnancy

- Details of all pregnancies in female subjects will be collected after the start of dosing (Visit 2) and until 16 weeks post-last dose.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 3.

7.7.3. Medical Device Incidents (Including Malfunctions)

GSK medical devices are being provided for use in this study. In order to fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 5.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 12.6 and Appendix 6 of the Protocol.

7.7.3.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented and reported during all periods of the study in which the GSK medical devices are available for use.

- If the investigator learns of any incident at any time after a subject has been discharged from the study, and such incident is reasonably related to a GSK medical device provided for the study, the investigator will promptly notify GSK.

  NOTE: The method of documenting Medical Device Incidents is provided in Appendix 5.

7.7.3.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE, will be followed until resolution of the event, until the condition stabilizes, until the condition is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.5). This applies to all subjects, including those withdrawn prematurely.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

7.7.3.3. Prompt Reporting of Medical Device Incidents to GSK

- Medical device incidents will be reported to GSK within 24 hours once the investigator determines that the event meets the protocol definition of a medical device incident.
- Facsimile transmission of the "Medical Device Incident Report Form" is the preferred method to transmit this information to the Medical Monitor.
- The same individual will be the contact for receipt of medical device reports and SAEs.
- In the absence of facsimile equipment, notification by telephone is acceptable for incidents, with a copy of the "Medical Device Incident Report Form" sent by overnight mail.

7.7.3.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all incidents occurring with any GSK medical device provided for use in the study in order for GSK to fulfil the legal responsibility to notify appropriate regulatory bodies and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution in Japan), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

7.7.4. Physical Exams

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded at Visit 1.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.7.5. Vital Signs

- As detailed in the Time and Events Schedule Table (Section 7.1), vital signs will be measured in semi-supine position after 5 minutes rest and will include systolic and diastolic blood pressure and pulse rate.
- Vital signs assessments will be taken **before** measurement of any ECGs at the specified time point.

7.7.6. Electrocardiogram (ECG)

- A single 12-lead ECG will be obtained at each timepoint specified in the Time and Events Schedule Table (Section 7.1) during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- If a routine single ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine whether the patient should be discontinued from the study. Refer to Section 5.5.3 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- ECG measurements will be made after the subject has rested in the supine position for 5 minutes. The ECG should be obtained after the vital signs assessments and followed by other study procedures.

7.7.7. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 3, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 3.

Table 3 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Haematology	Platelet Count; RBC Count; Hemoglobin; Hematocrit *RBC Indices*: MCV; MCH *WBC count with Differential:* Neutrophils; Lymphocytes; Monocytes; Eosinophils; Basophils
Clinical Chemistry [1]	BUN; Potassium; AST (SGOT); Total and direct bilirubin Creatinine; Sodium; ALT (SGPT); Total Protein Glucose; Calcium; Alkaline phosphatase; Albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• FSH and estradiol (as needed in women of non-child bearing potential only) • Urine hCG Pregnancy test (as needed for women of child bearing potential) [2] • Parasitic screening (only required in countries with high-risk or for subjects who have visited high-risk countries in the past 6 months). Sites should use local laboratories.

NOTES :

1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.5.2 and Appendix 4.
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

RBC: Red blood cell; MCV: Mean corpuscular volume; MCH: Mean corpuscular haemoglobin;BUN: Blood urea nitrogen; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; FSH: Follicle stimulating hormone

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

7.8. Pharmacodynamic Markers

Blood eosinophil counts will be recorded as part of the standard haematological assessments performed at the visits specified in the Time and Events Schedule (Section 7.1).

7.9. Pharmacokinetics

Blood samples for analysis of mepolizumab plasma concentration will be obtained as per the Time and Events table (Section 7.1). Samples obtained at Visits 2, 3, 4 and 5 should be drawn prior to dosing. The date and exact time of collection for each sample will be documented in the eCRF.

Details for collection and processing of samples may be found in the SRM.

7.10. Immunogenicity

Blood samples will be collected for the determination of anti-mepolizumab antibodies, prior to dosing, as detailed in the Time and Events Schedule (Section 7.1)

Details for sample collection and processing may be found in the SRM.

7.11. Genetics

Information regarding genetic research is included in Appendix 7. IEC/IRB and, where required, the applicable regulatory agency must approve the genetic assessments before these can be conducted at the site. The approval(s) must be in writing and will clearly specify approval of the genetic assessments (i.e., approval of Appendix 7). In some cases, approval of the genetic assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the genetic assessments is being deferred and the study, except for pharmacogenetics (PGx) and genetic assessments, can be initiated. When genetic assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, genetic assessments will not be conducted.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.

- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The study is designed to descriptively evaluate the mepolizumab liquid drug product in safety syringe for self-administration by subjects with severe eosinophilic asthma.

No formal statistical hypothesis testing is planned. The number and percentage of subjects successfully able to self-administer their mepolizumab dose will be summarized together with 95% confidence intervals (CI).

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

No formal sample size calculations were performed. Assuming a ~30% dropout rate during screening, approximately 75 subjects will be screened in order to enrol 55 subjects (attempting at least one self-administration of mepolizumab). Assuming a dropout rate of up to 10% during the study, 55 enrolled subjects should provide at least 50 subjects with complete study data.

No sample size re-assessment/adjustment is planned.

9.2.2. Sample Size Sensitivity

The estimated precision for the proportion of subjects successfully able to self-administer their mepolizumab dose is presented below, assuming 50 completed subjects:-

Observed Proportion (%)	95% CI (Exact Method)
70	55, 82
80	66, 90
82	69, 91
84	71, 93
86	73, 94
88	76, 95
90	78, 97
92	81, 98
94	83, 99
96	86, 100
98	89, 100

9.3. Data Analysis Considerations

Full details of all pre-specified analyses will be described in the Reporting and Analysis Plan (RAP).

9.3.1. Analysis Populations

All Subjects Population

The 'All Subjects' population will comprise all enrolled subjects (i.e. attempting at least one self-administration of mepolizumab). This population will be used for the evaluation of the mepolizumab liquid drug product in safety syringe and for the summaries relating to the safety and tolerability of mepolizumab.

PK Population:

The PK population will be defined as all enrolled subjects for whom at least one PK sample was obtained and analyzed. This will be the primary population for assessing PK.

PD Population:

The PD population is defined as all enrolled subjects who also have a baseline PD measurement and at least one post-treatment PD measurement. This will be the primary population for assessing PD.

9.3.2. Treatment Comparisons

This is a single arm study. There are no treatment comparisons. All analyses will be descriptive.

9.3.3. Interim Analysis

No interim analysis is planned.

9.4. Key Elements of Analysis Plan

9.4.1. Analyses to Evaluate Safety Syringe

Primary Endpoint

The number and percentage of subjects successfully able to self-administer their observed third dose at Week 8 will be summarized together with 95% confidence intervals. The denominator for the percentage calculation will be the number of subjects attempting an injection at Week 8.

Secondary Endpoints

The following will be summarized, including 95% CIs:-

- The number and percentage of subjects successfully able to self-administer their unobserved second dose at Week 4. The denominator for the percentage calculation will be the number of subjects attempting an injection at Week 4.

- The number and percentage of subjects successfully able to self-administer their observed first dose at Week 0. The denominator for the percentage calculation will be the number of subjects attempting an injection at Week 0.

- The number and percentage of subjects successfully able to self-administer both their unobserved second dose at Week 4 and their observed third dose at Week 8. The denominator for the percentage calculation will be the number of subjects attempting an injection at both Week 4 and Week 8.

- The number and percentage of subjects successfully able to self-administer all three doses at Week 0, 4 and 8. The denominator for the percentage calculation will be the number of subjects attempting all 3 doses at Week 0, 4 and 8.

Data collected on the Observation Checklist relating to the correct use of the safety syringe and any device related issues preventing the full dose being administered will be summarised at each visit.

The root cause evaluation of each unsuccessful injection via the Safety Syringe Error/Failure Reporting Form, including any observations noted by GSK Device Engineering, will be summarized separately by GSK Device Engineering for inclusion into the study report.

Device usability/functionality assessed at the end of the study will be summarised.

9.4.2. Safety Analyses

AEs will be coded using the MedDRA coding dictionary and summarized by preferred term. Separate summaries will be provided for all AEs, IP-related AEs, SAEs, events of special interest (including systemic reactions and local injection site reactions) and for AEs leading to permanent discontinuation of study treatment. All laboratory parameters for clinical chemistry and hematology will be summarized and tabulated.

Exacerbations will be summarized and listed.

Each ECG parameter at every assessed time point will be summarized using summary statistics. Summary statistics of QT interval corrected for heart rate according to Fridericia's formula (QTcF) and QT interval corrected for heart rate according to Bazett's formula (QTcB) as well as change from baseline value will be presented by visit.

Summary statistics of pulse rate and systolic and diastolic blood pressure will be presented by visit.

Pain VAS scores and categorical pain assessments will be summarized by visit and time post injection (immediately following, 1- and 24-hours post injection).

Immunogenicity will be summarized using appropriate descriptive statistics.

9.4.3. Pharmacodynamic Analyses

Ratio to baseline (Visit 2) in blood eosinophil count will be summarized by visit, using summary statistics appropriate for log-normal data, overall, by previous mepolizumab use (i.e. not receiving mepolizumab treatment at Visit 1 or receiving 100 mg SC mepolizumab administered for the treatment of severe eosinophilic asthma every 4 weeks for at least 12 weeks prior to Visit 1) and by injection site. Values below the lower limit of quantification will be imputed as half the lower limit of quantification.

9.4.4. Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling & Simulation department within GSK.

PK concentrations will be presented in graphical and/or tabular form and will be summarized descriptively overall, by previous mepolizumab use (i.e. not receiving mepolizumab treatment at Visit 1 or receiving 100 mg SC mepolizumab administered for the treatment of severe eosinophilic asthma every 4 weeks for at least 12 weeks prior to Visit 1) and by injection site.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

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

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a 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, and with GSK policy.

The study will also be conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent

- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including 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 also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

GSK will monitor the study and site activity to verify 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.

10.4. 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.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the 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 maintained to allow easy and timely retrieval, 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 these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to 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 and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator

must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

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

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

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ACQ	Asthma Control Questionnaire
ADA	Anti-drug antibody
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotrasferase
BUN	Blood urea nitrogen
CI	Confidence Interval
CONSORT	Consolidated Standard of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CS	Corticosteroid
Ctrough	Trough concentration at the end of the dosing interval
CV	Cardiovascular
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Emergency Department
EGPA	Eosinophilic granulomatosis with polyangiitis
EMEA	European Medicines Agency
EU	European Union
FAAN	Food Allergy and Anaphylaxis Network
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FP	Fluticasone Propionate
FRP	Females of Reproductive Potential
FSH	Follicle stimulating hormone
G	Gauge
g	gram
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GINA	Global Initiative for Asthma
GSK	GlaxoSmithKline
hCG	Human chorionic gonadotropin
HES	Hypereosinophilic Syndrome
hIL	Human interleukin
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation

ICS	Inhaled corticosteroids
IEC	Independent Ethics Committee
IFU	Instructions for Use
IgG	Immunoglobulin
IL	Interleukin
IM	Intramuscular
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
LABA	Lon-acting beta-2-agonist
LTRA	Leukotriene receptor antagonist
mAb	Monoclonal antibody
mcg	Microgram
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mm Hg	Milliliter of mercury
MSDS	Material Safety Data Sheet
N/A	Not applicable
NAb	Neutralising antibody
NIAID	National Institute of Allergy and Infectious Disease
NIH	National Heart Lung and Blood Institute
OCS	Oral corticosteroids
PCSA	Placebo controlled severe asthma
PD	Pharmacodynamic
PEF	Peak expiratory flow
PGx	Pharmacogenetics
PK	Pharmacokinetic
QTc	QI interval corrected for heart rate
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
R&D	Research & Development
RAP	Reporting and Analysis plan
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SC	Subcutaneous(ly)
SGRQ	St George's Respiratory Questionnaire
SRM	Study reference manual
UK	United Kingdom
ULN	Upper limit of normal
US	United States
V	Visit

VAS	Visual Analogue Scale
WFI	Water for injection

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NUCALA

Trademarks not owned by the GlaxoSmithKline group of companies
SAS
Xolair (omalizumab)

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

References

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12.3. Appendix 3: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

12.3.1. Definition of post menopausal female

Post menopausal female is defined as:

- Females 60 years of age or older
- Menopause is the phase associated with complete cessation of menstrual cycles and implies the loss of reproductive potential by ovarian failure. This typically occurs around 50 years of age, although it may occur earlier or later. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile, e.g., age appropriate, >45 years, in the absence of hormone replacement therapy (HRT) or medical suppression of the menstrual cycle (e.g., leuprolide treatment).
- In questionable cases for women < 60 years of age, a blood sample with simultaneous follicle stimulating hormone and estradiol falling into the central laboratory's postmenopausal reference range is confirmatory (these levels need to be adjusted for specific laboratories/assays) [Kronenberg, 2008; Strauss, 2004].
- Females under 60 years of age, who are on HRT and wish to continue, and whose menopausal status is in doubt, are required to use a highly effective method to avoid pregnancy, as outlined in the protocol. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment. For most forms of HRT, at least 2 to 4 weeks will 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 highly effective method to avoid pregnancy. If laboratory values for FSH and estradiol are drawn and the results do not confirm menopause on a potential subject that otherwise met the specifications for being post-menopausal defined above without question, the subject may still enrol in the study as a FNRP if approved by the GSK Medical Monitor and the safety physician.

12.3.2. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
4. Injectable progestogen [Hatcher, 2011]

5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.3.3. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 6. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will be withdrawn from the study.

12.3.4. References

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12.4. Appendix 4: Liver Safety Required Actions and Follow up Assessments

12.4.1. Liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• Immediately discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment. Permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments	• Viral hepatitis serology[4] • 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[5]. • Blood sample for pharmacokinetic (PK) analysis, obtained within 4 weeks after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia. Note: The mechanism of action of mepolizumab leads to lowering of eosinophils.

Liver Chemistry Stopping Criteria - Liver Stopping Event	
MONITORING: **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: 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
5. If hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].

6. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment 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 SRM.

12.4.2. Liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **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. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

References

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12.5. Appendix 5: Definition of and Procedures for Documenting Medical Device Incidents

12.5.1. Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 6.2 for the list of GSK medical devices).

Medical Device Incident Definition:

- Incident – Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient/user/other persons or to a serious deterioration in their state of health.
- Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- an **incident** associated with a device happened and
- the **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include:

- life-threatening illness
- permanent impairment of body function or permanent damage to a body structure
- a condition necessitating medical or surgical intervention to prevent one of the above
- fetal distress, fetal death or any congenital abnormality or birth defects

Examples of incidents

- a patient, user, care giver or professional is injured as a result of a medical device failure or its misuse
- a patient's treatment is interrupted or compromised by a medical device failure
- misdiagnosis due to medical device failure leads to inappropriate treatment
- a patient's health deteriorates due to medical device failure

12.5.2. Documenting Medical Device Incidents

Medical Device Incident Documenting:
• Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 6. • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to GSK. • It is very important that the investigator provides his/her assessment of causality to the medical device provided by GSK at the time of the initial report, and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the design to prevent recurrence.

12.6. Appendix 6: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.6.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is 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.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • 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). • The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • 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.

- 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.

12.6.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as 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

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. Other situations:

- 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. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥3xULN and total bilirubin* ≥2xULN (>35% direct), **or**
- ALT ≥3xULN and INR** >1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥3xULN and total bilirubin ≥2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.6.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

12.6.4. Recording of AEs and SAEs

AEs and SAE Recording:
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. • The investigator will then record all relevant information regarding an AE/SAE in the CRF • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.6.5. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. • The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.6.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

SAE reporting to GSK via paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE data collection tool sent by overnight mail • Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE receipt can be found at this beginning of the protocol on the Sponsor/Medical Monitor Contact Information page.

12.7. Appendix 7: Genetic Research

Genetics – Background

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration (AMD) are reported to account for much of the risk for the condition [Gorin, 2012] with certain variants reported to influence treatment response [Chen, 2012]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including mepolizumab or any concomitant medicines;
- Asthma susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been

identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 2 ml blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A blood sample is collected at the baseline visit, after the subject has been enrolled and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any blood being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

References:

Chen H, Yu KD, Xu GZ. Association between Variant Y402H in Age-Related Macular Degeneration (AMD) Susceptibility Gene CFH and Treatment Response of AMD: A Meta-Analysis. PloS ONE 2012; 7: e42464

Gorin MB. Genetic insights into age-related macular degeneration: Controversies addressing risk, causality, and therapeutics. Mol. Asp. Med. 2012; 33: 467-486.

12.8. Appendix 8: Country Specific Requirements

No country-specific requirements exist.

12.9. Appendix 9: Protocol changes

Scope:

This amendment applies to all sites.

Protocol Changes specified in Amendment No.1 are summarised below.

Strike through text refers to deleted text and underlined refers to added text.

Protocol Changes

Sponsor Legal Registered Address

Rationale for change: EudraCT number different to the 204959 Autoinjector protocol

Regulatory Agency Identifying Number(s): IND No 006971, EudraCT No: 2016-001831-10 ~~001832-36~~

Section 1 Protocol Synopsis Objective(s)/Endpoints

Rationale for change: To present the primary endpoint in a tabular format and include the secondary endpoint, as per GSK protocol template standard.

Revised text:

~~The primary endpoint is the proportion of subjects successfully able to self-administer their observed third dose using the safety syringe at the clinic at Week 8.~~

The primary and secondary objectives and associated endpoints are outlined below:

Objectives	Endpoints
Primary	
• To assess the use of the combination product, mepolizumab liquid drug product in safety syringe for the subcutaneous self-administration of mepolizumab by subjects with severe eosinophilic asthma	• Proportion of subjects successfully able to self-administer their observed third dose at Week 8
Secondary	
• To assess the use of mepolizumab liquid drug product in safety syringe outside the clinic setting	• Proportion of subjects successfully able to self-administer their unobserved second dose outside the clinic setting at Week 4

Section 4.1 Overall Design

Rationale for change: To refine the criteria for a successful injection following a use-related risk review

Revised text:

- ~~Safety syringe positioned with the entire needle inserted at an angle into skin that has been pinched and a full dose administered by slowly depressing the plunger until the stopper reaches the bottom of the syringe, thumb moved up allowing plunger to rise~~

- Full dose administered: subject fully inserts the needle, slowly depresses the plunger until the stopper reaches the bottom of the syringe and activates the needle guard by moving the thumb up

Section 5.1 Inclusion Criterion No. 9/ Exclusion Criterion No. 15

Rationale for change: Included additional text to Inclusion Criterion 9 to allow Exclusion Criterion 15 to be removed:

Revised text:

9. **Gender:** Male or Female

Females:

A female subject is eligible to participate if she is not pregnant (as confirmed by a negative urine human chorionic gonadotrophin (hCG) test), planning to become pregnant during the time of study participation (and up to 16 weeks after the last dose), not lactating, and at least one of the following conditions applies:

~~**15. Pregnancy:** Subjects who are pregnant or breastfeeding. Patients should not be enrolled if they plan to become pregnant during the time of study participation (and up to 16 weeks after the last dose).~~

Section 5.1 Exclusion Criterion No. 7

Rationale for change: To allow Bazett's to be used as the correction formula for heart rate when measuring the QT interval consistent with text elsewhere in the protocol.

Revised Text:

7. ECG Assessment: QT interval corrected for heart rate by either Fridericia's or Bazett's formula QTc(F)/QTc(B) ≥450msec or QTc(F)/QTc(B) ≥480 msec for subjects with Bundle Branch Block at Visit 1.

Section 7.3 Assessment of Safety Syringe Use

Rational for change: To refine the criteria for a successful injection following a use-related risk review

Revised text:

At Visit 2 (Week 0), and at Visit 4 (Week 8), the investigator or designee will observe, using a checklist based on the safety syringe IFU, the ability of the subject/caregiver to (self)-administer the injection. The Observer Checklist (see SRM) will be used to determine if each step, according to the IFU, was completed easily, with some difficulty or not completed/intervention required.

Failure to perform one of the critical steps ~~(~~i.e., correct choice of injection site~~, safety syringe positioned with the entire needle inserted at an angle into skin that has been pinched~~ and a full dose administered (determined by the subject fully inserting the needle~~.~~ ~~by~~ slowly depressing the plunger until the stopper reaches the bottom of the syringe, and activating the needle guard by moving the thumb up ~~thumb moved up allowing plunger to rise~~) will be deemed to be a failure to successfully administer the injection.

Section 10.7 Provision of Study Results to Investigators

Rationale for change: Delete text related to randomization codes as study is open-label and randomization codes will not be used.

Revised text:

~~GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.~~

Section 11 References

Rationale for change: References not cited in the document.

Revised text:

~~Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(a): 24. Table 3-2.~~

~~Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(b): 28.~~

Section 12.3.4 Appendix 3

Rationale for change: References not cited in document

Revised text:

~~CHMP, 2005 - EMA - Guideline on Adjuvants in Vaccines for Human Use, (CHMP/VEG/134716/2004), January 2005.~~

~~Cole LA, Khanlian SA, Sutton JM, Davies S, Rayburn WF. Accuracy of home pregnancy tests at the time of missed menses. Am J Ob Gyn 2004(190):100-5.~~

~~EMA/CHMP/ICH/449035/2009: General principles to address virus and vector shedding. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002680.pdf Accessed 28 Nov 2014.~~

~~EMEA/CHMP/GTWP/125459/2006: Guideline on the Nonclinical Studies Required Before First Clinical Use of Gene Therapy Medicinal Products [2008]~~

~~FDA CBER Guidance for industry, "Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications. U.S. FDA; Feb. 2006.~~

~~FDA Medical Devices Safety Alerts and Notices, "Blood human chorionic gonadotropin (hCG) assays: What laboratorians should know about false-positive results", http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/TipsandArticlesonDeviceSafety/ucm109390.htm, accessed 17 Nov 2014.~~

~~International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals For Human Use. ICH Harmonized Tripartite Guideline. Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility. Parent Guideline dated 24 June 1993 (Addendum dated 9 November 2000 incorporated in November 2005. ICH S5 (R2)~~

~~International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals For Human Use. ICH Harmonized Tripartite Guideline. Nonclinical Evaluation for Anticancer Pharmaceuticals. ICH S9. 2009.~~

~~International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals For Human Use. ICH Harmonized Tripartite Guideline. Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. ICH M3 (R2). 2009.~~

~~International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals For Human Use. ICH Harmonized Tripartite Guideline. Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. ICH S6 and Addendum ICH S6 (R1). 2011.~~

~~U.S. Dept of Health and Human Services, FDA, Center For Biologics Evaluation and Research: Guidance for Human Somatic Cell Therapy and Gene Therapy [1998]~~

~~WHO, 2013 - WHO - Guidelines on the Nonclinical Evaluation of Vaccine Adjuvants and Adjuvanted Vaccines, 2013~~

~~World Health Organization. WHO/CONRAD Technical Consultation on Nonoxynol-9. World Health Organization; Department of Reproductive Health and Research; Geneva; 9-10 October 2001. Summary Report. 2001. WHO/RHR/03.8.~~