# TITLE PAGE

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

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| **Title:** | An open-label study to characterize the pharmacokinetics and pharmacodynamics of mepolizumab administered subcutaneously in children from 6 to 11 years of age with severe eosinophilic asthma |

**Compound Number:** SB-240563

**Development Phase:** II

**Effective Date:** 18-JAN-2017

**Protocol Amendment Number:** 05

**Author (s):** PPD

**Revision Chronology**

| **GlaxoSmithKline Document Number** | **Date** | **Version** |
|---|---|---|
| 2014N216964_00 | 2014-DEC-14 | Original |
| 2014N216964_01 | 2015-JUN-10 | Amendment No. 1 |
| 1. Addition of the C-ACT questionnaire to assess asthma control<br><br>2. To allow of the use of the ACQ tool to be administered in each country for which there is a validated translation available<br><br>3. Use of the Global Lung Function Initiative 2012 equations by Quanjer (2012) to estimate FEV1 predicted values in place of NHANES III<br><br>4. To correct typographical errors in the Time and Events Table 3, to remove the reference to "fasting" in Table 4 and to update the name of the central laboratory manual in Section 7.2.6<br><br>5. To remove reference to the "pharmacy manual" and to clarify that all instructions for preparing Investigational Product are provided in the "Study Reference Manual"<br><br>6. To add a copy of the ACQ-7 questionnaire to Appendix 12.5<br><br>7. To add a copy of the ACQ-IA questionnaire to Appendix 12.6<br><br>8. To add a copy of the C-ACT questionnaire to Appendix 12.9<br><br>9. To clarify that a draft version of the ACQ-IA may be used until a final linguistically validated version becomes available<br><br>10. To clarify that blood samples will be stored for up to 15 years after the end of the study. | | |
| 2014N216964_02 | 2015-SEP-30 | Amendment No. 2 |
| 1. To change the details of the Primary and Secondary Medical Monitors for the study.<br><br>2. To permit extended mepolizumab treatment for a minimum of 52 weeks upon completion of the pharmacokinetic/pharmacodynamic phase (Part A) of the protocol.<br><br>3. To add long-term safety (52 weeks) as the primary objective for the extended treatment phase (Part B).<br><br>4. To add long-term pharmacodynamic response as a secondary objective for the extended treatment phase.<br><br>5. To add a Time & Events table (Table 4) to specify assessments and procedures to be conducted during the extended treatment phase.<br><br>6. To amend Section 9.3.2 to specify a pre-planned interim analyses to report results of the initial pharmacokinetic/pharmacodynamic phase upon completion of all required assessment for all subjects. | | |

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| 7. To add Section 9.5 to define the primary and secondary analysis plans for the extended treatment phase. | | |
| 2014N216964_03 | 2016-MAR-30 | Amendment No. 3 |

1. Protocol Synopsis, Treatment Arms and Duration, Part A Treatment: To add guidance regarding the capabilities required at site during post-SC administration monitoring of subjects.

2. Protocol Synopsis, Treatment Arms and Duration, Part A Treatment: to clarify that subjects will receive either 40mg or 100mg study medication during Part A

3. Protocol Synopsis, Treatment Arms and Duration, Part B Treatment: to clarify that subjects will have their treatment dose adjusted to 100mg from the time their bodyweight reaches 40kg

4. Section 4, Study Design Part A Treatment: to clarify that subjects will receive either 40mg or 100mg study medication during Part A

5. Section 4: Study Design. To clarify that the Time and Events Table includes both Table 3 and Table 4

6. Section 4 Part A Follow-up: To change "positive neutralizing antibody" to "positive anti-mepolizumab antibody" and to clarify the timeline for obtaining a repeat sample

7. Section 4: To clarify that subjects should be monitored for 1 hour post-dose during Part A only and thereafter monitoring in Part B will be according to standard practice at the site and to give guidance regarding the capability requirements at site during this monitoring.

8. Section 4.3: Type and number of subjects. To clarify that sample size is not determined for Part B and that all subjects completing Part A are eligible for Part B.

9. Section 5.1 Inclusion Criteria for Part A: To clarify the inclusion criterion 4 in-line with GINA 2015 guidelines for treatment of 6-11 year olds.

10. Section 5.1 Inclusion Criteria for Part A: To update inclusion criterion 7 in-line with inclusion criterion 4

11. To include an exclusion criterion for Positive Hepatitis B Surface Antigen or positive Hepatitis C antibody at Visit 1

12. Section 5.1: To correct an omission in inclusion criterion 9 and add the "Exit Visit" for Part A to the list of visits at which a urine pregnancy test is performed

13. Section 5.1: Inclusion Criteria Part A: To clarify that FEV1 predicted should be calculated using the Quanjer 2012 equations.

14. Section 5.5 Withdrawal/Stopping Criteria: To clarify that the Early Withdrawal Visit should be completed for subjects withdrawing from the study.

15. Section 6.2: Preparation of Investigational Product (Part A and Part B): To clarify that the assigned dose will remain the same throughout Part A only.

16. Section 6.2 Dosage and Administration: To clarify that treatment numbers will not be generated for this study

17. Section 6.8, Treatment after completion of Part A and Part B: To remove the reference to approval needed from GSK for subjects to continue into Part B

18. Section 6.9.1: Permitted Medications and Non-Drug Therapies: To clarify that time of administration of concomitant medications is not required in the eCRF. To clarify that rescue medication will be provided for the study. To clarify that oral corticosteroids are permitted during this study and to clarify that baseline ICS and Baseline controller levels should not be changed between screening and Visit 2.

19. Section 7, Table 3 Time and Events Table Footnotes 2, 3, 7 and 8: To clarify that the Exit Visit date should be conducted as close as possible to the planned visit date (Week 12), to clarify that footnote 7 is applicable to subjects withdrawn, and to clarify that Visit 8 assessments should not be duplicated at Visit 9 if the visits are performed on the same day.

20. Section 7.7: Correct "ACQ" to "ACQ-IA".

21. Section 7.8: The Childhood Asthma Control Test: One sentence removed for incorrectness and one duplicate sentence removed.

22. Section 9.2 Sample Size Assumptions: To correct sample size assumptions

23. Section 9.3.1.1 and Section 9.3.1.5: To correct the Safety Populations for Part A and Part B.

24. Section 9.5.2 and Section 9.5.3: To correct the Secondary and Exploratory Analyses assumptions for Part B.

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|---|---|---|
| 2014N216964_04 | 2016-MAY-05 | Amendment No. 4 |
| 1. Section 5.1 Inclusion Criteria for Part A: To correct an error in Protocol Amendment 03 when text was deleted from Inclusion Criterion 4 in error. | | |
| 2014N216964_05 | 2017-JAN-18 | Amendment No. 5 |
| 1. Section 1, Protocol Synopsis, Rationale: To clarify that Part B follow-up is not required for subjects transitioning to the long-term access program.<br><br>2. Section 1, Protocol Synopsis, Objective(s)/Endpoint(s): Secondary and Exploratory Endpoints will be measured from Week 0 in Part A instead of Week 20 in Part B: "Change from Week 20 (Visit 9)" is amended to "Change from Week 0 (Visit 2)" and that Secondary and Exploratory Endpoints will be measured at Week 80 only for subjects that will not transition to the long-term access program. | | |

3. Section 1, Protocol Synopsis, Overall Design: Long Term Safety/Pharmacodynamic Phase (Part B) updated to clarify that Part B follow-up is only required for subjects not transitioning to the long-term access program.

4. Section 1, Protocol Synopsis, Treatment Arms and Duration: Part B Follow-up paragraph is updated to clarify that Part B follow-up is only required for subjects not transitioning to the long-term access program.

5. Section 3, Objectives and Endpoints, Part B: Secondary and Exploratory Endpoints will be measured from Week 0 in Part A instead of Week 20 in Part B: "Change from Week 20 (Visit 9)" is amended to "Change from Week 0 (Visit 2)"

6. Section 3, Objectives and Endpoints, Part B: Secondary and Exploratory Endpoints will be measured at Week 80 only for subjects that will not transition to the long-term access program.

7. Section 4, Study Design: Sentence added to clarify that Part B follow-up is not required for subjects transitioning to the long term access program.

8. Section 4, Long-Term Safety/Pharmacodymamic Phase (Part B), Follow-up section updated to clarify that Part B follow-up is only required for subjects not transitioning to the long-term access program and to add the duration of Part B for subjects transitioning to the long-term access program.

9. Section 4, Long-Term Safety/Pharmacodynamic Phase (Part B), Follow-up section updated to clarify the definition of "completed subject" for subjects transitioning to the long-term access program and for those that do not transition.

10. Section 4.1, Overall Design, Long-Term Safety/Pharmacodymamic Phase (Part B): updated to clarify that Part B follow-up is only required for subjects not transitioning to the long-term access program

11. Section 4.2, Treatment Arms and Duration, Long-Term Safety/Pharmacodynamic Phase (Part B): Updated to add the duration of Part B for subjects transitioning to the long-term access program.

12. Section 4.4, Design Justification: Updated to clarify that Part B follow-up is only required for subjects not transitioning to the long-term access program

13. Section 5.6, Subject and Study Completion: Updated to clarify the definition of "completed subject" for subjects transitioning to the long-term access program and for those that do not transition.

14. Section 6.8, Treatment After the Completion of Part A and Part B: Updated to include the long-term access program as an option for treatment of subjects after the end of Part B.

15. Section 7, Study Assessments and Procedures, Table 3: Updated to clarify that IgE

"total" only will be measured for this study.

16. Section 7, Study Assessments and Procedures, Table 4: Footnote added to Table 4 to clarify that Visit 23 (Week 80) is only applicable for subjects not transitioning to the long term access program.

17. Section 7.2.6, Clinical Safety Laboratory Assessments: Updated to clarify that instructions for preparing all laboratory samples may be found in the $Q^2$ Solutions, Investigator Manual instead of the Study reference Manual (SRM)

18. Section 7.3, Pharmacokinetics: Updated to clarify that instructions for preparing all laboratory samples may be found in the $Q^2$ Solutions Investigator Manual instead of the Study reference Manual (SRM)

19. Section 7.5, Immunogenicity: Updated to clarify that instructions for preparing all laboratory samples may be found in the $Q^2$ Solutions Investigator Manual instead of the Study reference Manual (SRM).

20. Section 9.2, Sample Size Considerations: Updated to clarify that the clearance mentioned in the section refers to apparent clearance.

21. Section 9.4.2, Secondary Analyses: Updated to quote the body-weight adjusted clearance value in adults (instead of the bodyweight-adjusted apparent clearance) and the 80-125% interval around this value, and to provide as additional information the value of the corresponding apparent clearance.

22. Section 12.1, Abbreviations and Trademarks: Apparent clearance after extravascular (e.g., subcutaneous) administration (CL/F) added.

23. Section 12.2, Appendix 2: Footnote updated to clarify that instructions for preparing all laboratory samples may be found in the $Q^2$ Solutions Investigator Manual instead of the Study reference Manual (SRM).

24. Section 12.3.6, Reporting of SAEs to GSK: Clarification made to the second bullet point regarding reporting SAEs when the electronic system is down.

**SPONSOR SIGNATORY**

PPD

Eric Bradford, PPD

Project Physician Lead
Director, Clinical Development
Respiratory R&D

1/18/2017
**Date**

PPD

# MEDICAL MONITOR/SPONSOR INFORMATION PAGE

**Medical Monitor/SAE Contact Information:**

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**Regulatory Agency Identifying Number(s):**
**IND No**. 006971

**EudraCT number:** 2014-002666-76

# INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number: 200363

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.

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| Investigator Name: | | |
| Investigator Address: | | |
| Investigator Phone Number: | | |
| | | |
| Investigator Signature | | Date |

## TABLE OF CONTENTS

**PAGE**

# 1. PROTOCOL SYNOPSIS FOR STUDY 200363

## Rationale

This pharmacokinetic/pharmacodynamic study is being conducted as part of an extrapolation strategy to support the use of mepolizumab in the 6-11 pediatric population with severe eosinophilic asthma. This study will provide pharmacokinetic and pharmacodynamic data for mepolizumab at 40 or 100mg SC, depending on subject bodyweight, when administered to children aged 6-11 who have severe eosinophilic asthma that are expected to support the extrapolation of safety and efficacy data observed in the adult population to this pediatric population. This study will also assess safety, tolerability, and immunogenicity of mepolizumab in this population along with clinical outcome measures, the ACQ-7 and the C-ACT.

Following the main study (Part A), subjects will be evaluated for eligibility to continue into the optional long-term extension phase (Part B) of this study. For those subjects determined to be eligible and for whom appropriate informed consent/assent has been obtained there will be the option of continuing to receive treatment with mepolizumab during a Long-Term Safety / Pharmacodynamic Phase (Part B) which will include Treatment and Follow-up phases (Part B Follow-up is not required for subjects transitioning to the long term access program at the end of Part B). Part B will provide data to assess the long-term safety and tolerability of mepolizumab in this paediatric population and will also provide data to assess the durability of the pharmacodynamic response to mepolizumab.

## Objective(s)/Endpoint(s)

### Pharmacokinetic/Pharmacodynamic Phase (Part A)

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To characterize the pharmacokinetics of mepolizumab administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma | • Population-PK model derived estimates of clearance, area under the plasma-concentration time curve ($AUC_{(0\text{-}inf)}$), maximum plasma concentration ($C_{max}$), and terminal phase elimination half-life ($t_{1/2}$) of mepolizumab |
| • To characterize the pharmacodynamics of mepolizumab administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma | • Change from baseline in absolute blood eosinophil count at week 12 |
| **Secondary** | |
| • To compare the bodyweight-adjusted clearance between adults and subjects | • Bodyweight-adjusted clearance estimates obtained by population PK |

| Objectives | Endpoints |
|---|---|
| aged 6 to 11 years old with severe eosinophilic asthma when mepolizumab is administered subcutaneously | methods. |
| • To characterize asthma control following subcutaneous administration of mepolizumab to subjects aged 6 to 11 years old with severe eosinophilic asthma | • Change from Baseline in ACQ-7 measured at week 12<br>• Change from Baseline in ACQ-7 measured at weeks 4,8,16 and 20<br>• Change from Baseline in C-ACT measured at week 12<br>• Change from Baseline in C-ACT measured at week 4,8, 16 and 20 |
| • To assess the safety and tolerability of mepolizumab when administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma | • Incidence of Adverse Events<br>• Incidence of clinically significant changes in clinical laboratory parameters<br>• Frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies<br>• Incidence of clinically significant changes in vital sign measurements |
| **Exploratory** | |
| • To assess the number of asthma exacerbations that occur during the study following subcutaneous administration of mepolizumab to subjects aged 6 to 11 years old with severe eosinophilic asthma | • Number of asthma exacerbations that occur while on treatment (week 0-week 12).<br>• Number of asthma exacerbations that occur on- treatment and post-treatment (week 0 - week 20) |
| • To assess Forced expiratory volume in 1 second (FEV1) following subcutaneous administration of mepolizumab to subjects aged 6 to 11 years old with severe eosinophilic asthma | • Change from Baseline in FEV1 measured at week 12 |

## Long-Term Safety / Long-Term Pharmacodynamic Phase (Part B)

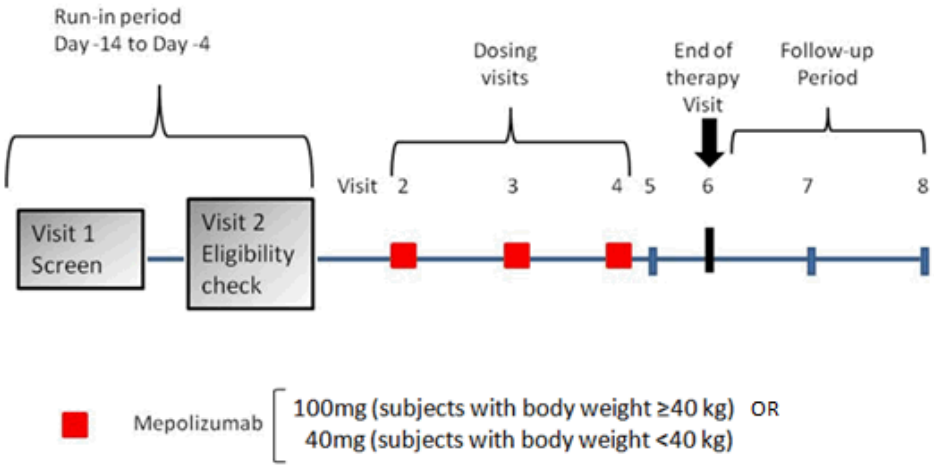
| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To assess the long-term (52 weeks) safety and tolerability of mepolizumab when administered subcutaneously to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Incidence of Adverse Events<br>• Frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies<br>• Incidence of clinically significant changes in vital sign measurements<br>• Incidence of clinically significant changes in clinical laboratory parameters |
| **Secondary** | |
| • To characterize the long-term (52 weeks) durability of pharmacodynamics of mepolizumab administered subcutaneously to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Change from Week 0 (Visit 2) in absolute blood eosinophil count at weeks 32, 44, 56, 68, 72 and 80**. |
| • **Exploratory** | |
| • To assess the number of asthma exacerbations that occur during the long-term (52 weeks) part of the study following subcutaneous administration of mepolizumab to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Incidence of asthma exacerbations |
| • To characterize the long-term (52 weeks) asthma control following subcutaneous administration of mepolizumab to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Change from Week 0 (Visit 2) in ACQ-7 and C-ACT at weeks 32, 44, 56, 68, 72 and 80**. |

*Subjects who reach their 12$^{th}$ birthday during Part A may participate in Part B

**Week 80 is not applicable to subjects transitioning to the long-term access program

## Overall Design

### Pharmacokinetic/Pharmacodynamic Phase (Part A)




This is a multi-centre, open-label study that will assess the pharmacokinetics and pharmacodynamics of three 4-weekly doses of mepolizumab, either 40 or 100mg depending on subject bodyweight, administered SC to subjects with severe eosinophilic asthma aged 6-11 years.

### Long-Term Safety / Pharmacodynamic Phase (Part B)

This is a long-term safety / pharmacodynamic phase in which extended treatment for a further 52 weeks will be offered on an optional basis to those subjects eligible for continued treatment. Subjects will receive either 40 or 100mg depending on subject bodyweight, administered SC every 4 weeks to subjects with severe eosinophilic asthma aged 6-11 years. At the end of the 52 weeks extended treatment in Part B, subjects will have an Exit Visit 4 weeks after last dose. Subjects not transitioning to the long-term access program will also have a Follow-Up visit 12 weeks after last dose.

## Treatment Arms and Duration

### Pharmacokinetic/Pharmacodynamic Phase (Part A)

Enrolled subjects in this study will be assigned to receive one of the following treatments:

| **Treatment Arm** | **SC dose** |
|---|---|
| Mepolizumab 40mg SC upper arm or thigh | Mepolizumab 40 mg SC<br>For subjects <40 kg bodyweight at Visit 2 (Week 0) |
| Mepolizumab 100mg SC upper arm or thigh | Mepolizumab 100mg SC<br>For subjects ≥40 kg bodyweight at Visit 2 (Week 0) |

This Pharmacokinetic/Pharmacodynamic Phase (Part A) study will consist of three stages: Pre-Screening/Screening/Run-in, Treatment and Follow-up.

**Pre-Screening/Screening/Run-in**: Subjects will attend an initial Pre-screening visit to assess their willingness and eligibility to participate in the study. The Pre-screening visit will include: informed consent, demography, exacerbations and concomitant medications. Visit 1(Screening) will include a physical exam, screening laboratory tests, screening ECG and other assessments to determine suitability to participate in this study. The Pre-screening visit may be conducted at the same clinic visit as Visit 1(Screening). Subjects meeting the Visit 1(Screening) eligibility criteria will enter a Run-in period of up to 2 weeks to allow for receipt and review of the lab results and ECG.

**Part A Treatment:** Those subjects meeting all of the inclusion/exclusion criteria by Visit 2 will receive mepolizumab 40 or 100 mg SC, depending on subject bodyweight (40 mg for subjects <40 kg and 100 mg for subjects ≥ 40 kg). Subjects will receive their first dose of mepolizumab at Visit 2 and enter into the Treatment phase of the study. Subjects shall be observed for a minimum of 60 minutes in the clinic following each injection. Safety monitoring of subjects will occur during SC administration and for 1 hour after the three administrations in Part A and then follow monitoring policies for the center in Part B. Such monitoring will include general safety monitoring including monitoring for both systemic hypersensitivity (i.e., allergic/IgE-mediated and non-allergic) and local site reactions. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of mepolizumab, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the patient 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.

Those subjects who enter the run-in period but do not meet all inclusion/exclusion criteria will be deemed Run-in failures and will not be dosed in the study. The reason for any Run-in failure will be recorded in the eCRF.

During the Part A Treatment phase, all subjects will receive mepolizumab either 40mg (subjects <40kg at Visit 2) or 100 mg SC (subjects ≥40kg at Visit 2) at week 0 (Visit 2), week 4 (Visit 3) and week 8 (Visit 4) which will provide therapeutic coverage through to week 12 (Visit 6/End of Therapy Visit). Visit 6 will mark the end of the treatment phase.

Subjects will visit the clinic at week 9 (Visit 5) to allow for measurement of the approximate peak mepolizumab concentration.

**Part A Follow-up:** Following completion of Visit 6, subjects will enter into the Follow-up phase which will consist of two additional visits at weeks 16 (Visit 7) and 20 (Visit 8).

### Long-Term Safety / Long Term Pharmacodynamic Phase (Part B)

| **Treatment Arm** | **SC dose** |
|---|---|
| Mepolizumab 40mg SC upper arm or thigh | Mepolizumab 40 mg SC<br>For subjects with bodyweight <40 kg at Visit 9 (Week 20). From visit 10, subjects should be weighed at each visit until bodyweight reaches 40kg when the dose should be adjusted to 100mg. From this time onwards, the dose will not be adjusted again. |
| Mepolizumab 100mg SC upper arm or thigh | Mepolizumab 100mg SC<br>For subjects with a bodyweight ≥40 kg at Visit 9 (Week 20) or from the time that bodyweight reaches 40kg. |

**Part B Treatment:** Those subjects meeting the eligibility criteria for the long-term phase of the study at Visit 9 will receive mepolizumab 40 or 100 mg SC, (depending on subject bodyweight measured at Visit 9; 40 mg for subjects <40 kg and 100 mg for subjects ≥ 40 kg). Subjects should be monitored post-SC administration according to standard practice at the site. From Visit 10 onwards subjects will receive mepolizumab at 4-weekly intervals for a total of 48 weeks. Subjects with bodyweight <40 kg at Visit 9 should be weighed at each subsequent visit and have their dose adjusted to 100mg once their bodyweight reaches 40 kg. Subjects weighing ≥40kg at Visit 9 will receive the 100mg dose at all subsequent treatment visits and will not be weighed again.

**Part B Follow-up:** Following completion of Visit 22, subjects not transitioning to the long term access program will enter into the Follow-up phase which will consist of one additional follow-up visit at week 80 (Visit 23).

## Type and Number of Subjects

For Part A, approximately 40 male or female subjects with severe eosinophilic asthma, aged 6 to 11 years inclusive at screening (Visit 1), will be screened to achieve approximately 28 eligible subjects entering the treatment phase to allow for availability of 20 evaluable subjects; with a minimum of six subjects enrolled in the < 40 kg bodyweight group. An evaluable subject is defined to be a subject who has received all three doses of mepolizumab and has had all PK and PD assessments completed through to Visit 6 (week 12).

Sample size is not determined for Part B. All subjects who completed Part A and meet the eligibility criteria for Part B will be allowed to participate in Part B.

## Analysis

Population-PK (Pop-PK) parameter estimates will be presented ($AUC_{(0\text{-inf})}$, clearance, $C_{max}$, $t_{1/2}$) for Part A. Descriptive statistics will be used to present the subject demographics, subject study accountability, post-hoc individual pharmacokinetic parameter estimates (e.g. $AUC_{(0\text{-inf})}$, clearance, $C_{max}$, $t_{1/2}$), blood eosinophil count and ratio of blood eosinophil count to baseline at week 12, IL5 levels, selected clinical outcome measures ($FEV_1$, ACQ-7, C-ACT, asthma exacerbations), and safety assessments (adverse events, vital signs, ECGs and laboratories) and immunogenicity. Confidence intervals may be applied where appropriate. In addition a pre-planned analysis comparing the bodyweight-adjusted clearance between adults and subjects 6-11 years with severe eosinophilic asthma will be conducted, with appropriate confidence intervals applied.

Safety and Pharmacodynamic data for Parts A and B will be summarized descriptively and 95% CIs will be presented where appropriate.

# 2. INTRODUCTION

Three randomized, double-blind, placebo-controlled trials have investigated the efficacy, tolerability, pharmacokinetics and pharmacodynamics of mepolizumab administered IV or SC in subjects 12 and older with severe eosinophilic asthma (Pavord, 2012, Ortega, 2014, Bel, 2014). Additionally, a randomized, double-blind trial with IV mepolizumab administration to treat eosinophilic esophagitis in children ages 2-17 years of age has been conducted. However, no trial for children aged less than 12 years old with severe eosinophilic asthma or with the SC route has been conducted.

The generated data from the current study will be used to support the extrapolation of the safety and efficacy results from the 3 randomized trials in adolescents and adults to children ages 6-11 and ultimately an alternative therapeutic option to treat school-age children with severe eosinophilic asthma. With therapeutic proteins, such as the monoclonal antibody mepolizumab, it is common to extrapolate the results of adult studies to pediatric subjects in consideration of the pharmacokinetic properties of such molecules (Xu, 2013). It is suggested that a principal reason this extrapolation is possible is that for monoclonal antibodies targeting a soluble ligand, such as mepolizumab, metabolism and clearance are unlikely to be affected by developmental differences in the major metabolic pathways. Monoclonal antibodies (mAbs) tend to be highly specific and therefore less likely to present off-target toxicity resulting in wider therapeutic index. The pharmacokinetics across age-groups is generally consistent once body-size is taken into account (Xu, 2013). Taking into account these characteristics, mAbs are an ideal class of medications for the extrapolation of safety and efficacy data from adults and adolescents to children. This approach permits a more efficient, stream-lined development program for this age-group and minimizes the need for large, redundant clinical trials in this sub-set of patients.

## 2.1. Study Rationale

Collecting information to provide access to as well as safe and efficacious use of new medicines to the pediatric population is of utmost importance. However the conduct of large efficacy trials might prove challenging in particular if the prevalence of disease particular phenotype (e.g., severe eosinophilic asthma) in the pediatric population is quite low. Nonetheless it remains equally important to provide alternative therapeutic options to the pediatric population. This pharmacokinetic/pharmacodynamic study is conducted to support the use of mepolizumab in children aged 6-11 with severe eosinophilic asthma. This study will provide pharmacokinetic and pharmacodynamic data for mepolizumab 40 or 100mg SC, depending on subject bodyweight, when administered to children ages 6-11 that have severe eosinophilic asthma and will ultimately support an extrapolation strategy of the safety and efficacy data observed in the adult population with severe eosinophilic asthma to this pediatric population. This study will also assess safety, tolerability, and immunogenicity of mepolizumab in this population along with clinical outcome measures, including the ACQ-7 (Juniper, 1999, Juniper, 2005, Juniper, 2006) and the C-ACT.

In addition a pre-planned analysis comparing the bodyweight-adjusted clearance between adults and subjects 6-11 years with severe eosinophilic asthma will be conducted. The goal of this analysis is to demonstrate that the PK in pediatric subjects would be predictable from the adult PK model. This study will also collect information on the blood eosinophil reduction afforded by mepolizumab 40 or 100 mg SC in this age group that can be compared to the adult and adolescent population. A Population-PK (Pop-PK) analysis of IV data from pediatric patients 2 to 17 years of age with eosinophilic esophagitis using the previous adult meta-analysis IV model showed that the adult IV pharmacokinetics model from multiple studies, diseases and populations, predicts pediatric IV pharmacokinetics (Assa'ad, 2011). This study aims to demonstrate this is also valid following SC administration.

## 2.2. Brief Background

### 2.2.1. Severe Eosinophilic Asthma in Children

In the western world, asthma is the most prevalent disorder in school-age children with an incidence of 5-8%. (CDC, 2013) A small subset of this population, approximately 5% (Bossley, 2012) are considered to have severe asthma, which is defined as patients with a lack of control despite step 4 or 5 of the Global Initiative for Asthma (GINA) guidelines or patients that will lose asthma control if they are stepped down from this treatment. (GINA, 2015). These children are often unable to lead a normal life and have an affected quality of life due to missed school days and limited ability to participate in physical activities due to persistent symptoms and the high frequency of exacerbations. (GINA, 2015). According to the Center for Disease Control and Prevention (CDC, 2013), children ages 5-17 with at least one asthma exacerbation per year miss a combined total of 10.5 million days of school (CDC, 2013). Significant asthma exacerbations also carry increased healthcare costs. In fact, patients who experience an exacerbation are three times more costly per year to treat compared to patients who remain exacerbation free (Lane, 2006). Another deleterious outcome for children with severe asthma is a

progressive loss of lung function. (Szefler, 2014). Despite the significant health and economic impact of severe asthma in children, there has been a paucity of new classes of medications developed for this condition. In the past decade, only 2 new classes of medications have been introduced: anti-leukotrienes and anti-IgE. There is a significant unmet need for new medications to provide asthma control in severe childhood asthma.

Three key efficacy studies support the efficacy and safety of mepolizumab in severe eosinophilic asthma in adults and adolescents (Pavord, 2012, Ortega, 2014, Bel, 2014). In addition a Dose-ranging Pharmacokinetic (PK)/Pharmacodynamic (PD) Study (MEA114092) characterized the dose response for blood eosinophil reduction.

The exacerbation studies and the OCS reduction study were randomized, double-blind, parallel-group, placebo-controlled designs. In addition to frequent exacerbations, the subjects in the severe eosinophilic asthma program have a significant burden of steroid use, thus reduction of OCS use while maintaining asthma control is an additional key treatment outcome. Since the exacerbation studies required maintenance of standard of care (no dose adjustments), the ability of mepolizumab to reduce OCS use was studied in a specific study (Bel, 2014).

### 2.2.2. Pharmacokinetics of mepolizumab

Mepolizumab is a humanized IgG1 monoclonal antibody (mAb) that exhibits dose-proportional and time-independent pharmacokinetics. After SC administration to adults and adolescents mepolizumab is absorbed slowly, with an absolute bioavailability in the arm of 74–80% and median time to maximum concentration (Tmax) values ranging from 4–8 days. Mepolizumab distributes into a central volume of distribution (Vc) similar to plasma volume with a distribution half-life of 1–2 days, and has a steady-state volume of distribution (Vss) of 1.5–2 times plasma volume (55–85 mL/kg). Mepolizumab is catabolized by ubiquitous proteolytic enzymes, not restricted to hepatic tissue, and is cleared slowly with a terminal-phase elimination half-life of approximately 20 days, irrespective of the route of administration, and mean systemic clearance (CL) of 1.9–3.3 mL/day/kg. Mepolizumab does not undergo target-mediated clearance. When dosed every four weeks, mepolizumab shows two-fold steady-state accumulation, irrespective of route of administration, consistent with the terminal-phase elimination half-life of 20 days.

The pharmacokinetics of IV mepolizumab are well-described using a two-compartment model with first-order distribution and elimination and the population PK parameter estimates consistent across analyses. Although bodyweight was found to have a statistically significant effect on both clearance and volume, the overall magnitude of the effect of body weight on mepolizumab exposure was not deemed clinically relevant. The pharmacokinetics of mepolizumab is consistent across studies, diseases and ethnicities, with pediatric pharmacokinetics predictable from adults. Of note, a previous study was conducted with mepolizumab IV in pediatric subjects 2-17 years old with eosinophilic esophagitis (Assa'ad, 2011). After adjusting for bodyweight via weight-based dosing, age was not a determinant of exposure. A population PK analysis of the data using the previous adult meta-analysis IV model described the data adequately without parameter

estimation or bias, implying that adult pharmacokinetics, estimated from multiple studies, diseases and populations, predicts pediatric pharmacokinetics.

### 2.2.3. Pharmacodynamics of mepolizumab

Mepolizumab pharmacodynamics has been studied in multiple Clinical Pharmacology and efficacy studies in multiple diseases. Mepolizumab treatment produces a consistent and sustained reduction in blood eosinophil count relative to baseline whose magnitude and duration is dose-dependent, implying that full saturation of IL-5 target can be achieved. There are non-linear dose- and concentration-responses to blood eosinophil reduction. Dose-response is unchanged by administration route, after adjusting for bioavailability. An inhibitory $I_{max}$ model estimated the SC doses resulting in 50% and 90% of the maximum effect (ID50 and ID90) to be 11 and 99 mg, respectively, corresponding to IV doses of 8 and 74 mg. This finding was further confirmed by the severe asthma phase 3 study MEA115588 where similar blood eosinophil reductions were observed at corresponding doses of mepolizumab IV 75 mg and SC 100 mg. Mepolizumab also reduces eosinophils in sputum and bone marrow (Pavord, 2012, Flood-Page, 2007).

Blood eosinophil counts assessed in a pediatric population aged 2–17 years with eosinophilic esophagitis (EoE) (Assa'ad, 2011) following IV administration showed the magnitude of the eosinophil reduction and time to return towards baseline were dose-dependent. At Week 12, following mepolizumab IV 0.55, 2.5 and 10 mg/kg eosinophil reductions were 77%, 69%, and 81%, respectively; similar to adult data at corresponding doses.

### 2.2.4. Safety of mepolizumab following administration in Children and Adolescents

Although no data are available in pediatric patients with severe asthma (aged 6- 11 years), pediatric subjects 2-17 years with EoE (Assa'ad, 2011) received one of three intravenous doses of mepolizumab (0.55, 2.5 or 10mg/kg) every 4 weeks for 12 weeks. With regards to safety, the most common AEs were vomiting, diarrhea, oropharyngeal pain, upper abdominal pain, symptoms known to be associated with the disease state (Sorser, 2013), and nasopharyngitis, headache, cough, and pyrexia. No AEs appeared to be dose-related. SAEs were reported for 3 subjects: chest discomfort, esophageal injury (occurred during esophagogastroduodenoscopy (EGD) study procedure), and foreign body trauma; none were considered related to mepolizumab by the investigator. Immunogenicity was conducted with the former analytical assay, which showed some transient positive anti-drug antibodies; however, there were no neutralizing antibodies detected. Furthermore, there was no apparent impact on the clinical, pharmacodynamic or pharmacokinetic profiles. These findings indicated low risks and/or concerns associated with the immunogenicity profile. Detailed electrocardiogram data showed no clinically relevant trends related to prolongation of the QT/QTc interval; no cardiac or ECG-related adverse events were reported. No clinically relevant trends in vital signs or laboratory data were observed. In summary, all doses of mepolizumab demonstrated a favorable safety profile; common adverse events were non-serious, not-unexpected with this disease, and manageable with minimal supportive care.

# 3. OBJECTIVE(S) AND ENDPOINT(S)

## Pharmacokinetic/Pharmacodynamic Phase (Part A)

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To characterize the pharmacokinetics of mepolizumab administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma | • Population-PK model derived estimates of clearance, area under the plasma-concentration time curve ($AUC_{(0\text{-}inf)}$, maximum plasma concentration ($C_{max}$), and terminal phase elimination half-life ($t_{1/2}$) of mepolizumab |
| • To characterize the pharmacodynamics of mepolizumab administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma | • Change from baseline in absolute blood eosinophil count at week 12 |
| **Secondary** | |
| • To compare the bodyweight-adjusted clearance between adults and subjects aged 6 to 11 years old with severe eosinophilic asthma when mepolizumab is administered subcutaneously | • Bodyweight-adjusted clearance estimates obtained by population PK methods. |
| • To characterize asthma control following subcutaneous administration of mepolizumab to subjects aged 6 to 11 years old with severe eosinophilic asthma | • Change from Baseline in ACQ-7 measured at week 12<br>• Change from Baseline in ACQ-7 measured at week 4,8,16 and 20<br>• Change from Baseline in C-ACT measured at week 12<br>• Change from Baseline in C-ACT measured at week 4,8, 16 and 20 |
| • To assess the safety and tolerability of mepolizumab when administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma | • Incidence of Adverse Events<br>• Incidence of clinically significant changes in clinical laboratory parameters<br>• Frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies<br>• Incidence of clinically significant changes in vital sign measurements |

| Objectives | Endpoints |
|---|---|
| **Exploratory** | |
| • To assess the number of asthma exacerbations that occur during the study following subcutaneous administration of mepolizumab to subjects aged 6 to 11 years old with severe eosinophilic asthma | • Number of asthma exacerbations that occur while on treatment (week 0-week 12).<br>• Number of asthma exacerbations that occur on- treatment and post-treatment (week 0 - week 20) |
| • To assess Forced expiratory volume in 1 second (FEV1) following subcutaneous administration of mepolizumab to subjects aged 6 to 11 years old with severe eosinophilic asthma | • Change from Baseline in FEV1 measured at week 12 |

## Long-Term Safety / Long-Term Pharmacodynamic Phase (Part B)

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To assess the long-term (52 weeks) safety and tolerability of mepolizumab when administered subcutaneously to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Incidence of Adverse Events<br>• Frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies<br>• Incidence of clinically significant changes in vital sign measurements<br>• Incidence of clinically significant changes in clinical laboratory parameters |
| **Secondary** | |
| • To characterize the long-term (52 weeks) durability of pharmacodynamics of mepolizumab administered subcutaneously to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Change from Week 0 (Visit 2) in absolute blood eosinophil count at weeks 32, 44, 56, 68, 72 and 80**. |
| • **Exploratory** | |
| • To assess the number of asthma exacerbations that occur during the long-term (52 weeks) part of the study following subcutaneous administration of mepolizumab to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Incidence of asthma exacerbations |

| Objectives | Endpoints |
|---|---|
| • To characterize the long-term (52 weeks) asthma control following subcutaneous administration of mepolizumab to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Change from Week 0 (Visit 2) in ACQ-7 and C-ACT at weeks 32, 44, 56, 68, 72 and 80**. |

*Subjects who reach their 12th birthday during Part A may continue into Part B

** Week 80 is not applicable to subjects transitioning to the long-term access program

# 4. STUDY DESIGN

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Tables (Table 3 and Table 4), are essential and required for study conduct.

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

This is a multi-centre, open-label study that will assess the pharmacokinetics and pharmacodynamics of three (4-weekly) doses of mepolizumab 40 or 100 mg SC, depending on subject bodyweight, administered to subjects with severe eosinophilic asthma ages 6-11 years.

This study will consist of two phases: Part A will consist of Pre-Screening/Screening/Run-in, Treatment, and Follow-up. Part B will consist of Long-Term Treatment and Follow-up. The Part B follow-up phase is not required for subjects transitioning to the long term access program.

## Pharmacokinetic/Pharmacodynamic Phase (Part A)

**Pre-Screening/Screening/Run-in**: Subjects will attend an initial Pre-screening visit to assess their willingness and eligibility to participate in the study. The Pre-screening visit will include: informed consent; demography exacerbations and concomitant medications. Visit 1(Screening) will include a physical exam, screening laboratory test, screening ECG and other assessments to determine suitability to participate in this study. The pre-screening visit may be conducted at the same clinic visit as Visit 1(Screening). Subjects meeting the Visit 1(Screening) eligibility criteria will enter a Run-in period of up to 2 weeks to allow for receipt and review of the lab results and ECG.

**Treatment:** Those subjects meeting all of the inclusion/exclusion criteria by Visit 2 will receive mepolizumab 40 or 100 mg SC, depending on subject bodyweight (40 mg for subjects <40 kg and 100 mg for subjects ≥ 40 kg). Subjects will receive their first dose of

mepolizumab at Visit 2 and enter into the Treatment phase of the study. Subjects shall be observed for a minimum of 60 minutes in the clinic following each injection. Safety monitoring of subjects will occur during SC administration and for 1 hour after the three administrations in Part A and then follow monitoring policies for the center in Part B. Such monitoring will include general safety monitoring including monitoring for both systemic hypersensitivity (i.e., allergic/IgE-mediated and non-allergic) and local site reactions. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of mepolizumab, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the patient 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.

Those subjects who enter the run-in period but do not meet all inclusion/exclusion criteria will be deemed Run-in failures and will not be dosed in the study. The reason for any Run-in failure will be recorded in the eCRF.

During the Treatment phase, all subjects will receive mepolizumab either 40mg SC (subjects <40kg at Visit 2) or 100 mg SC (subjects ≥40kg at Visit 2) at week 0 (Visit 2), week 4 (Visit 3) and week 8 (Visit 4). These doses should provide therapeutic coverage through to week 12 (Visit 6/End of Therapy Visit). Visit 6 will mark the end of the treatment phase.

Subjects will visit the clinic at week 9 (Visit 5) to provide a blood sample to measure the approximate peak mepolizumab concentration.

Study visits will have a window of ± 3 days; except for Visit 5 which should be scheduled ± 1 day.

**Follow-up:** Following completion of Visit 6, subjects will enter into the Follow-up phase which will consist of two additional visits at weeks 16 (Visit 7) and 20 (Visit 8).For subjects who had a positive anti-mepolizumab antibody response at the Follow-up (Visit 8) (or last study visit at which immunogenicity was assessed if the Follow-up (Visit 8) immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-mepolizumab antibodies at least 4 months after the last dose of study drug in Part A or upon completion of Part A, whichever is later.

A subject will be regarded as having completed Part A if they complete all phases of Part A (Pre-Screening/Screening/Run-in, Treatment, and Follow-up). Subjects who complete Part A will participate for approximately 22 weeks.

**Long-Term Safety / Pharmacodynamic Phase (Part B)**

At the end of Part A, a benefit/risk assessment will be performed by the Investigator and if this assessment supports continued therapy with mepolizumab the subject can continue into Part B following the Part A Follow-up (Visit 8).

**Long-Term Treatment:** Those subjects meeting the eligibility criteria for the long-term phase of the study at Visit 9 will receive mepolizumab 40 or 100 mg SC, (depending on subject bodyweight measured at Visit 9; 40 mg for subjects <40 kg and 100 mg for

subjects ≥ 40 kg). Subjects should be monitored post-SC administration according to standard practice at the site.

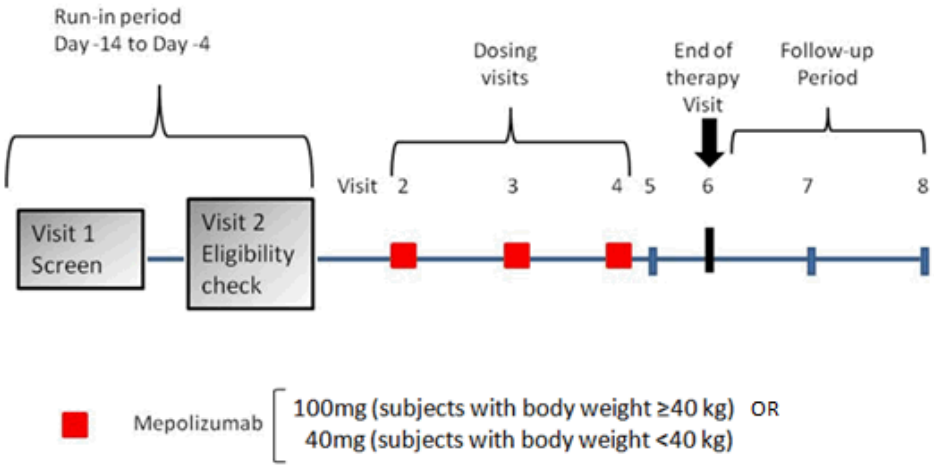
From Visit 10 onwards subjects will receive mepolizumab at 4-weekly intervals for a total of 48 weeks. Subjects with bodyweight <40 kg at Visit 9 should be weighed at each subsequent visit and have their dose adjusted once their bodyweight exceeds ≥40 kg.

**Follow-up:** Following completion of Visit 22, subjects not transitioning to the long term access program will enter into the Follow-up phase which will consist of one additional follow-up visit at week 80 (Visit 23).

Study visits in Part B will have a window of ± 5 days. The total duration of Part B is approximately 60 weeks (52 weeks for subjects transitioning to the long-term access program). A subject not transitioning to the long term access program will be regarded as having completed Part B if they complete all phases of Part B (Long-Term Treatment and Follow-up). A subject transitioning to the long term access program will be regarded as having completed Part B if they complete all the Treatment phase of Part B.

## 4.1. Overall Design

### Pharmacokinetic/Pharmacodynamic Phase (Part A)




This is a multi-centre, open-label study that will assess the pharmacokinetics pharmacodynamics of three 4-weekly doses of mepolizumab, either 40 or 100mg depending on subject bodyweight, administered SC to subjects with severe eosinophilic asthma aged 6-11 years.

### Long-Term Safety / Pharmacodynamic Phase (Part B)

This is a long-term safety / pharmacodynamic phase in which extended treatment for a further 52 weeks will be offered on an optional basis to those subjects eligible for continued treatment. Subjects will receive either 40 or 100mg depending on subject bodyweight, administered SC every 4 weeks to subjects with severe eosinophilic asthma

aged 6-11 years. At the end of the 52 weeks extended treatment in Part B, subjects will have an Exit Visit 4 weeks after last dose. Subjects not transitioning to the long term access program will have a Follow-Up visit 12 weeks after last dose.

## 4.2. Treatment Arms and Duration

### Pharmacokinetic/Pharmacodynamic Phase (Part A)

Enrolled subjects in this study will be assigned to receive one of the following treatments:

| **Treatment Arm** | **SC dose** |
|---|---|
| Mepolizumab 40 mg SC upper arm or thigh | Mepolizumab 40 mg SC<br>For subjects <40 kg bodyweight at Visit 2 (Week 0) |
| Mepolizumab 100 mg SC upper arm or thigh | Mepolizumab 100mg SC<br>For subjects ≥40 kg bodyweight at Visit 2 (Week 0) |

The total duration of Part A will be 22 weeks and will include a run-in period of 1-2 weeks, a treatment period of 12 weeks and a follow-up phase of 8 weeks.

### Long-Term Safety / Long Term Pharmacodynamic Phase (Part B)

| **Treatment Arm** | **SC dose** |
|---|---|
| Mepolizumab 40mg SC upper arm or thigh | Mepolizumab 40 mg SC<br>For subjects <40 kg bodyweight at Visit 9 (Week 20). From visit 10, subjects should be weighed at each visit until bodyweight reaches 40kg when the dose should be adjusted to 100mg. From this time onwards, the dose will not be adjusted again. |
| Mepolizumab 100mg SC upper arm or thigh | Mepolizumab 100mg SC<br>For subjects bodyweight at Visit 9 (Week 20) or from the time that bodyweight reaches 40 kg |

Following completion of Part A subjects will be evaluated for eligibility to continue into Part B of this study. For those subjects determined to be eligible and for whom appropriate informed consent/assent has been obtained there will be a Long-Term Safety / Pharmacodynamic Phase (Part B). The total duration of Part B is approximately 60 weeks (52 weeks for subjects transitioning to the long-term access program).

## 4.3. Type and Number of Subjects

Approximately 40 male or female subjects with severe eosinophilic asthma, aged 6 to 11 years inclusive at screening (Visit 1), will be screened to achieve approximately 28 eligible subjects entering the Part A treatment phase to allow availability of 20 evaluable subjects, with a minimum of six subjects enrolled in the < 40 kg bodyweight group. An evaluable subject is defined to be a subject who has received all three doses of mepolizumab and has all PK and PD assessments completed through to Visit 6 (week 12).

Sample size is not determined for Part B. All subjects who completed Part A and meet the eligibility criteria for Part B will be allowed to participate in Part B.

## 4.4. Design Justification

This study is designed to characterize the pharmacokinetics and pharmacodynamics of mepolizumab as add-on to best standard of care in children with severe eosinophilic asthma aged 6 to 11 years to support the extrapolation of the safety and efficacy data observed in the adult/adolescent population to this pediatric population. The design of the study aims to balance the challenging access to the target pediatric population and the study constraints with the scientific evidence to support the use of mepolizumab in this population.

An additional secondary objective of the study is to compare the bodyweight-adjusted clearance between adults and subjects aged 6 to 11 years old. Three repeat doses of mepolizumab administered every 4 weeks subcutaneously to subjects aged 6 to 11 years is considered adequate to achieve the PK and PD objectives of the study. Blood eosinophil count is consistently reduced following mepolizumab administration, which make blood eosinophils a suitable PD endpoint for evaluation.

The study population reflects the intended population for therapeutic use to support the extrapolation strategy.

A treatment phase duration of 12 weeks is considered sufficient to support the primary PK and PD endpoint of the study. A dose ranging PK/PD study (MEA114092) of mepolizumab administered intravenously (75 mg) or subcutaneously (12.5, 125 and 250 mg) with a similar duration was conducted in adult asthmatic subjects with elevated blood eosinophil levels. Concordance in the blood eosinophil reduction at 75 mg IV between this study and the 12-month duration phase 2/3 study (Pavord, 2012) confirms suitability of the 12 weeks duration treatment for the chosen endpoint. Furthermore, comparable blood eosinophil count reduction was observed at 75 mg IV and 100 mg SC in a phase 3 study (MEA115588) with consistent blood eosinophil reduction observed from 12 weeks onwards. These data support conducting a study of 12 weeks duration and will allow comparison with adult/adolescent data to support the extrapolation of the safety and efficacy data observed in adults/adolescents in the severe asthma phase 3 program to the 6-11 pediatric population. Subjects will be followed-up for a total of 12 weeks after the last dose in Part A, which is consistent with the follow-up duration in adult studies.

To minimise the blood sample collection in this pediatric population and to take into consideration the constraint of the trial, sparse blood sampling collection has been implemented. It is therefore important to assess the operational characteristics of the design in order to meet the primary objective of the study. To this effect, simulations of different scenario varying the number of subjects included in the trial and evaluating different PK sampling schemes were conducted to test the robustness of the study design. A sample on week 9 (Visit 5) was included to collect information close to mepolizumab $T_{max}$ following SC administration (see Section 9.2 for further details).

The assumption is the PK in pediatric subjects 6-11 years old is comparable to the PK in adults therefore the adult PK model was used to generate a database of pediatric subjects from which random subjects with clinical trial characteristics were selected. Data from the different trials were then fitted, bodyweight-adjusted clearance estimated and compared to the known value (i.e. the true value from which the pediatric subjects were simulated from) (see Section 9.2 for further details).

No long-term data (up to 52 weeks) documenting the safety and tolerability of mepolizumab in children aged 6 to 11 years with severe eosinophilic asthma are currently available. As it is expected that treatment with mepolizumab in this population may be long-term it is essential that such data be collected. Extended treatment with mepolizumab during Part B of this protocol also permits an assessment of the durability of the pharmacodynamic response to mepolizumab in this population.

## 4.5. Dose Justification

Doses of 40 mg or 100 mg SC, depending on the subject bodyweight, administered every 4 weeks has been selected for this 6-11 years old pediatric population which is predicted to provide similar exposure to the SC dose that was investigated in the adult/adolescent population in the phase 3 program. This dose was shown to be efficacious and well tolerated and therefore the doses selected in this study are expected to confer clinical activity in the 6-11 years old age group. A non-linear inhibitory dose-response model identified 99 mg administered SC as providing 90% of the maximum achievable blood eosinophil reduction in the adult program. A similar baseline blood eosinophil count is anticipated in the severe eosinophilic asthma pediatric population, as was seen in adults (Giubergia, 2012; Jenkins, 2003), hence a similar magnitude of blood eosinophil reduction is also expected.

An extrapolation of exposure ($AUC_{(0\text{-inf})}$) using allometric principles confirmed from pediatric subjects with EoE in study MEE103219 (Assa'ad, 2011) showed that for the weight range to be studied, (15 kg and upwards), two weight bands of 15 to less than 40 and ≥40 kg provided a mean exposure within 25% of the adult 100 mg SC target exposure across the entire weight range. This precision compares very favourably with an optimal solution of 21% across the wider weight range 1 – 100 kg based on five weight bands (GSK Document Number 2014N223495_00).

These proposed doses are further supported by the safety data collected in the previously conducted study MEE103219 in which intravenous doses up to 10 mg/kg were investigated in pediatric subjects 2-17 years old with eosinophilic esophagitis, from

pediatric patients in the on-going hypereosinophilic syndrome (HES) compassionate use program and the extensive safety database in adults.

## 4.6. Benefit:Risk Assessment

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

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

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

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

### 4.6.1. Risk Assessment

**Table 1 Assessment of Risk**

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Investigational Product (IP) SB 240563** | | |
| Risk of Systemic Allergic and Non-allergic Reactions, including Anaphylaxis and local injection site reactions | Based on data from the completed Ph 3 program in severe eosinophilic asthma, incidence rates of systemic reactions were low and similar between mepolizumab and placebo treatment groups.<br><br>Acute and delayed systemic reactions, including hypersensitivity, have occurred following mepolizumab administration; most reactions have been non-serious and resolved without sequelae. These reactions generally occur within hours of administration, but in some instances had a delayed onset (i.e., days).<br><br>An increase in the incidence of local site reactions was observed with SC administration of mepolizumab compared with placebo, but the overall incidence was low. The most common symptoms associated with subcutaneous injections included: pain, erythema, swelling, itching, and burning sensation.<br><br>Reactions reported to date across the mepolizumab program are summarized in the IB; see 'Special Warnings and Special | Daily monitoring of serious adverse events (SAEs) by Serious Adverse Events (SAE) Co-ordinator (project Medical Monitor); regular systematic review of adverse event (AE)/SAE data from ongoing studies by a GSK safety review team.<br><br>Specific case report form (eCRF) pages utilized for targeted collection of reactions data.<br><br>Use of Joint NIAID/FAAN 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (Appendix 9: Anaphylaxis Criteria).<br><br>In addition to normal institutional practices, subjects will be observed for a minimum of 60 minutes in the clinic following each injection up-to and including Visit 4. From Visit 9 onwards, monitoring post-injection should be according to the standard procedure at each site. |

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | Precautions for Use' section located in Section 6 titled 'Summary of Data and Guidance for the Investigator'. | |
| Risk of Immunogenicity | Biopharmaceutical products may elicit anti-drug antibody (ADA) and neutralizing antibody (NAB), which have the potential to modulate pharmacokinetic (PK), pharmacodynamic (PD) or produce adverse reactions. However, humanized and fully human antibodies are less immunogenic than mouse or chimeric monoclonal antibodies.<br><br>Mepolizumab has low immunogenic potential and anti-mepolizumab antibody formation is not expected to impact the overall clinical benefit of mepolizumab treatment. Both incidence and titer data from completed studies demonstrate a low risk for loss of efficacy associated with AEs and/or altered PK/PD.<br><br>Immunogenicity data reported to date across the mepolizumab development program are summarized in the IB; See Section 5.4 'Clinical Immunogenicity' and a summary of immunogenicity findings in Section 6 'Other Potentially Clinically Relevant Information for the Investigator'. | Blood samples are collected in clinical studies for detection of both ADA and Nab.<br><br>See previous risk for mitigation strategy related to clinical safety risks. |

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| Potential risk for adverse cardiovascular (CV) effects | Mepolizumab binding was restricted to human lymphoid tissues in an immunohistochemistry tissue binding study suggesting a low likelihood of non-pharmacologic effects on cardiovascular (CV) function.<br><br>No AEs concerning cardiac conduction or repolarization evident in cynomolgus monkeys at doses at least 10-fold in excess of humans dosed at 10 mg/kg or 750 mg.<br><br>No clinically relevant trends observed in ECG data in humans.<br><br>In one study in subjects with severe refractory asthma, cardiac events were reported in similar frequencies across treatment groups with a small numerical increase observed in serious ischemic cardiac events in the mepolizumab-treated groups. However, an integrated safety analysis of all placebo-controlled multiple dose asthma trials showed similar frequency of SAEs reported overall from the cardiac and vascular system organ class (SOC). Additionally, similar findings were observed in other SOCs with thrombotic events (e.g., stroke in the Nervous System SOC). Data from 2 subsequently completed placebo-controlled severe asthma trials did not show an increased risk of serious ischemic cardiac events; there were no new reports in any treatment groups including | Daily monitoring of SAE Serious Adverse Events (SAE) Co-ordinator (project Medical Monitor); regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team.<br><br>CV monitoring for study includes:<br><br>• ECG<br><br>• Use of standardized CRFs to collect relevant data on CV events of interest (i.e., myocardial infarction, hospitalization for unstable angina and congestive heart failure, arterial thrombosis, pulmonary embolism and deep vein thrombosis). |

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | placebo. Based on these data, the overall risk of cardiotoxicity associated with mepolizumab treatment is low. | |
| Potential risk for increase in infections – a theoretical concern with biologics; however, the pharmacological properties of mepolizumab suggest the risk is low. | No evidence of increased incidence of infections in any preclinical studies.<br><br>Murine data demonstrate that IL-5 antagonism is unlikely to influence cellular or humoral immunity, particularly in response to parasitic infections.<br><br>No mepolizumab-related effects on lymphocyte Immunophenotyping in monkeys or humans, including T-cell activation, distribution of CD4/CD8 subtypes or Th1/Th2 cytokine patterns, B-cells, NK cells or γδ-T-cells.<br><br>In studies completed to date in severe eosinophilic asthma patients, reports of overall, serious and opportunistic infections were similar across treatment groups. Based on these data, the overall risk of infections associated with mepolizumab treatment is low.<br><br>Infections reported to date across the mepolizumab development program are summarized in the IB; see 'Special Precautions and Warnings' (for exclusion of subjects with underlying parasitic infections) and 'Undesirable Effects' (for common infections | Daily monitoring of SAE by Serious Adverse Events (SAE) Co-ordinator (project Medical Monitor); regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team.<br><br>Safety assessments to be conducted as outlined in protocols. |

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| | of pharyngitis, lower respiratory tract infection and urinary tract infection reported in patients with severe asthma) sections located in Section 6 titled 'Summary of Data and Guidance for the Investigator' | |
| Potential risk for increase in malignancies - theoretical concern with biologics; however, blockade of IL-5 is not associated with generalized immuno-suppression or impaired host resistance. | Role of IL-5 and eosinophils in tumor surveillance is not fully characterised in the literature.<br><br>No evidence of defective tumor surveillance in IL-5 or eosinophil-deficient mice.<br><br>Direct assessment of the carcinogenic potential of long-term IL-5 blockade in rodent models not technically feasible.<br><br>Based on data from the completed severe eosinophilic asthma Phase 3 clinical program, both benign and malignant neoplasms were reported with a similar frequency across treatment groups. Non-clinical and clinical experience does not support a role for mepolizumab in the development of malignancies.<br><br>Malignancies reported to date across the mepolizumab development program are summarized in the IB. | Daily monitoring of SAE by Serious Adverse Events (SAE) Co-ordinator (project Medical Monitor); regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team.<br><br>Standard safety assessments to be conducted as outlined in protocols. |

| Potential Risk of Clinical Significance | Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| Potential risk for rebound eosinophilia with associated clinical consequences | Early published data with Schering-Plough anti-IL5 mAb suggested potential for rebound eosinophilia and disease exacerbation when treatment was stopped in patients with hypereosinophilic syndromes [Kim, 2004; Gevaert, 2006]; however, no standard definition of rebound was used and criteria for reporting were variable.<br><br>There have been no verbatim reports of 'rebound' from completed clinical trials of subjects with asthma, atopic dermatitis and eosinophilic esophagitis. Furthermore, based on results from the completed severe eosinophilic asthma Phase 3 clinical program the data do not support an exaggerated return of symptoms after cessation of treatment. | Daily monitoring of SAE by Serious Adverse Events (SAE) Co-ordinator (project Medical Monitor); regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team.<br><br>Standard safety assessments to be conducted as outlined in protocols. |
| **Study Procedures** | | |
| Potential risk for injury with phlebotomy | Risks with phlebotomy include bruising, bleeding, infection, nerve damage. | Procedures to be performed by trained personnel (i.e., study nurse). Local anaesthetic will be recommended at phlebotomy site. |

### 4.6.2. Benefit Assessment

Study 200363 will characterize the pharmacokinetics and pharmacodynamics of mepolizumab administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma. This pediatric population of asthma subjects has not been evaluated as having received benefit from treatment with mepolizumab. However, GSK conducted a randomized, double-blind, parallel group clinical trial to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of mepolizumab in 59 children and adolescents 2 to 17 years old with eosinophilic esophagitis (Assa'ad, 2011). Each subject received one of three intravenous doses (0.55, 2.5 or 10mg/kg) every 4 weeks for 12 weeks. The pharmacodynamic effect observed (reduction of blood eosinophils) was consistent with phase 3 studies (Bel, 2014 and Ortega, 2014). In addition to investigating the pharmacokinetics and pharmacodynamics of mepolizumab in a pediatric population with severe asthma, this study 200363 will assess the incidence of adverse events and the rate of exacerbations to assess safety and efficacy of the treatment in this population.

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

### 4.6.3. Overall Benefit: Risk Conclusion

Data from mepolizumab preclinical and clinical development demonstrate the ability of mepolizumab to inhibit IL-5 and, consequently, treat inflammatory conditions linked to an eosinophilic signal, such as asthma subjects predisposed to exacerbations. To date, the safety profile of mepolizumab across other mepolizumab studies has been favorable for all the patient populations studied. Adverse events (AEs) reported commonly have been manageable with minimal medical intervention. Furthermore, preclinical data and the observed safety profile to date in over 2000 clinical trial subjects, as well as the history of mepolizumab use for at least one year in the severe asthma patient population, has not identified a safety concern that would preclude continued use. Therefore, investigation of the pharmacokinetics, pharmacodynamics, safety, efficacy, and tolerability of mepolizumab in this pediatric population with severe asthma and a continuing unmet need is thereby justified in Study 200363.

## 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.

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

## 5.1. Inclusion Criteria for Part A

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

| [1] AGE |
|---|
| 1. Between 6 and 11 years of age inclusive, at the time of screening. |
| [2] TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY |
| 2. Diagnosis of severe asthma, defined by the regional asthma guidelines (i.e., NIH, GINA, etc.), for at least 12 months prior to Visit 1. If the subject is naïve to the study site, the subject/guardian must self-report a physician diagnosis of asthma and the investigator must confirm by review of medical history with the subject/guardian.<br><br>3. Eosinophilic airway inflammation that is related to asthma characterized as eosinophilic in nature as indicated by:<br><br>• elevated peripheral blood eosinophil count of ≥300 cells/μL demonstrated in the past 12 months OR<br><br>• elevated peripheral blood eosinophil count of ≥150/μL at visit 1.<br><br>4. A well-documented requirement for regular treatment with inhaled corticosteroid (>200 μg/day fluticasone propionate (DPI) or equivalent daily) in the 12 months prior to Visit 1 with or without maintenance oral corticosteroids (OCS). The ICS dose should represent medium or high dose in children aged 6-11 years of age [GINA, 2015].<br><br>5. Current treatment with an additional controller medication for at least 3 months or a documented failure in the past 12 months of an additional controller medication for at least 3 successive months. [e.g., long-acting beta-2-agonist (LABA), leukotriene receptor antagonist (LTRA), or theophylline.]<br><br>6. $FEV_1$: Persistent airflow obstruction at either visit 1 or Visit 2 ($FEV_1$ performed prior to first dose of study medication) as indicated by:<br><br>• A pre-bronchodilator FEV1 <110% predicted (Quanjer, 2012) OR<br><br>• FEV1:FVC ratio < 0.8<br><br>7. Previously confirmed history of two or more exacerbations requiring treatment with systemic CS (intramuscular (IM), intravenous, or oral), in the 12 months prior to visit 1, despite the use of inhaled corticosteroids (ICS). For subjects receiving maintenance OCS, treatment for the exacerbations must have been a two-fold increase or greater in the CS dose.<br><br>8. No changes in the dose or regimen of baseline ICS and/or additional controller medication during the run-in period. |

| [3] SEX |
|---|
| 9. Male or female: Females of childbearing potential must commit to consistent and correct use of an acceptable method of contraception (see Appendix 7) for the duration of the trial and for 4 months after the last dose of investigational product. A urine pregnancy test is required of girls of childbearing potential. This test will be performed at the initial screening visit (Visit 1) and will be performed at each scheduled treatment visit prior to the administration of investigational product, and during the Exit Visit, Early Withdrawal and Follow-up Visits. |
| [4] INFORMED CONSENT |
| 10. Parent(s)/guardian able to give written informed consent prior to participation in the study, which will include the ability to comply with the requirements and restrictions listed in the consent form. If applicable, the subject must be able and willing to give assent to take part in the study according to the local requirement. |

## 5.2. Exclusion Criteria for Part A

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

| [1] CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND ECG) |
|---|
| 1. Subjects with any history of life threatening asthma (e.g. requiring intubation), immunosuppressive medications intake or immunodeficiency disorder |
| 2. Subjects with any medical condition or circumstance making the volunteer unsuitable for participation in the study. |
| 3. Significant abnormality of rate, interval, conduction or rhythm in the 12-lead ECG, determined by the investigator in conjunction with the age and gender of the child at Visit 1. |
| 4. ALT, and bilirubin > 2xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%) at Visit 1. |
| 5. Positive Hepatitis B Surface Antigen or positive Hepatitis C antibody at Visit 1 |
| 6. Parent/guardian has a history of psychiatric disease, intellectual deficiency, substance abuse, or other condition (e.g. inability to read, comprehend and write) which will limit the validity of consent to participate in this study. |
| 7. Unwillingness or inability of the subject or parent/guardian to follow the procedures outlined in the protocol. |
| 8. Subject who is mentally or legally incapacitated. |
| 9. Children who are wards of the state or government. |
| 10. A subject will not be eligible for this study if he/she is an immediate family member of the participating investigator, sub-investigator, study coordinator, or employee of the participating investigator. |

| |
|---|
| [2] CONCOMITANT MEDICATIONS |
| 11. Xolair: Subjects who have received omalizumab [Xolair] within 130 days of Visit 1.<br>12. Other Biologics: Subjects who have received any biological (other than Xolair) to treat inflammatory disease within 5 half-lives of visit 1. |
| [3] CONTRAINDICATIONS |
| 13. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.<br>14. Hypersensitivity: Subjects with allergy/intolerance to a monoclonal antibody or biologic. |
| [4] DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA |
| 15. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer). |

## 5.3. Eligibility Criteria for Part B

- The subject has completed all study assessments up-to and including Visit 8 and received all 3 doses of IP in Part A
- The PI has performed a benefit/risk assessment and this assessment supports continued therapy with mepolizumab.
- The subject's parents (or guardian) have given consent and the subject has given assent for continued treatment

## 5.4. Pre-Screening/Screening/Run-in Failures

Subjects will be assigned a study number at the time of signing the consent (Pre-screening Visit 0). Subjects who do not progress to the screen visit will be deemed a Pre-screen Failure. The reason for screen failure will be captured in the eCRF for these subjects. Rescreen will be permitted with approval of the GSK Medical Monitor. Any subject rescreened will be assigned a new subject number and this will be recorded in the eCRF.

Those subjects that complete at least one additional visit 1 (screen) procedure, but do not enter the run-in period will be designated as screen failures.

Those subjects that enter the run-in period, but are not dosed, will be designated as run-in failures.

Information to be collected for screen failure and run-in failures will be detailed in the eCRF completion guidelines, and any Serious Adverse Events reported as associated with study procedures will be recorded in the eCRF.

## 5.5. Withdrawal/Stopping Criteria

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

Liver chemistry stopping criteria are detailed in Section 5.5.1

Subjects are also free to withdraw consent to participate in the study at anytime. Every effort should be made to have them return to the clinic for an Early Withdrawal Visit (See Table 3 and Table 4) and to return all study related materials. In those instances where the subject specifies the reason for withdrawal of consent, this information will be captured in the eCRF.

A subject should only be designated as lost to follow-up if the site is unable to establish contact with the subject after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc).

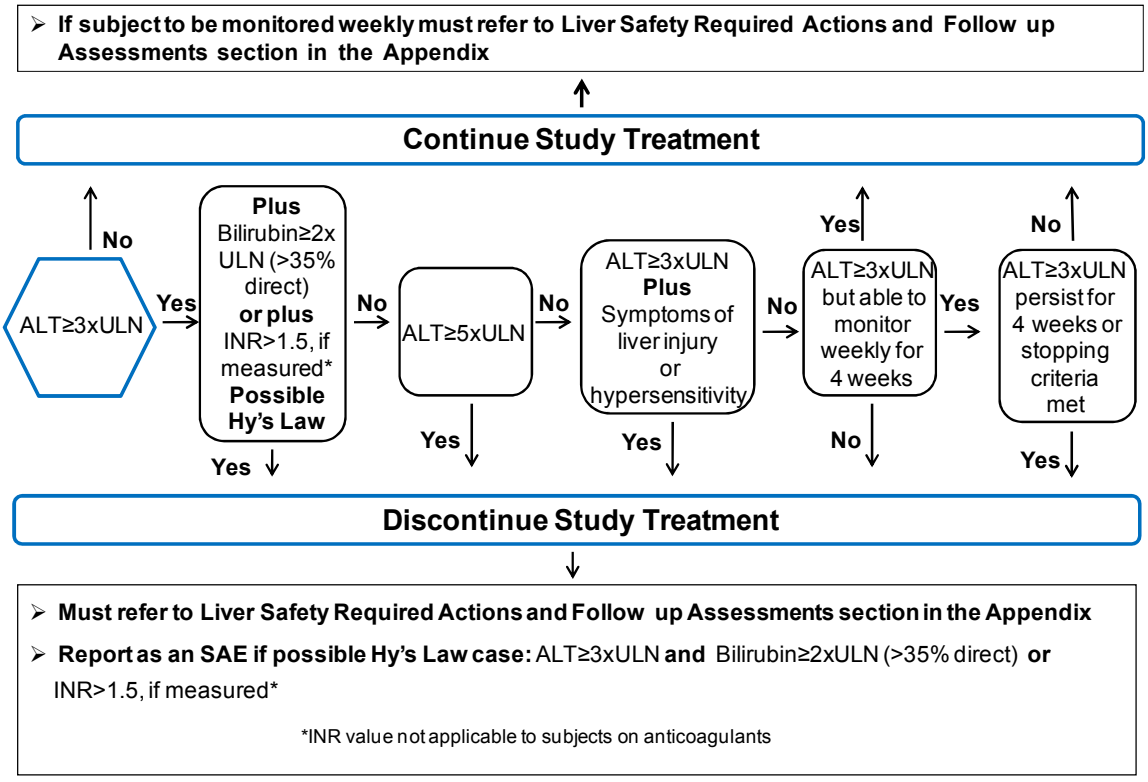
For both Part A and Part B of this study an Exit Visit should be conducted within 4 weeks of the last dose received. In the event that a subject withdraws at, or during, a scheduled visit, an Early Withdrawal Visit should be performed at this visit instead. A Follow-up Visit should then be scheduled 12 weeks after the last dose of investigational product (Visit 8 or Visit 23 for subjects withdrawing from study Parts A or B, respectively).

Any data collected up until the point of withdrawal will be used in the analyses.

### 5.5.1. Liver Chemistry Stopping Criteria

**Liver chemistry stopping and increased monitoring criteria** have been designed to assure subject safety and evaluate liver event etiology (Food and Drug Administration Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation 2009).

**Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm**




Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2

#### 5.5.1.1. 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 permitted**.

## 5.6. Subject and Study Completion

In Part A, a completed subject is one who has completed all phases of the study including the Part A follow-up visit. In Part B, for subjects not transitioning to the long-term access program, a completed subject is one who has completed all phases of Part B (including the Part B follow-Up Visit) and for subjects transitioning to the long term access program a completed subject is one who has completed the Treatment Phase of Part B.

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

# 6. STUDY TREATMENT

## 6.1. Investigational Product

| | Study Treatment |
|---|---|
| **Product name:** | Mepolizumab |
| **Dosage form:** | Mepolizumab (SB240563) 100 mg vial<br>Lyophile for reconstitution |
| **Unit dose strength(s)/Dosage level(s):** | 40 and 100 mg |
| **Route of Administration** | Subcutaneous, upper arm or thigh. |
| **Dosing instructions:** | For subcutaneous injection only |

Mepolizumab (SB-240563) is a humanised monoclonal antibody (IgG1, kappa) with human heavy and light chain frameworks. Mepolizumab will be provided as a lyophilised cake in sterile vials for individual use. The vial will be reconstituted with Sterile Water for Injection, just prior to use. Further details of dose preparation and administration can be found in the Clinical Investigator's Brochure (CIB), and the Study Reference Manual (SRM).

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

## 6.2. Dosage and Administration

### Pharmacokinetic/Pharmacodynamic Phase (Part A)

Enrolled subjects in this study will be dosed with the following treatment:

| Treatment Arm | SC dose |
|---|---|
| Mepolizumab 40 mg SC upper arm or thigh | Mepolizumab 40 mg SC<br>For subjects < 40 kg bodyweight at Visit 2 (Week 0) |
| Mepolizumab 100 mg SC upper arm or thigh | Mepolizumab 100mg SC<br>For subjects ≥ 40 kg bodyweight at Visit 2 (Week 0) |

### Long-Term Safety / Long-Term Pharmacodynamic Phase (Part B)

| Treatment Arm | SC dose |
|---|---|
| Mepolizumab 40mg SC upper arm or thigh | Mepolizumab 40 mg SC<br>For subjects with bodyweight <40 kg at Visit 9 (Week 20) and at any subsequent visits |
| Mepolizumab 100mg SC upper arm or thigh | Mepolizumab 100mg SC<br>For subjects with bodyweight ≥40kg at Visit 9 (Week 20) or from the visit at which bodyweight reaches 40 kg) |

**Preparation of Investigational Product (Part A and Part B)**

Site staff member assigned to the study will be required to prepare the appropriate medication according to the study subject's treatment assignment. Subjects eligible to enter the study will be assigned to treatment based on bodyweight at Visit 2. Assigned dose will remain the same irrespective of bodyweight changes during the treatment phase of Part A. Within Part B the subject's dose will be adjusted to 100mg SC from the time the subject's bodyweight reaches 40 kg.

Prior to administration, each vial of mepolizumab will need to be reconstituted and swirled gently to enable complete dissolution of the product. Detailed instructions can be found within the Study Reference Manual (SRM). Subjects assigned to the 40 mg treatment group will receive 0.4 mL of reconstituted mepolizumab. Subjects assigned to the 100 mg treatment group will receive 1.0 mL of reconstituted mepolizumab. Injected volume may be split between two injection sites for subjects receiving 100 mg (1.0 mL) and given as 2x0.5mL injections. Investigator should consider the use of a local anaesthetic at the injections sites.

## 6.3. Compliance with Study Treatment Administration

All study treatment will be administered at a clinic visit. The dose will be administered by clinic staff in accordance with specific guidance in the Study Reference Manual. When the individual SC dose for a subject is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff. Subjects will receive study treatment directly from the investigator or designee, under medical supervision. The injection volume (mL); and date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study drug administration (injection volume, date, and time) will be reported in the eCRF.

## 6.4. Blinding

This will be an open-label study; therefore, investigators have direct access to the subject's individual study treatment.

## 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

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

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

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

A description of the methods and materials required for mepolizumab will be detailed in the Study Reference Manual (SRM).

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. 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 authorized 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.

## 6.7. Treatment of Study Treatment Overdose

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

## 6.8. Treatment after the Completion of Part A and Part B

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

At the end of Part A, a benefit/risk assessment will be performed by the Investigator and if this assessment supports continued therapy with mepolizumab the subject will be offered the opportunity to enrol in Part B following the Part A Follow-up visit (Visit 8). Part B will continue for 52 weeks of additional mepolizumab treatment.

At the end of Part B, when feasible, subjects will transition to a long term access program. At the end of the Treatment Phase of Part B, subjects that are not able to transition to the long term access program will return to usual care and will be prescribed appropriate alternative asthma therapy, as required.

## 6.9. Concomitant Medications and Non-Drug Therapies

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

All concomitant medications taken during the study will be recorded on the electronic Case Report Form (eCRF). Asthma medications taken during the 12 months prior to Visit 1 should be recorded in the eCRF. The minimum requirement is that drug name and all dates of administration are to be recorded. Permitted medications include:

- Existing stable asthma therapy (inhaled fluticasone propionate (DPI) or equivalent, total daily dose greater than or equal to 200 mcg or equivalent daily) will be permitted during the run-in and active treatment period. Current treatment with an additional controller medication [e.g., long-acting beta-2-agonist (LABA), leukotriene receptor antagonist (LTRA), or theophylline] will be permitted during the run-in and active treatment period.
- Short acting beta 2 agonist inhalation aerosol (albuterol/salbutamol) will be permitted as rescue medication for symptomatic relief of asthma symptoms. Albuterol/salbutamol will be provided locally (except for US sites where it will be provided by the GSK Global Supply Organisation) and dispensed at each visit from Screening Visit 1, as required.
- Oral corticosteroids
- Low potency topical corticosteroids (≤1% hydrocortisone).
- Acetaminophen.

Other concomitant medication may be considered on a case by case basis by the GSK Medical Monitor.

No changes in the dose or regimen of baseline ICS and/or additional controller medication are permitted during the run-in period.

### 6.9.2. Prohibited Medications and Non-Drug Therapies

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

**Table 2 Prohibited Medications**

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

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

## 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 Tables (Table 3 and Table 4).

## Table 3 Time and Events Table - Pharmacokinetic/Pharmacodynamic Phase (Part A)

| Procedure | Pre-Screen[1] | Screening | Treatment Period | | | | Exit Visit[3] | Follow-up | | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8[8] | |
| **Week of Study** (visit window ± 3 days, ±1 day Visit 5)) | Prior to or same day as Visit 1 | (up to 14 days prior to Visit 2) | 0 | 4 | 8 | 9 | 12 | 16 | 20 | |
| | | | | | | | | | | |
| **Subject Screen** | | | | | | | | | | |
| Informed consent | X | | | | | | | | | |
| Inclusion and exclusion criteria | | X | X | | | | | | | |
| Demography | X | | | | | | | | | |
| Medical history, including bronchodilator reversibility history[4] | | X | | | | | | | | |
| Past and current medical conditions | | X | | | | | | | | |
| Asthma exacerbation history | | X | | | | | | | | |
| | | | | | | | | | | |
| **Safety Assessments** | | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X |
| Hematology (including eosinophils) | | X | X | X | X | X | X | X | X | X |
| Clinical Chemistry | | X | | X | X | | X | | X | X |
| 12-lead ECG | | X | | X | | | X | | | X |
| Vital signs | | X | X | X | X | X | X | X | X | X |
| Bodyweight | | | X | | | | | | | |
| Brief physical examination | | X | | | | | | | | |
| Adverse events | | X | X | X | X | X | X | X | X | X |
| Cardiovascular events | | X | X | X | X | X | X | X | X | X |
| Liver events | | X | X | X | X | X | X | X | X | X |
| | | | | | | | | | | |
| **Laboratory Assessments** | | | | | | | | | | |
| Urinalysis | | X | | | | | | | X | X |
| Pregnancy Test | | U | U[5] | U[5] | U[5] | | U | U | U | U |
| HBsAg and hepatitis C antibody | | X[6] | | | | | | | | |
| Serum IgE (total) | | | X[5] | | | | | | | |
| PK blood sample | | | | X[5] | X[5] | X | X | X | X | X |

| Procedure | Pre-Screen[1] | Screening | Treatment Period | | | | Exit Visit[3] | Follow-up | | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8[8] | |
| **Week of Study** (visit window ± 3 days, ±1 day Visit 5)) | Prior to or same day as Visit 1 | (up to 14 days prior to Visit 2) | 0 | 4 | 8 | 9 | 12 | 16 | 20 | |
| IL5 serum sample | | | X[5] | | | | X | | | |
| Blood sample for immunogenicity[2,7] | | | X[5] | | | | | X | X[2] | X |
| | | | | | | | | | | |
| **Outcomes Assessments** | | | | | | | | | | |
| FEV1 | | X | X | X | X | | X | X | X | X |
| ACQ-7 | | | X | X | X | | X | X | X | X |
| C-ACT | | | X | X | X | | X | X | X | X |
| Assessment of exacerbation | X | X | X | X | X | X | X | X | X | X |
| | | | | | | | | | | |
| **Investigational Product** | | | | | | | | | | |
| Mepolizumab SC dose administered | | | X | X | X | | | | | |
| | | | | | | | | | | |
| **Study Administration** | | | | | | | | | | |
| Email to GSK Operational Lead | X | X | X | X | X | X | X | X | X | X |
| Complete eCRF | X | X | X | X | X | X | X | X | X | X |

1. Pre-screen must be completed prior to or on the same day as Screen Visit.
2. For subjects who had a positive anti-mepolizumab antibody response at the 12 week post-last-dose follow-up assessment (Visit 8) (or last study visit at which immunogenicity was assessed if the Follow-up (Visit 8) immunogenicity sample is not available) an attempt will be made to obtain a serum sample for anti-mepolizumab antibodies at least 4 months after the last dose of study drug in Part A or upon completion of Part A, whichever is later.
3. Exit visit should be performed as close as possible to the planned week 12 visit date.
4. Therapy history to include a detailed review of prior biologics received for treatment of asthma, including prior investigational anti-IL5 or anti-IL13 preparations.
5. During the treatment period, all lab samples and procedures should be obtained prior to study treatment administration.
6. A positive Hepatitis B Surface Antigen and Hepatitis C antibody is exclusionary
7. This immunogenicity sample must always be collected 12 weeks (± 7 days) post-last-dose of study treatment; therefore, for subjects who withdraw from study treatment early, this sample must be collected 12 weeks (± 7 days) after their confirmed last dose of study treatment (i.e., prior to Visit 8). In the event that this sample collection date coincides with an Early Withdrawal Visit, only one immunogenicity sample should be collected.
8. Visit 8 to be performed 12 weeks post last dose. For subjects continuing into the long-term extension phase Part B, Visit 9 should be conducted on the same day as Visit 8 once all of the visit 8 assessments have been completed. Assessments performed at Visit 8 that are also listed for Visit 9 should not be duplicated if Visit 8 and Visit 9 are performed on the same day.

**Table 4 Time and Events Table Long-Term Safety / Pharmacodynamic Phase (Part B)**

| Procedure | Eligibility Check / First Dose | Treatment Period | | | | | | | | | | | | Exit Visit | Follow-up[3] | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | |
| Week of Study (visit window ± 5 days) | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | 80 | |
| | | | | | | | | | | | | | | | | |
| **Subject Screen** | | | | | | | | | | | | | | | | |
| Informed consent | X[1] | | | | | | | | | | | | | | | |
| Inclusion and exclusion criteria | X[1] | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| **Safety Assessments** | | | | | | | | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hematology (including eosinophils)[2] | X | | | X | | | X | | | X | | | X | X | X | X |
| Clinical Chemistry[2] | X | | | X | | | X | | | X | | | X | X | | X |
| 12-lead ECG | | | | | | | | | | | | | | X | | X |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Bodyweight | X | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | | | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Cardiovascular events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Liver events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | | | | | | | | | | | | | | |
| **Laboratory Assessments[2]** | | | | | | | | | | | | | | | | |
| Urinalysis | X[1] | | | | | X | | | | | | | | X | | X |
| Pregnancy Test | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U |
| Blood sample for immunogenicity[2] | | | | | | | X | | | | | | X | | X | X |
| | | | | | | | | | | | | | | | | |
| **Outcomes Assessments** | | | | | | | | | | | | | | | | |
| FEV1 | X[1] | | | X | | | X | | | X | | | X | X | X | X |
| ACQ-7 | X[1] | | | X | | | X | | | X | | | X | X | X | X |
| C-ACT | X[1] | | | X | | | X | | | X | | | X | X | X | X |

| Procedure | Eligibility Check / First Dose | Treatment Period | | | | | | | | | | | | Exit Visit | Follow-up[3] | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | |
| Week of Study (visit window ± 5 days) | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | 80 | |
| Assessment of exacerbation | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | | | | | | | | | | | | | | |
| **Investigational Product** | | | | | | | | | | | | | | | | |
| Mepolizumab SC dose administered | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| | | | | | | | | | | | | | | | | |
| **Study Administration** | | | | | | | | | | | | | | | | |
| Email to GSK Operational Lead | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Complete eCRF | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

1. Bodyweight will be measured at Visit 9 and at each visit until such time as the subject reaches 40kg in weight. Subjects with bodyweight ≥40Kg at Visit 9 will not be weighed again during Part B.
2. All laboratory samples should be collected prior to the administration of study medication
3. The 12-week post-dose follow-up visit (Visit 23) is not required for subjects transitioning to the long-term access program.

## 7.1. Screening and Critical Baseline Assessments

### 7.1.1. Pre-Screening Failures (Visit 0)

A subject will be assigned a subject number at the time the informed consent is signed. A subject who is assigned a subject number but is not screened further will be considered a pre-screen failure. Note: Visit 0 (Pre-Screening) and Visit 1 (Screening) may be conducted on the same day as part of the same clinic visit. Visit 0 is required to ensure full accountability of eligible and non-eligible subjects offered participation in this study.

The following information will be collected for subjects who are pre-screen failures:

a. Date of ICF signature
b. Details of asthma medications within 30 days of Visit 0
c. Details of asthma exacerbation between date of informed consent and pre-screening, if applicable
d. Serious adverse events (SAEs) that occur between the date of informed consent form and Screening Visit if related to study participation are recorded in inform and on a paper SAE form and sent to GSK safety within 24 hours
e. Demographic information including age, gender, race and ethnicity
f. Subject number
g. Investigator signature page

### 7.1.2. Screening (Visit 1)

A subject not considered a Pre-Screen Failure will continue further with the assessments for Visit 1 per Table 3

## 7.2. Safety

Planned time points for all safety assessments are listed in the Time and Events Tables (Table 3 and Table 4). Additional time points for safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

### 7.2.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

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

In line with clinical practice, monitoring of patients following administration of a biologic agent including mepolizumab should be done to detect and report the occurrence of systemic (i.e., allergic/hypersensitivity and non-allergic) reactions. Hypersensitivity reactions will be monitored using the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis [Sampson, 2006]

(Appendix 9). Information will be also collected on the occurrence of local injection site reactions.

#### 7.2.1.1. Definition of an Adverse Event (AE)

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

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

Events meeting the definition of an AE include:

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

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

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

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

#### 7.2.1.2. Definition of a Serious Adverse Event (SAE)

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

a. Results in death

b. Is life-threatening

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

c. Requires hospitalization or prolongation of existing hospitalization

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

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

d. Results in disability/incapacity, or

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

e. Is a congenital anomaly/birth defect

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

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

NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of urinary bilirubin detectable on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

#### 7.2.1.3. Time period and Frequency for collecting AE and SAE information

- AEs and SAEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.2.1.5), at the timepoints specified in the Time and Events Table (Table 3 and Table 4).
- 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 eCRF.
- 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.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 3.
- 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 3.

#### 7.2.1.4. 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 does your child seem to feel?"
- "Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?"
- "Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?"

#### 7.2.1.5. 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 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 3.

#### 7.2.1.6. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs and non-serious AEs 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.

### 7.2.2. Pregnancy

The investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Section 12.3.6. 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 have study treatment discontinued, but will be requested to continue study visits through the Follow-up phase.

### 7.2.3. Physical Exams

- A brief physical examination will include, at a minimum assessments of the lungs, cardiovascular system, and abdomen (liver and spleen).

- Investigators should pay special attention to clinical signs related to previous serious illnesses.

### 7.2.4. Vital Signs

Sitting pulse rate and blood pressure measurements will be performed by the investigator or qualified site staff, as outlined in Time and Events schedule (Table 3 and Table 4). Measurements will be done pre-infusion/injection with the subject sitting, having rested in this position for at least 5 minutes before each reading. They will be taken before measurement of any clinic lung function tests or ECGs at the specified time point.

### 7.2.5. Electrocardiogram (ECG)

Twelve-lead ECGs will be performed at the visits specified in the Time and Events schedule (Table 3 and Table 4).

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

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

Subjects with evidence of significant abnormality in the 12-lead at screening will be excluded from enrolment into the Part A treatment phase.

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

### 7.2.6. Clinical Safety Laboratory Assessments

Clinical laboratory tests will be conducted at the visits specified in the Time and Events schedule (Table 3 and Table 4). Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed below:

**Table 5 Laboratory Evaluations**

**Hematology**

| | | |
|---|---|---|
| Platelet Count | *RBC Indices*: | *Automated WBC Differential:* |
| RBC Count | MCV | Neutrophils |
| WBC Count (absolute) | MCH | Lymphocytes |
| Reticulocyte Count | MCHC | Monocytes |
| Hemoglobin | | Eosinophils |
| Hematocrit | | Basophils |

**Clinical Chemistry**

| | | | |
|---|---|---|---|
| BUN | Potassium | AST (SGOT) | Total and direct bilirubin |
| Creatinine | Chloride | ALT (SGPT) | Uric Acid |
| Glucose, | Total $CO_2$ | GGT | Albumin |
| Sodium | Calcium | Alkaline phosphatase | Total Protein |

**Routine Urinalysis**

| |
|---|
| Specific gravity, pH, glucose, protein, blood and ketones by dipstick |
| Microscopic examination (if blood or protein is abnormal) |

All blood samples which will be taken prior to each administration of study medication will be sent to a central laboratory for analysis (details provided in the $Q^2$ Solutions Investigator Manual). Standard reference ranges will be used.

Full details of the collection and shipping requirements for the central laboratory are provided in the Quest Diagnostics Clinical Trials Investigator Manual. The central laboratory will fax laboratory results to the Investigator and will transmit the results electronically to GlaxoSmithKline.

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. Subjects may request that their samples are destroyed at any time.

## 7.3. Pharmacokinetics

Blood samples for analysis of mepolizumab plasma concentration will be obtained as per the Part A Time and Events table (Table 3). Samples obtained at visit 3 and 4 must be drawn prior to mepolizumab 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 $Q^2$ Solutions Investigator Manual.

## 7.4. Pharmacodynamics

Blood eosinophil counts will be recorded as part of the standard haematological assessments performed at the visits specified in the Time and Events table (Table 3 and Table 4).

## 7.5. Immunogenicity

Blood samples will be collected for the determination of anti-mepolizumab antibodies, prior to dosing at Visit 2 (Week 0), and subsequently at Visit 7 (Week 16), and at Visit 8 (Week 20) and Early Withdrawal.

For subjects who had a positive anti-mepolizumab antibody response at the Follow-up (Visit 8) (or last study visit at which immunogenicity was assessed if the Follow-up (Visit 8) immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-mepolizumab antibodies at least 4 months after the last dose of study drug in Part A or upon completion of Part A, whichever is later.

In Part B, immunogenicity samples will be collected prior to dosing at Visit 15 (week 44), Visit 21 (week 68) and, when applicable, at Follow-up Visit 23 (week 80) and Early Withdrawal.

Details for sample collection and processing may be found in the $Q^2$ Solutions Investigator Manual.

## 7.6. Forced Expiratory Volume-1 ($FEV_1$)

To permit investigator staff completion of the ACQ-7 questionnaire (Section 7.7 below) spirometry will be conducted, using the site's own equipment at the visits specified in the Time and Events schedule (Table 3 and Table 4). The spirometer should meet American Thoracic Society standards and produce a printout of all data generated, which should be stored in the subject's notes. The spirometer should be calibrated in accordance with the manufacturer's instructions and a calibration log maintained. Spirometry must be performed at the same time (±1 hour) of the Visit 2 spirometry. Subjects should try to withhold short-acting beta-2-agonists (SABAs) for ≥6 hours and LABAs for ≥12 hours prior to clinic visit, if possible. Assessments to be recorded will include $FEV_1$, and FVC. For predicted $FEV_1$ values, reference is made to the multi-ethnic reference values for spirometry for the 3-95-yr age range: using the Global Lung Function Initiative 2012 equations and look-up tables (Quanjer, 2012). See the Study Reference Manual (SRM) for further details

## 7.7. Asthma Control Questionnaire-7 (ACQ-7)

The ACQ-7 (Juniper, 1999, Juniper, 2005, Juniper, 2006, Juniper, 2010) will be administered by a trained clinic staff member at each visit indicated in the Time and Events schedule (Table 3 and Table 4). The ACQ-7 is a simple questionnaire to measure the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment (Appendix 5). The questionnaire includes 7 items; and requires a 1 week recall (for items on symptoms and rescue inhaler use). The ACQ-IA has a multidimensional construct assessing symptoms (5 items administered by clinic staff to the child using the interviewer administer format) and rescue bronchodilator use (query to child or parent), and FEV1% (1 item) completed by clinic staff (Appendix 6). The ACQ-7 uses a 7-point scale (0=no impairment, 6= maximum impairment for symptoms and rescue use; and 7 categories for FEV1%). The instrument has a reported high test-retest reproducibility with an intraclass correlation coefficient =0.90. The minimally important change in score is 0.5. The ACQ-IA will be administered to subjects for whom an appropriate translation is available. If necessary, the draft ACQ-IA will be administered until a final linguistically validated version becomes available. The draft version of the ACQ-IA includes the linguistically validated ACQ-7 items, final instructions for each language and draft alternative item prompts to

facilitate administration to children. Use of the ACQ-7 is authorized by permission of the author.

## 7.8. Childhood Asthma Control Test (C-ACT)

The Childhood Asthma Control Test (C-ACT) assesses asthma control in children 4-11 years of age (Liu, 2007, Liu, 2010). The ACT will be completed on paper. The C-ACT should be completed prior to other study procedures to ensure that responses are not influenced by interactions with study site staff. The C-ACT is a 7-question, 2-part questionnaire, with items one through 4 to be completed by the child (with assistance from a caregiver, as needed) and items 5 to 7 to be completed by the caregiver (Appendix 10). A total sum score based upon responses to all items is calculated to provide an overall measure of asthma control.

## 7.9. Asthma Exacerbations

At each study visit the investigator will make an assessment of the occurrence of an asthma exacerbation. Any asthma exacerbation will be recorded on the appropriate eCRF page.

***An exacerbation*** of asthma as defined as:

Worsening of asthma which requires use of systemic corticosteroids[1] and/or hospitalisation and/or Emergency Department (ED) visits.

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

# 8. DATA MANAGEMENT

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

No formal hypothesis will be tested.

Population-PK (Pop-PK) parameter estimates will be presented ($AUC_{(0\text{-inf})}$, clearance, Cmax, $t_{1/2}$). Descriptive statistics will be used to present the subject demographics, subject study accountability, post-hoc individual pharmacokinetic parameter estimates (e.g. $AUC_{(0\text{-inf})}$, clearance, $C_{max}$, $t_{1/2}$), blood eosinophil count and ratio of blood eosinophil count to baseline at week 12, IL5 levels, selected clinical outcome measures ($FEV_1$, ACQ-7, C-ACT, asthma exacerbations), and safety assessments (adverse events, vital signs, ECGs and laboratories) and immunogenicity. Confidence intervals may be applied where appropriate. In addition a pre-planned analysis comparing the bodyweight-adjusted clearance between adults and subjects 6-11 years with severe eosinophilic asthma will be conducted, with appropriate confidence intervals applied.

Details of the statistical considerations and data analyses will be detailed in the Reporting and Analysis Plan (RAP).

## 9.1. Hypotheses

Formal hypothesis testing will not be performed.

## 9.2. Sample Size Considerations

The sample size was determined by the number of subjects needed for the PK and PD evaluations of Part A of the study, based on previous PK/PD studies. A pediatric population-PK trial simulation (GSK Document Number 2014N223495_00) was used to determine the Root Mean Square Error (RMSE, i.e. standard deviation) in estimated exposure ($AUC_{(0\text{-inf})}$ ) as a function of sample size, pharmacokinetic sampling scheme and model assumptions. Based on 1000 trial simulations per scenario, a sample size of 16-32 subjects is sufficient to maintain precision in exposure estimation (and hence bodyweight-adjusted clearance) below 20%, (as compared with the guideline 40%), providing five pharmacokinetic samples (including one close to Tmax) are collected and four parameters are fixed from adult values in the population-PK model.

For blood eosinophils it is expected that this trial will have a similar residual variance to that observed in the MEA115588 trial, where a residual SD of 0.7867 on the log transformed scale was observed. Based on this assumption, a total of 20 subjects should provide sufficient precision for the 95% confidence interval for the ratio to baseline to lie within a ratio of 50% of the observed value. For example if the observed ratio to baseline for blood eosinophils is 0.14, the reduction observed in trial MEA115588, the 95% confidence interval is expected to be from 0.09 to 0.20.

With regards to the pre-planned secondary analysis, the trial simulations also showed that for the proposed sample size and sampling scheme, 80% of simulated trials yielded a bodyweight-adjusted apparent clearance with 90% confidence limits falling within the bounds 0.8 – 1.25 of the adult apparent clearance value (CL/F of 0.29 L/day). This

precision is deemed sufficient for extrapolation purposes from adults to pediatric subjects aged 6 to 11 years supported by this study (GSK Document Number 2014N223495_00).

Patients who complete Part A and who meet the eligibility criteria for Part B will be allowed to participate in Part B and no specific sample size requirements are defined.

### 9.2.1. Sample Size Assumptions

No sample size assumptions are assumed beyond the demonstrated comparability between adult pharmacokinetic parameters and those observed in an intravenous study in children aged 2-17 years with eosinophilic esophagitis.

### 9.2.2. Sample Size Sensitivity

Further details of the PK trial simulation sample size estimation methodology are provided in GSK Document Number 2014N223495_00.

### 9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation or adjustment will be performed.

## 9.3. Data Analysis Considerations

### 9.3.1. Analysis Populations Part A

#### 9.3.1.1. Safety Population Part A

All subjects receiving at least one dose of mepolizumab beginning at Visit 2 will be included in the safety population for Part A analyses.

#### 9.3.1.2. Pharmacokinetic Population Part A

All subjects receiving at least one dose of mepolizumab beginning at Visit 2 and having at least one blood sample taken at Visit 3 or thereafter with measurable mepolizumab plasma concentration will be included in the pharmacokinetic population for Part A analyses.

#### 9.3.1.3. Pharmacodynamic Population (Blood Eosinophils) Part A

All subjects receiving at least one dose of mepolizumab beginning at Visit 2 and having at least one blood sample taken for blood eosinophil count post dosing at Visit 2 will be included in the pharmacodynamic population (blood eosinophils) for Part A analyses.

#### 9.3.1.4. Pharmacodynamic Population (Outcome Assessments) Part A

All subjects receiving at least one dose of mepolizumab beginning at Visit 2 and having at least one assessment of pharmacodynamic outcomes (ACQ-7, ACT, asthma exacerbation, or $FEV_{1,}$) post dosing at Visit 2 will be included in the pharmacodynamic population (outcomes) for Part A analyses.

#### 9.3.1.5. Safety Population Part B

All subjects receiving at least one dose of study medication beginning at Visit 9 will be included in the safety population for Part B analyses.

#### 9.3.1.6. Pharmacodynamic Population (Blood Eosinophils) Part B

All subjects receiving at least one dose of mepolizumab beginning at Visit 9 and having at least one blood sample taken for blood eosinophil count post dosing at Visit 9 will be included in the pharmacodynamic population (blood eosinophils) for Part B analyses.

#### 9.3.1.7. Pharmacodynamic Population (Outcome Assessments) Part B

All subjects receiving at least one dose of mepolizumab beginning at Visit 9 and having at least one assessment of pharmacodynamic outcomes (ACQ-7, ACT, asthma exacerbation, or $FEV_{1,}$) post dosing at Visit 9 will be included in the pharmacodynamic population (outcomes) for Part B analyses.

### 9.3.2. Interim Analysis

A full interim analysis is planned at the completion of the Pharmacokinetic/Pharmacodynamic Phase (Part A) of this study. All eCRF data will be monitored, queried, and a soft-database lock will be performed on all subject data through Visit 8 following last subject achieving Visit 8. A statistical output will be prepared in accordance with all study objectives and endpoints for Part A.

## 9.4. Key Elements of Analysis Plan (Part A)

### 9.4.1. Primary Analyses

The primary endpoints of plasma mepolizumab PK parameters will be evaluated by population PK methods. A number of pharmacokinetic parameters will be fixed from adult values in support of the sparse sampling, and estimated population-PK parameter estimates will be provided. Additionally, the post-hoc individual PK parameter estimates (including the derived parameters e.g. $AUC_{(0\text{-inf})}$, clearance, $C_{max}$ and $t_{1/2}$) will be summarised using descriptive statistics, when appropriate.

Blood eosinophil count, the primary pharmacodynamic endpoint, will be log transformed prior to analysis and will also be summarised using descriptive statistics.

Confidence intervals will be presented when appropriate. The analysis schema will be outlined in the RAP.

### 9.4.2. Secondary Analyses

Secondary endpoints including ACQ-7, C-ACT, incidence in adverse events, frequency of positive anti-mepolizumab antibodies, and clinically significant changes in laboratory parameters and vital signs will be summarised using descriptive statistics. Formal hypothesis testing will not be performed.

The comparison of bodyweight-adjusted clearance between the 6-11 year olds and adults will be made by comparing the point estimate and 90% CI of bodyweight-adjusted clearance in this study with the historic value in adults of L/day (corresponding to an apparent clearance of 0.29 L/day assuming an absolute bioavailability of 75%) along with a proposed 80-125% interval around this estimate (i.e., 0.18-0.28 L/day).

Confidence intervals will be presented when appropriate. The analysis schema will be outlined in the RAP.

### 9.4.3. Exploratory Analyses

Exploratory endpoints of number of asthma exacerbations both on- and post-mepolizumab treatment and $FEV_1$ will be summarised using descriptive statistics.

Confidence intervals will be presented when appropriate. The analysis schema will be outlined in the RAP.

## 9.5. Key Elements of Analysis Plan (Part B)

### 9.5.1. Primary Analysis

The incidence in adverse events, frequency of positive anti-mepolizumab antibodies, and clinically significant changes in laboratory parameters and vital signs will be summarised using descriptive statistics.

### 9.5.2. Secondary Analyses

Blood eosinophil count will be log transformed prior to analysis and will also be summarised using descriptive statistics.

### 9.5.3. Exploratory Analyses

Exploratory endpoints including ACQ-7, C-ACT and number of exacerbations will be summarised using descriptive statistics, Confidence intervals will be presented when appropriate. The analysis schema will be outlined in the RAP.

# 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 favorable 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 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
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- 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.

## 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 CRF 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.

One or more manuscripts will be progressed for publication in the scientific literature.

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# 12. APPENDICES

## 12.1. Appendix 1: Abbreviations and Trademarks

### Abbreviations

| | |
|---|---|
| ACQ-7 | Asthma Control Questionnaire-7 |
| ADA | Anti-drug Antibody |
| AE | Adverse Event |
| ALT | Alanine aminotransferase (SGPT) |
| AST | Aspartate aminotransferase (SGOT) |
| AUC | Area under concentration-time curve |
| $AUC_{(0\text{-inf})}$ | Area under concentration time curve to infinity |
| β-HCG | Beta-Human Chorionic Gonadotropin |
| BUN | Blood urea nitrogen |
| C-ACT | Childhood Asthma Control Test |
| CC | Cubic Centimeter |
| CI | Confidence Interval |
| CL | Systemic clearance of parent drug |
| CL/F | Apparent clearance after extravascular (e.g., subcutaneous) administration |
| Cmax | Maximum observed concentration |
| CDC | Centers for Disease Control (US) |
| $CO_2$ | Carbon dioxide |
| CPK | Creatine phosphokinase |
| CPSR | Clinical Pharmacology Study Report |
| eCRF | Electronic Case Report Form |
| CS | Corticosteroids |
| CV | Cardiovascular |
| DCSI | Developmental Core Safety Information |
| DPI | Dry Powder Inhaler |
| ECG | Electrocardiogram |
| ED | Emergency Department |
| EGD | Esophagogastroduodenoscopy |
| EoE | Eosionophilic Esophagitis |
| FAAN | Food Allergy and Anaphylaxis Network |
| $FEV_1$ | Forced Expiratory Volume in 1 second |
| FVC | Forced Vital Capacity |
| GCP | Good Clinical Practice |
| GCSP | Global Clinical Safety and Pharmacovigilence |
| GGT | Gamma glutamyltransferase |
| GINA | Global Initiative for Asthma |
| GSK | GlaxoSmithKline |
| HBsAg | Hepatitis B surface antigen |
| hCG | Human chorionic gonadotropin |
| HES | Hypereosinophilic syndrome |

| | |
|---|---|
| HR | Heart rate |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ICS | Inhaled Corticosteroids |
| ID50/90 | 50% or 90% Inhibition of Maximum Effect |
| IEC | Independent Ethics Committee |
| IgG | Immunoglobulin |
| IL-5 | Interleukin 5 |
| IM | Intramuscular |
| $I_{max}$ | Maximum Inhibition Model |
| IP | Investigational Product |
| IRB | Institutional Review Board |
| IUD | Intrauterine Device |
| IV | Intravenous |
| kg | Kilogram |
| LABA | Long acting inhaled β2 adrenoceptor agonist |
| LRTA | Leukotriene Receptor Antagonist |
| µg | Microgram |
| µL | Microliter |
| mAb | Monoclonal Antibody |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| MCV | Mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligrams |
| mL | Milliliter |
| MSDS | Material Safety Data Sheet |
| Nab | Neutralizing Antibody |
| NIAID | National Institute of Allergy and Infectious Diseases (US) |
| NIH | National Institute of Health (US) |
| OCS | Oral Corticosteroids |
| OLE | Open label extension |
| PD | Pharmacodynamic |
| PK | Pharmacokinetic |
| Pop-PK | Population Pharmacokinetics |
| QT | The QT interval is measured from the beginning of the QRS complex to the end of the T wave |
| QTc | QT duration corrected for heart rate |
| RAP | Reporting and Analysis Plan |
| SAE | Serious adverse event(s) |
| SAS | Statistical Analysis Software |
| SC | subcutaneous |
| SGOT | Serum glutamic-oxaloacetic transaminase |
| SGPT | Serum glutamic pyruvic transaminase |

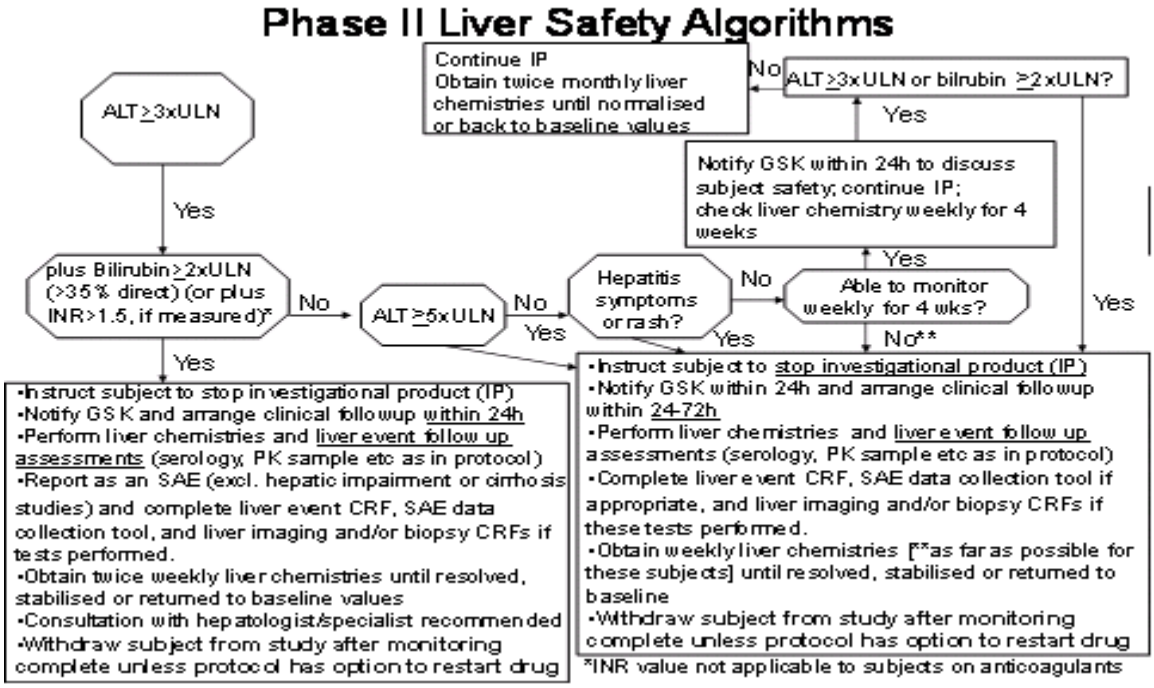
| | |
|---|---|
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SRM | Study Reference Manual |
| SRT | Safety Review Team |
| SUSAR | Suspected, Unexpected, Serious Adverse drug Reaction |
| t½ | Terminal phase half-life |
| Tmax | Time of occurrence of Cmax |
| TTS | Study Specific Technical Agreement Memo |
| µL | Microliter |
| ULN | Upper limit of normal |
| UK | United Kingdom |
| US | United States |
| Vc | Central Volume of Distribution |
| WBC | White blood cells |
| Vss | Steady State Volume of Distribution |

## Trademark Information

| Trademarks of the GlaxoSmithKline group of companies |
|---|
| NONE |

| Trademarks not owned by the GlaxoSmithKline group of companies |
|---|
| QOL Technologies Ltd |
| SAS |
| WinNonlin |
| Xolair |

## 12.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments




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

**Phase II liver chemistry stopping criteria and required follow up assessments**

| Liver Chemistry Stopping Criteria – Liver Stopping Event | |
|---|---|
| **ALT-absolute** | ALT ≥ 5xULN |
| **ALT Increase** | ALT ≥ 3xULN 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 ≥ 3xULN 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<br>• Report the event to GSK **within 24 hours**<br>• Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]<br>• Perform liver event follow up assessments<br>• Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below)<br>• **Do not restart/rechallenge** subject with study treatment<br><br>**MONITORING:**<br>**<u>For bilirubin or INR criteria:</u>**<br>• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs**<br>• Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline<br>• A specialist or hepatology consultation is recommended<br>**<u>For All other criteria:</u>**<br>• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs**<br>• Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline | • Viral hepatitis serology[4]<br>• Blood sample for pharmacokinetic (PK) analysis[5]<br>• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).<br>• Fractionate bilirubin, if total bilirubin≥2xULN<br>• Obtain complete blood count with differential to assess eosinophilia<br>• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form<br>• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.<br>• Record alcohol use on the liver event alcohol intake case report form<br>**<u>For bilirubin or INR criteria:</u>**<br>• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).<br>• Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week). **NOTE: not required in China**<br>• 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. 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 $Q^2$ Solutions Investigator Manual.

## Phase II liver chemistry increased monitoring criteria with continued therapy

| **Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event** | |
|---|---|
| **Criteria** | **Actions** |
| 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.<br>• Subject can continue study<br>• Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline<br>• If at any time subject meets the liver chemistry stopping criteria, proceed as described above<br>• If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline. |

## 12.3. Appendix 3: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

### 12.3.1. 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.<br>• 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.<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected interaction.<br>• 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).<br>• "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. |

| **Events <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.<br>• 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.

### 12.3.2. 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:**<br>• 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.<br>• 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:**<br>• ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**<br>• ALT ≥ 3xULN and INR** > 1.5.<br>* 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.<br>** 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. |

### 12.3.3. 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:<br>• Myocardial infarction/unstable angina<br>• Congestive heart failure<br>• Arrhythmias<br>• Valvulopathy<br>• Pulmonary hypertension<br>• Cerebrovascular events/stroke and transient ischemic attack<br>• Peripheral arterial thromboembolism |

- Deep venous thrombosis/pulmonary embolism
- Revascularization

### 12.3.4. 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.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

### 12.3.5. 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.

### 12.3.6. Reporting of SAEs to GSK

| **AE reporting to GSK via electronic data collection tool** |
|---|
| • Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool<br>• If the electronic system is unavailable, the site will use the paper SAE data collection tool and fax it to the SAE coordinator within 24 hours.<br>• Site will enter the serious adverse event data into the electronic system as soon as it becomes available.<br>• 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<br>• 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 SAE coordinator by telephone.<br>• Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page. |

## 12.4. Appendix 4: Collection of Pregnancy Information

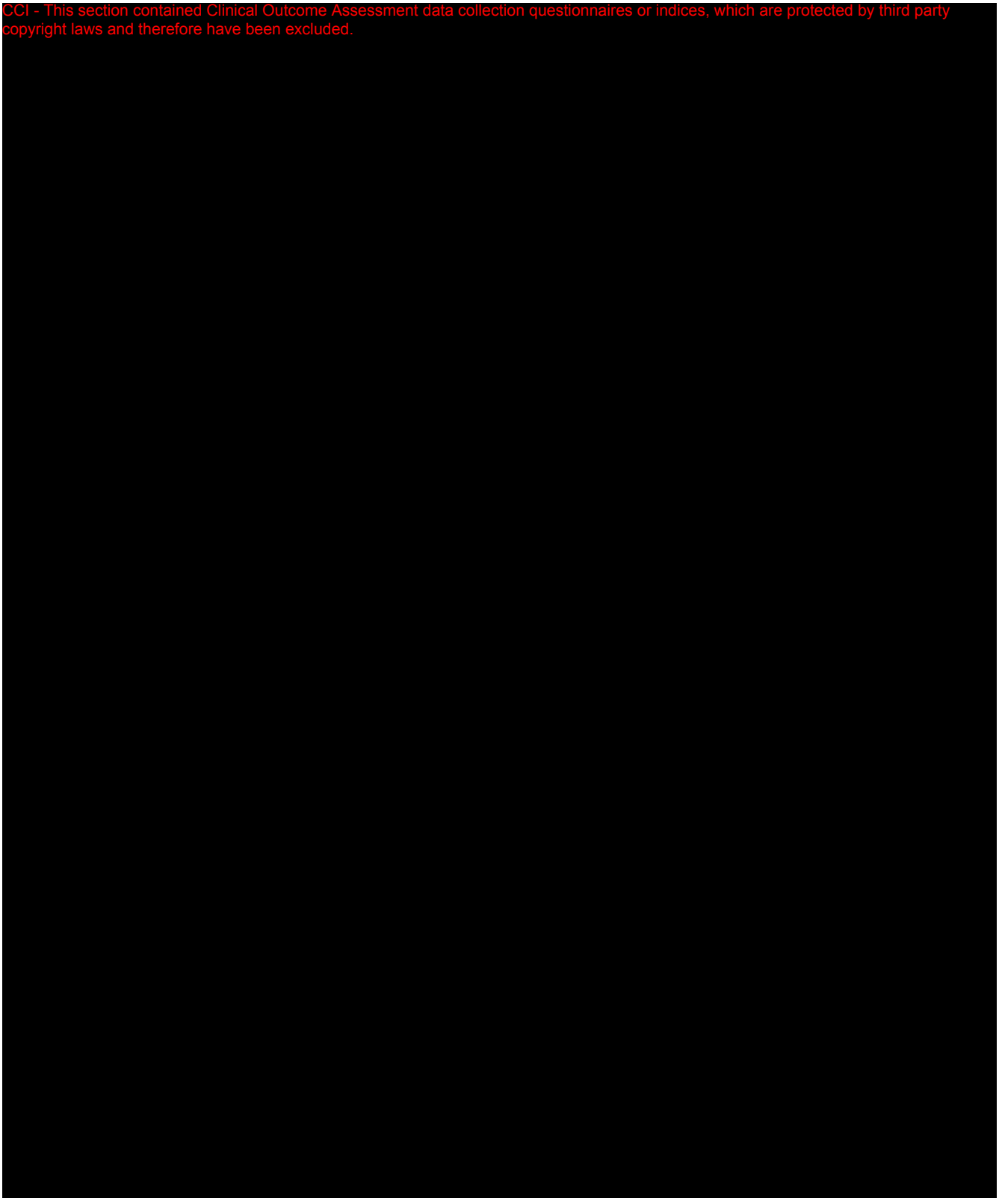
- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the 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 3. 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

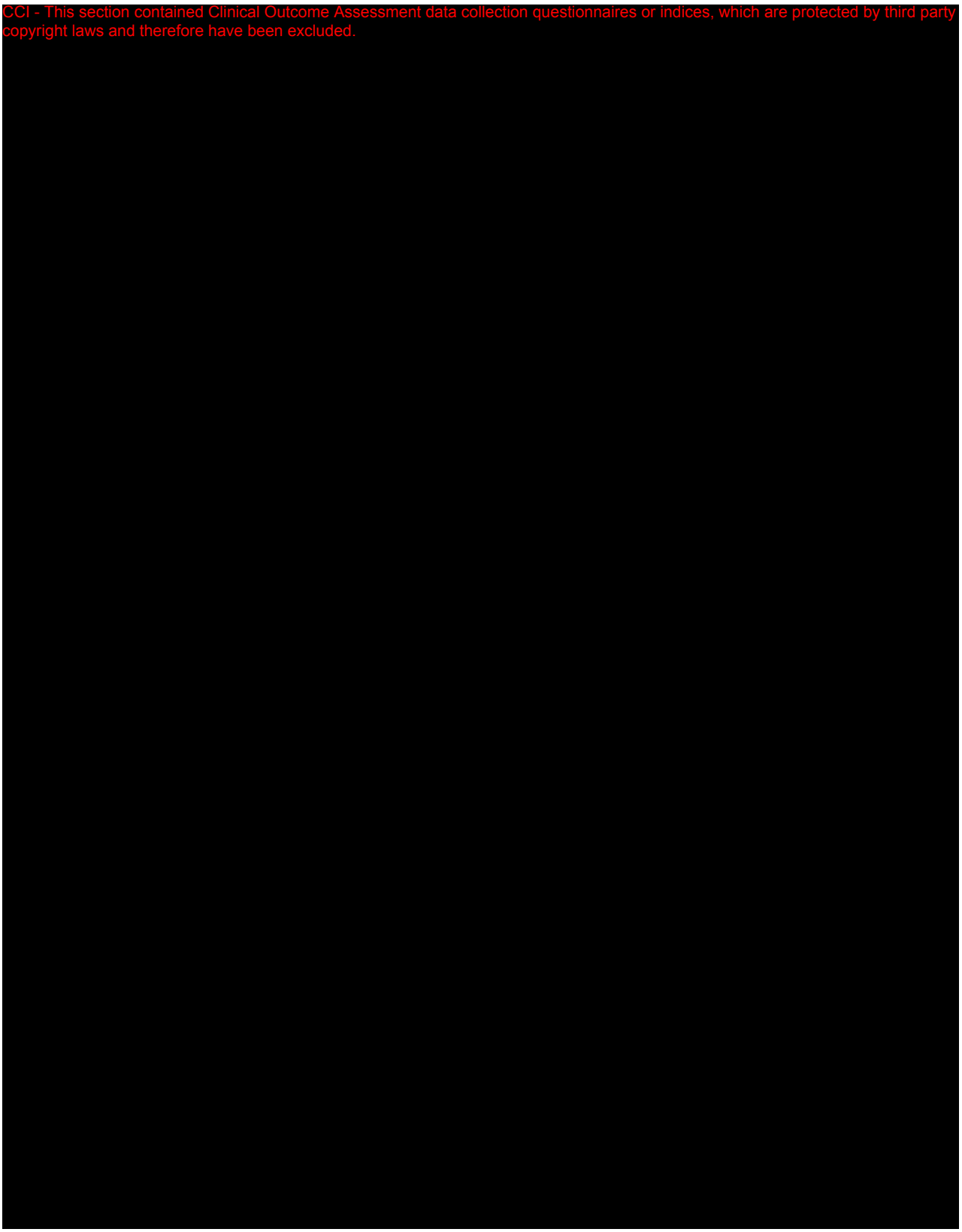
## 12.5. Appendix 5: Sample ACQ-7 Questionnaire

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



## 12.6. Appendix 6: Sample ACQ-IA Questionnaire

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



## 12.7. Appendix 7: Acceptable Birth Control

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

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

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

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

Menarche is the onset of menses for the first time in a young female and is preceded by several changes associated with puberty including breast development and pubic hair growth. Menarche usually occurs within 1-2 years of breast development, thelarche. However, a young female can become pregnant before her first menses. Thus, a conservative definition of non-childbearing potential in a pre-menarcheal female is a young female who has not yet entered puberty as evidenced by lack of breast development (palpable glandular breast tissue).

Based on the absence of an identified reproductive hazard from preclinical studies, absence of a genotoxic potential, and very low levels of mepolizumab that might be present in semen, there is no recognized risk for mepolizumab to affect human sperm or

the fetus if transferred to a female partner via semen. Therefore, the use of condoms or other methods of contraception in the male study subject is not required.

## 12.8. Appendix 8: Country Specific Requirements

No country-specific requirements exist.

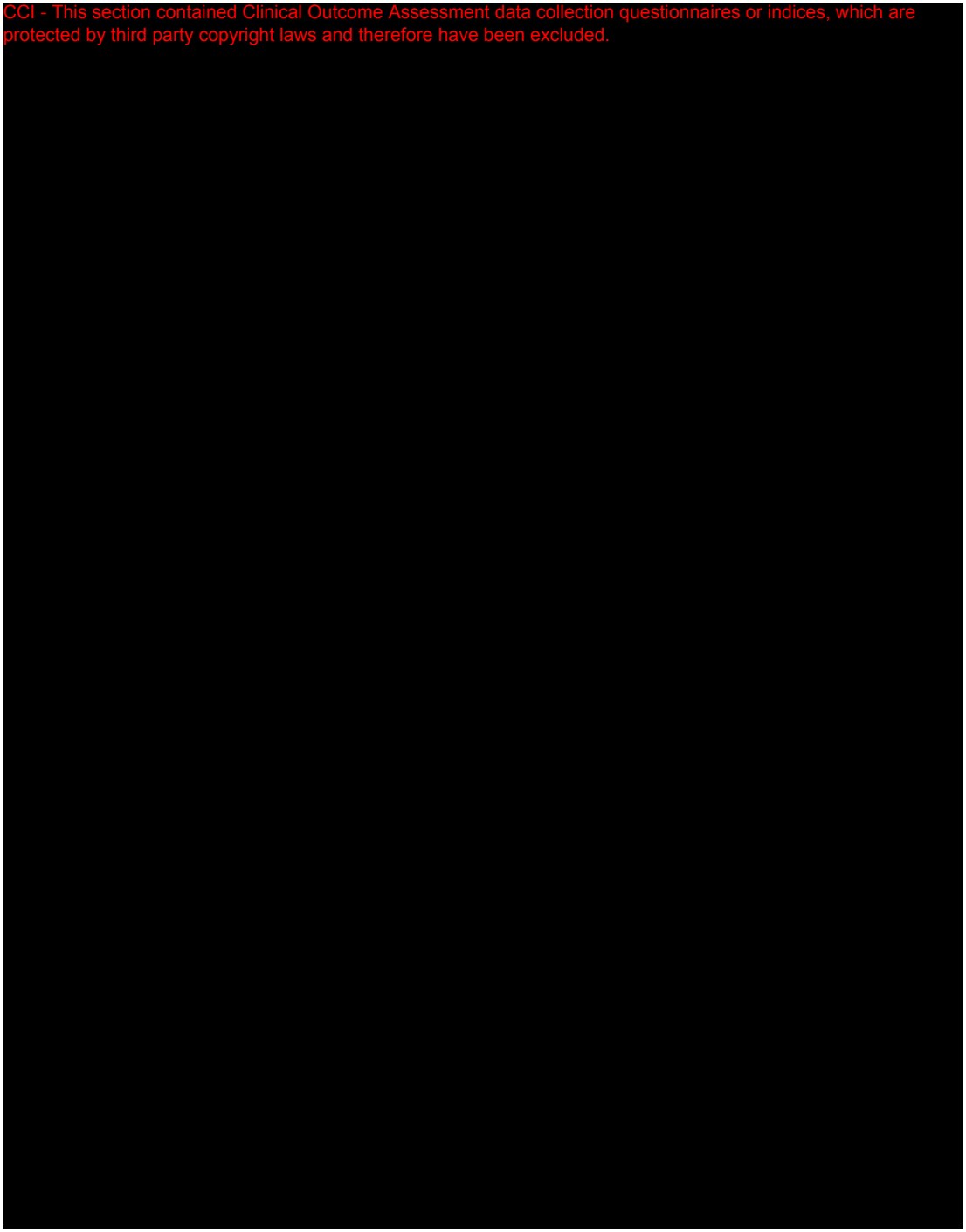
## 12.9. Appendix 9: Anaphylaxis Criteria

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

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

## 12.10. Appendix 10: Childhood Asthma Control Test (C-ACT)

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



## 12.11. Appendix 11: Protocol Amendment Changes

### Protocol Amendment 01

| **SCOPE:** This amendment applies to all countries participating in the study. |
|---|

1. Addition of the C-ACT questionnaire to assess asthma control:

   Section 1 and Section 3. Objective(s)/Endpoint(s), Secondary Endpoints:

   Original Text:

- Bodyweight-adjusted clearance estimates obtained by population PK methods.
- Change from Baseline in ACQ-7 measured at week 12
- Change from Baseline in ACQ-7 measured at weeks 4,8,16 and 20
- Incidence of Adverse Events
- Incidence of clinically significant changes in clinical laboratory parameters
- Frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies
- Incidence of clinically significant changes in vital sign measurements

   Amended Text:

- Bodyweight-adjusted clearance estimates obtained by population PK methods.
- Change from Baseline in ACQ-7 measured at week 12
- Change from Baseline in ACQ-7 measured at weeks 4,8,16 and 20
- Change from Baseline in C-ACT measured at week 12
- Change from Baseline in C-ACT measured at week 4,8, 16 and 20
- Incidence of Adverse Events
- Incidence of clinically significant changes in clinical laboratory parameters
- Frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies
- Incidence of clinically significant changes in vital sign measurements

   Section 7, Table 3 Time and Events Table:

   C-ACT added to visits 2, 3, 4, 6, 7, 8 and Early Withdrawal

   Section 7.8: Childhood Asthma Control Test: A new section describing the C-ACT has been added to describe the use of the C-ACT for this study:

   Additional Text:

The Childhood Asthma Control Test (C-ACT) assesses asthma control in children 4-11 years of age with asthma (Liu, 2007, Liu, 2010). The C-ACT was designed to be self-administered, to incorporate input from parent and child. The C-ACT is a self-administered questionnaire. It is intended to complement pulmonary function testing and

other assessments by health care providers. Before seeing the health care provider, patients will complete the questionnaire (with help from their custodial caregiver). This self administered test is a clinically validated age-specific instrument to assess asthma control and can be completed in a short period of time. The C-ACT is a 7-question, 2-part questionnaire, with one part to be completed by the child with caregiver assistance and the other part to be completed by the caregiver (Appendix 10).

Section 1, Analysis and Section 9 and Section 9.2, : C-ACT added to the list of clinical outcome measures and secondary endpoints.

Appendix 10: Childhood Asthma Control Test: A copy of the C-ACT has been added to Appendix 10.

2. Inclusion Criteria: Heading numbers corrected:

Original numbering:

| [1] AGE |
|---|
| 1. Between 6 and 11 years of age inclusive, at the time of screening. |
| [2] TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY |
| 2. Diagnosis of severe asthma, defined by the regional asthma guidelines (i.e., NIH, GINA, etc.), for at least 12 months prior to Visit 1. If the subject is naïve to the study site, the subject/guardian must self-report a physician diagnosis of asthma and the investigator must confirm by review of medical history with the subject/guardian.<br><br>3. Eosinophilic airway inflammation that is related to asthma characterized as eosinophilic in nature as indicated by:<br><br>• elevated peripheral blood eosinophil count of ≥300 cells/μL demonstrated in the past 12 months OR<br><br>• elevated peripheral blood eosinophil count of ≥150/μL at visit 1.<br><br>4. A well-documented requirement for regular treatment with inhaled corticosteroid (≥400 μg/day fluticasone propionate (DPI) or equivalent daily) in the 12 months prior to Visit 1 with or without maintenance oral corticosteroids (OCS).<br><br>5. Current treatment with an additional controller medication for at least 3 months or a documented failure in the past 12 months of an additional controller medication for at least 3 successive months. [e.g., long-acting beta-2-agonist (LABA), leukotriene receptor antagonist (LTRA), or theophylline.]<br><br>6. $FEV_1$: Persistent airflow obstruction at either visit 1 or Visit 2 ($FEV_1$ performed prior to first dose of study medication) as indicated by:<br><br>• A pre-bronchodilator FEV1 <110% predicted OR |

| |
|---|
| • FEV1:FVC ratio < 0.8 recorded at visit 1<br><br>7. Previously confirmed history of two or more exacerbations requiring treatment with systemic CS (intramuscular (IM), intravenous, or oral), in the 12 months prior to visit 1, despite the use of high-dose inhaled corticosteroids (ICS). For subjects receiving maintenance CS, the CS treatment for the exacerbations must have been a two-fold increase or greater in the dose.<br><br>8. No changes in the dose or regimen of baseline ICS and/or additional controller medication during the run-in period. |
| [4] SEX |
| 9. Male or female: Females of childbearing potential must commit to consistent and correct use of an acceptable method of contraception (see Appendix 7) for the duration of the trial and for 4 months after the last dose of investigational product. A urine pregnancy test is required of girls of childbearing potential. This test will be performed at the initial screening visit (Visit 1) and will be performed at each scheduled study visit prior to the administration of investigational product, and during the Early Withdrawal and Follow-up Visits. |
| [5] INFORMED CONSENT |
| 10. Parent(s)/guardian able to give written informed consent prior to participation in the study, which will include the ability to comply with the requirements and restrictions listed in the consent form. If applicable, the subject must be able and willing to give assent to take part in the study according to the local requirement. |

Amended numbering:

| |
|---|
| [1] AGE |
| 1. Between 6 and 11 years of age inclusive, at the time of screening. |
| [2] TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY |
| 2. Diagnosis of severe asthma, defined by the regional asthma guidelines (i.e., NIH, GINA, etc.), for at least 12 months prior to Visit 1. If the subject is naïve to the study site, the subject/guardian must self-report a physician diagnosis of asthma and the investigator must confirm by review of medical history with the subject/guardian.<br><br>3. Eosinophilic airway inflammation that is related to asthma characterized as eosinophilic in nature as indicated by:<br><br>• elevated peripheral blood eosinophil count of ≥300 cells/μL demonstrated in the past 12 months OR<br><br>• elevated peripheral blood eosinophil count of ≥150/μL at visit 1.<br><br>4. A well-documented requirement for regular treatment with inhaled corticosteroid (≥400 μg/day fluticasone propionate (DPI) or equivalent daily) in the 12 months prior to Visit 1 with or without maintenance oral corticosteroids (OCS). |

| |
|---|
| 5. Current treatment with an additional controller medication for at least 3 months or a documented failure in the past 12 months of an additional controller medication for at least 3 successive months. [e.g., long-acting beta-2-agonist (LABA), leukotriene receptor antagonist (LTRA), or theophylline.]<br><br>6. $FEV_1$: Persistent airflow obstruction at either visit 1 or Visit 2 ($FEV_1$ performed prior to first dose of study medication) as indicated by:<br><br>• A pre-bronchodilator FEV1 <110% predicted OR<br><br>• FEV1:FVC ratio < 0.8 recorded at visit 1<br><br>7. Previously confirmed history of two or more exacerbations requiring treatment with systemic CS (intramuscular (IM), intravenous, or oral), in the 12 months prior to visit 1, despite the use of high-dose inhaled corticosteroids (ICS). For subjects receiving maintenance CS, the CS treatment for the exacerbations must have been a two-fold increase or greater in the dose.<br><br>8. No changes in the dose or regimen of baseline ICS and/or additional controller medication during the run-in period. |
| [3] SEX |
| 9. Male or female: Females of childbearing potential must commit to consistent and correct use of an acceptable method of contraception (see Appendix 7) for the duration of the trial and for 4 months after the last dose of investigational product. A urine pregnancy test is required of girls of childbearing potential. This test will be performed at the initial screening visit (Visit 1) and will be performed at each scheduled study visit prior to the administration of investigational product, and during the Early Withdrawal and Follow-up Visits. |
| [4] INFORMED CONSENT |
| 10. Parent(s)/guardian able to give written informed consent prior to participation in the study, which will include the ability to comply with the requirements and restrictions listed in the consent form. If applicable, the subject must be able and willing to give assent to take part in the study according to the local requirement. |

3. Section 7.6: Forced Expiratory Volume-1 (FEV1). Change to the predicted values from NHANES III to Quanjer (2012).

   Original Text:

To permit investigator staff completion of the ACQ-7 questionnaire (Section 7.7 below) spirometry will be conducted, using the site's own equipment at the visits specified in the Time and Events schedule (Table 3). The spirometer should meet American Thoracic Society standards and produce a printout of all data generated, which should be stored in the subject's notes. The spirometer should be calibrated in accordance with the manufacturer's instructions and a calibration log maintained. Spirometry must be performed at the same time (±1 hour) of the Visit 2 spirometry. Subjects should try to withhold short-acting beta-2-agonists (SABAs) for ≥6 hours and LABAs for ≥12 hours

prior to clinic visit, if possible. Assessments to be recorded will include $FEV_1$, and FVC. For predicted $FEV_1$ values, NHANES III values will be used and adjustments to these values will be made for race (Juniper, 1999). If a subject is recorded as having Hispanic or Latino ethnicity, then the Mexican-American equations will be used (irrespective of race). If a subject is recorded as being of African American/African Heritage race, then the African American equations will be used. If a subject is recorded as being of Asian race, then the Asian equations will be used. Otherwise, the Caucasian equations will be used.

Amended Text:

To permit investigator staff completion of the ACQ-7 questionnaire (Section 7.7 below) spirometry will be conducted, using the site's own equipment at the visits specified in the Time and Events schedule (Table 3). The spirometer should meet American Thoracic Society standards and produce a printout of all data generated, which should be stored in the subject's notes. The spirometer should be calibrated in accordance with the manufacturer's instructions and a calibration log maintained. Spirometry must be performed at the same time (±1 hour) of the Visit 2 spirometry. Subjects should try to withhold short-acting beta-2-agonists (SABAs) for ≥6 hours and LABAs for ≥12 hours prior to clinic visit, if possible. Assessments to be recorded will include $FEV_1$, and FVC. For predicted $FEV_1$ values, reference is made to the multi-ethnic reference values for spirometry for the 3-95-yr age range: using the Global Lung Function Initiative 2012 equations and look-up tables (Quanjer, 2012). A link to a simple online tool for calculating the percent predicted $FEV_1$ is provided in the Study Reference Manual.

4. Section 7.7: Asthma Control Questionnaire-7 (ACQ-7): Wording changed to clarify that the ACQ-7 will be used in countries where a validated translation is available.

   The ACQ-7 (Juniper, 1999, Juniper, 2005, Juniper, 2006) will be administered by a trained clinic staff member at each visit indicated in the Time and Events schedule (Table 3). The ACQ-7 is a simple questionnaire to measure the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment (Appendix 5). The questionnaire includes 7 items; and requires a 1 week recall (for items on symptoms and rescue inhaler use). The ACQ has a multidimensional construct assessing symptoms (5 items administered by clinic staff to the child) and rescue bronchodilator use (query to child or parent), and FEV1% (1 item) completed by clinic staff. The ACQ-7 uses a 7-point scale (0=no impairment, 6= maximum impairment for symptoms and rescue use; and 7 categories for FEV1%). The instrument has a reported high test-retest reproducibility with an intraclass correlation coefficient =0.90. The minimally important change in score is 0.5. The instrument has validated language versions for each country participating in this study. Use of the ACQ-7 is authorized by permission of the author.

   Amended Text:

   The ACQ-7 (Juniper, 1999, Juniper, 2005, Juniper, 2006) will be administered by a trained clinic staff member at each visit indicated in the Time and Events schedule (Table 3). The ACQ-7 is a simple questionnaire to measure the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment (Appendix 5). The questionnaire includes 7 items; and requires a 1 week

recall (for items on symptoms and rescue inhaler use). The ACQ has a multidimensional construct assessing symptoms (5 items administered by clinic staff to the child) and rescue bronchodilator use (query to child or parent), and FEV1% (1 item) completed by clinic staff. The ACQ-7 uses a 7-point scale (0=no impairment, 6= maximum impairment for symptoms and rescue use; and 7 categories for FEV1%). The instrument has a reported high test-retest reproducibility with an intraclass correlation coefficient =0.90. The minimally important change in score is 0.5. The instrument will be administered in each country for which there is a validated translation. Use of the ACQ-7 is authorized by permission of the author.

5. Section 6.2: Clarification that the 100mg (1.0ML) injection can be administered as 2 x 0.5ML injections

   Original Text:

Injected volume may be split between two injection sites for subjects receiving 100 mg (1.0 mL ). Investigator should consider the use of a local anaesthetic at the injections sites.

   Amended Text:

Injected volume may be split between two injection sites for subjects receiving 100 mg (1.0 mL ) and given as 2x0.5mL injections. Investigator should consider the use of a local anaesthetic at the injections sites.

6. Section 7.2.6 Clinical Safety Laboratory Assessments: Typographical errors corrected in Table 4:

   Reference to “fasting” removed as glucose will be tested “non-fasting”.

   Specific gravity included in the dipstick test.

   The “Central Laboratory Investigator Manual” has been corrected to “Quest Diagnostics Clinical Trials Investigator Manual”

7. Section 6.2: Reference to the “Pharmacy Manual” has been corrected to the “Study Procedures Manual (SPM)”

   Section 6.6: Amended to clarify that all instructions for preparing Investigational Product may be found in the Study Reference Manual (SRM) instead of the pharmacy manual

      Original Text:

      A description of the methods and materials required for mepolizumab will be detailed in a Study Specific Technical Agreement/Memo (TTS) or Pharmacy Manual which will be accompanied by a Quality Agreement.

Amended Text:

A description of the methods and materials required for mepolizumab will be detailed in the Study Reference Manual (SRM).

8. Section 7.7: A sentence has been added to clarify that a draft version of the ACQ-IA may be used until a validated translation becomes available.

Original text:

The instrument has a reported high test-retest reproducibility with an intraclass correlation coefficient =0.90. The minimally important change in score is 0.5. The instrument will be administered in subjects for whom an appropriate linguistically valid translation is available. Use of the ACQ-7 is authorized by permission of the author.

Amended text:

The instrument has a reported high test-retest reproducibility with an intraclass correlation coefficient =0.90. The minimally important change in score is 0.5. The ACQ-IA will be administered to subjects for whom an appropriate translation is available. If necessary, the draft ACQ-IA will be administered until a final linguistically validated version becomes available. The draft version of the ACQ-IA includes the linguistically validated ACQ-7 items, final instructions for each language and draft alternative item prompts to facilitate administration to children. Use of the ACQ-7 is authorized by permission of the author.

9. Section 7.2.6: A paragraph has been added to clarify that blood samples will be stored for up to 15 years after the end of the study.

Amended text:

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. Subjects may request that their samples are destroyed at any time.

## Protocol Amendment 02

1. To change details of the Primary and Secondary Medical Monitors for the study:

**Medical Monitor Sponsor Information Page**

Original Text:

| **Role** | Name | Day Time Phone Number and email address | After-hours Phone/Cell/ Pager Number | Site Address |
|---|---|---|---|---|
| Primary Medical Monitor | PPD MD | PPD | | Stockley Park West,United Kingdom |
| Secondary Medical Monitor | PPD ,MD | | | 5 Moore Dr , RTP NC 27709 |

Amended Text:

| **Role** | Name | Day Time Phone Number and email address | After-hours Phone/Cell/ Pager Number | Site Address |
|---|---|---|---|---|
| Primary Medical Monitor | PPD MD | PPD | | 709 Swedeland Road, UW25-3077B King of Prussia, PA 19406 |
| Secondary Medical Monitor | PPD MD | | | Stockley Park West,United Kingdom |

Original Text:

**Sponsor Global Medical Monitor Contact Information:**
PPD MD (Medical Monitor, Respiratory Research and Development)
Mobile: PPD

**Sponsor Back-up Global Medical Monitor Contact Information:**
PPD MD ScD (Director, Physician Lead, Respiratory Research and Development)
Tel: PPD
Mobile: PPD

Amended Text:

**Sponsor Global Medical Monitor Contact Information:**
PPD MD (Director, Respiratory Research and Development)
Tel: PPD
Mobile: PPD
Email: PPD

**Sponsor Back-up Global Medical Monitor Contact Information:**
PPD MD (Medical Monitor, Respiratory Research and Development)
Mobile: PPD

2. To permit extended mepolizumab treatment for a minimum of 52 weeks upon completion of the pharmacokinetic/pharmacodynamic phase (Part A) of the protocol.

PROTOCOL SYNOPSIS FOR STUDY 200363

Original Text:

**Rationale**

This pharmacokinetic/pharmacodynamic study is being conducted as part of an extrapolation strategy to support the use of mepolizumab in the 6-11 pediatric population with severe eosinophilic asthma. This study will provide pharmacokinetic and pharmacodynamic data for mepolizumab at 40 or 100mg SC, depending on subject bodyweight, when administered to children aged 6-11 who have severe eosinophilic asthma that are expected to support the extrapolation of safety and efficacy data observed in the adult population to this pediatric population. This study will also assess safety, tolerability, and immunogenicity of mepolizumab in this population along with clinical outcome measures, the ACQ-7 and the C-ACT.

Amended Text:

**Rationale**

This pharmacokinetic/pharmacodynamic study is being conducted as part of an extrapolation strategy to support the use of mepolizumab in the 6-11 pediatric population with severe eosinophilic asthma. This study will provide pharmacokinetic and pharmacodynamic data for mepolizumab at 40 or 100mg SC, depending on subject bodyweight, when administered to children aged 6-11 who have severe eosinophilic asthma that are expected to support the extrapolation of safety and efficacy data observed in the adult population to this pediatric population. This study will also assess safety, tolerability, and immunogenicity of mepolizumab in this population along with clinical outcome measures, the ACQ-7 and the C-ACT.

Following the main study (Part A), subjects will be evaluated for eligibility to continue into the optional long-term extension phase (Part B) of this study. For those subjects determined to be eligible and for whom appropriate informed consent/assent has been obtained there will be the option of continuing to receive treatment with mepolizumab

during a Long-Term Safety / Pharmacodynamic Phase (Part B) which will include Treatment and Follow-up phases. Part B will provide data to assess the long-term safety and tolerability of mepolizumab in this paediatric population and will also provide data to assess the durability of the pharmacodynamic response to mepolizumab.

3. To add long-term safety (52 weeks) as the primary objective for the extended treatment phase (Part B)

To add long-term pharmacodynamic response as a secondary objective for the extended treatment phase

Protocol Synopsis and Section 3: **Objective(s)/Endpoint(s)**

Additional text:

## Long-Term Safety / Long-Term Pharmacodynamic Phase (Part B)

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To assess the long-term (52 weeks) safety and tolerability of mepolizumab when administered subcutaneously to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Incidence of Adverse Events<br>• Frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies<br>• Incidence of clinically significant changes in vital sign measurements<br>• Incidence of clinically significant changes in clinical laboratory parameters |
| **Secondary** | |
| • To characterize the long-term (52 weeks) durability of pharmacodynamics of mepolizumab administered subcutaneously to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Change from Week 20 (Visit 9) in absolute blood eosinophil count at weeks 32, 44, 56, 68, 72 and 80. |

| Objectives | Endpoints |
|---|---|
| • **Exploratory** | |
| • To assess the number of asthma exacerbations that occur during the long-term (52 weeks) part of the study following subcutaneous administration of mepolizumab to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Incidence of asthma exacerbations |
| • To characterize the long-term (52 weeks) asthma control following subcutaneous administration of mepolizumab to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Change from Week 20 (Visit 9) in ACQ and C-ACT at weeks 32, 44, 56, 68, 72 and 80. |

***Subjects who reach their 12th birthday during Part may continue into Part B**

**Protocol Synopsis**

Additional text:

## Long-Term Safety / Pharmacodynamic Phase (Part B)

This is a long-term safety / pharmacodynamic phase in which extended treatment for a further 52 weeks will be offered on an optional basis to those subjects eligible for continued treatment. Subjects will receive either 40 or 100mg depending on subject bodyweight, administered SC every 4 weeks to subjects with severe eosinophilic asthma aged 6-11 years. At the end of the 52 weeks extended treatment in Part B, subjects will have an Exit Visit 4 weeks after last dose and a Follow-Up visit 12 weeks after last dose.

Protocol Synopsis

Treatment Arms and Duration:

Original Text:

This study will consist of three phases: Pre-Screening/Screening/Run-in, Treatment and Follow-up.

**Pre-Screening/Screening/Run-in**: Subjects will attend an initial Pre-screening visit to assess their willingness and eligibility to participate in the study. The Pre-screening visit will include: informed consent, demography, exacerbations and concomitant medications. Visit 1 Screening (which for convenience may be conducted as the same clinic attendance) will include a physical exam, screening laboratory tests, screening ECG and other assessments to determine suitability to participate in this study. Subjects meeting the Visit 1/Screening eligibility criteria will enter a Run-in period of up to 2 weeks to allow for receipt and review of the lab results and ECG.

Amended text:

This Pharmacokinetic/Pharmacodynamic Phase (Part A) study will consist of three stages: Pre-Screening/Screening/Run-in, Treatment and Follow-up.

**Pre-Screening/Screening/Run-in**: Subjects will attend an initial Pre-screening visit to assess their willingness and eligibility to participate in the study. The Pre-screening visit will include: informed consent, demography, exacerbations and concomitant medications. Visit 1(Screening) will include a physical exam, screening laboratory tests, screening ECG and other assessments to determine suitability to participate in this study. The Pre-screening visit may be conducted at the same clinic visit as Visit 1(Screening). Subjects meeting the Visit 1(Screening) eligibility criteria will enter a Run-in period of up to 2 weeks to allow for receipt and review of the lab results and ECG.

**Part A Treatment:** Those subjects meeting all of the inclusion/exclusion criteria by Visit 2 will receive mepolizumab 40 or 100 mg SC, depending on subject bodyweight (40 mg for subjects <40 kg and 100 mg for subjects ≥ 40 kg). Subjects will receive their first dose of mepolizumab at Visit 2 and enter into the Treatment phase of the study. Subjects shall be observed for a minimum of 60 minutes in the clinic following each injection. Those subjects who enter the run-in period but do not meet all inclusion/exclusion criteria will be deemed Run-in failures and will not be dosed in the study. The reason for any Run-in failure will be recorded in the eCRF.

During the Part A Treatment phase, all subjects will receive mepolizumab 40 or 100 mg SC, depending on subject bodyweight, at week 0 (Visit 2), week 4 (Visit 3) and week 8 (Visit 4) which will provide therapeutic coverage through to week 12 (Visit 6/End of Therapy Visit). Visit 6 will mark the end of the treatment phase.

Subjects will visit the clinic at week 9 (Visit 5) to allow for measurement of the approximate peak mepolizumab concentration.

**Part A Follow-up:** Following completion of Visit 6, subjects will enter into the Follow-up phase which will consist of two additional visits at weeks 16 (Visit 7) and 20 (Visit 8).

## Long-Term Safety / Long Term Pharmacodynamic Phase (Part B)

| Treatment Arm | SC dose |
|---|---|
| Mepolizumab 40mg SC upper arm or thigh | Mepolizumab 40 mg SC<br>For subjects with bodyweight <40 kg at Visit 9 (Week 20). From visit 10, subjects should be weighed at each visit until bodyweight reaches 40kg when the dose should be adjusted to 100mg. From this time onwards, the dose will not be adjusted again. |
| Mepolizumab 100mg SC upper arm or thigh | Mepolizumab 100mg SC<br>For subjects with a bodyweight ≥40 kg at Visit 9 (Week 20) or from the time that bodyweight reaches 40kg. |

**Part B Treatment:** Those subjects meeting the eligibility criteria for the long-term phase of the study at Visit 9 will receive mepolizumab 40 or 100 mg SC, (depending on subject bodyweight measured at Visit 9; 40 mg for subjects <40 kg and 100 mg for subjects ≥ 40 kg). Subjects shall be observed for a minimum of 60 minutes in the clinic following injection at Visit 9 and at subsequent visits subjects should be monitored according to standard practice at the site. From Visit 10 onwards subjects will receive the same dose of mepolizumab at 4-weekly intervals for a total of 48 weeks. Subjects with bodyweight <40 kg at Visit 9 should be weighed at each subsequent visit and have their dose adjusted once their bodyweight exceeds 40 kg.

**Part B Follow-up:** Following completion of Visit 22, subjects will enter into the Follow-up phase which will consist of one additional follow-up visit at week 80 (Visit 23).

**Protocol Synopsis, Type and Number of Subjects:**

Original Text:

Approximately 40 male or female subjects with severe eosinophilic asthma, aged 6 to 11 years inclusive at screening (Visit 1), will be screened to achieve approximately 28 eligible subjects entering the treatment phase to allow for availability of 20 evaluable subjects; with a minimum of six subjects enrolled in the < 40 kg bodyweight group. An evaluable subject is defined to be a subject who has received all three doses of mepolizumab and has had all PK and PD assessments completed through to Visit 6 (week 12).

Amended text:

For Part A, approximately 40 male or female subjects with severe eosinophilic asthma, aged 6 to 11 years inclusive at screening (Visit 1), will be screened to achieve

approximately 28 eligible subjects entering the treatment phase to allow for availability of 20 evaluable subjects; with a minimum of six subjects enrolled in the < 40 kg bodyweight group. An evaluable subject is defined to be a subject who has received all three doses of mepolizumab and has had all PK and PD assessments completed through to Visit 6 (week 12).

Sample size is not determined for Part B. All subjects who completed Part A and meet the eligibility criteria for Part B will be allowed to participate in Part B.

**Protocol Synopsis, Analysis:**

Original Text:

## Analysis

Population-PK (Pop-PK) parameter estimates will be presented ($AUC_{(0\text{-inf})}$, clearance, $C_{max}$, $t_{1/2}$). Descriptive statistics will be used to present the subject demographics, subject study accountability, post-hoc individual pharmacokinetic parameter estimates (e.g. $AUC_{(0\text{-inf})}$, clearance, $C_{max}$, $t_{1/2}$), blood eosinophil count and ratio of blood eosinophil count to baseline at week 12, IL5 levels, selected clinical outcome measures ($FEV_1$, ACQ-7, C-ACT, asthma exacerbations), and safety assessments (adverse events, vital signs, ECGs and laboratories) and immunogenicity. Confidence intervals may be applied where appropriate. In addition a pre-planned analysis comparing the bodyweight-adjusted clearance between adults and subjects 6-11 years with severe eosinophilic asthma will be conducted, with appropriate confidence intervals applied.

Amended Text:

## Analysis

Population-PK (Pop-PK) parameter estimates will be presented ($AUC_{(0\text{-inf})}$, clearance, $C_{max}$, $t_{1/2}$) for Part A. Descriptive statistics will be used to present the subject demographics, subject study accountability, post-hoc individual pharmacokinetic parameter estimates (e.g. $AUC_{(0\text{-inf})}$, clearance, $C_{max}$, $t_{1/2}$), blood eosinophil count and ratio of blood eosinophil count to baseline at week 12, IL5 levels, selected clinical outcome measures ($FEV_1$, ACQ-7, C-ACT, asthma exacerbations), and safety assessments (adverse events, vital signs, ECGs and laboratories) and immunogenicity. Confidence intervals may be applied where appropriate. In addition a pre-planned analysis comparing the bodyweight-adjusted clearance between adults and subjects 6-11 years with severe eosinophilic asthma will be conducted, with appropriate confidence intervals applied.

Safety and Pharmacodynamic data for Parts A and B will be summarized descriptively and 95% CIs will be presented where appropriate.

opSection 4, Study Design:

Original text:

This study will consist of three phases: Pre-Screening/Screening/Run-in, Treatment, and Follow-up.

**Pre-Screening/Screening/Run-in**: Subjects will attend an initial Pre-screening visit to assess their willingness and eligibility to participate in the study. The Pre-screening visit will include: informed consent; demography exacerbations and concomitant medications. Visit 1 Screening (which for convenience may be conducted as the same clinic attendance) will include a physical exam, screening laboratory test, screening ECG and other assessments to determine suitability to participate in this study. Subjects meeting the Visit 1/Screening eligibility criteria will enter a Run-in period of up to 2 weeks to allow for receipt and review of the lab results and ECG.

Amended text:

This study will consist of two phases: Part A will consist of Pre-Screening/Screening/Run-in, Treatment, and Follow-up. Part B will consist of Long-Term Treatment and Follow-up.

## Pharmacokinetic/Pharmacodynamic Phase (Part A)

**Pre-Screening/Screening/Run-in**: Subjects will attend an initial Pre-screening visit to assess their willingness and eligibility to participate in the study. The Pre-screening visit will include: informed consent; demography exacerbations and concomitant medications. Visit 1(Screening) will include a physical exam, screening laboratory test, screening ECG and other assessments to determine suitability to participate in this study. The pre-screening visit may be conducted at the same clinic visit as Visit 1(Screening). Subjects meeting the Visit 1(Screening) eligibility criteria will enter a Run-in period of up to 2 weeks to allow for receipt and review of the lab results and ECG.

Section 4, Study Design:

Original text:

**Follow-up:** Following completion of Visit 6, subjects will enter into the Follow-up phase which will consist of two additional visits at weeks 16 (Visit 7) and 20 (Visit 8).

Study visits will have a window of ± 3 days; except for Visit 5 which should be scheduled ± 1 day.

**Study Completion and Open-Label Extension study (OLE)**

A subject will be regarded as having completed the study if they complete all phases of the study (Pre-Screening/Screening/Run-in, Treatment, and Follow-up). Subjects who complete the study will participate for approximately 22 weeks.

Subjects who are considered to be at risk of experiencing a life-threatening exacerbation of their asthma or whose functional health status will become significantly worse on regular basis if returned to standard of care may be eligible for an OLE study. If the subject is likely to benefit from continued mepolizumab treatment, as judged by the investigator and agreed by GSK, the subject will be offered the opportunity to enrol in an extended treatment study with mepolizumab following the Follow-up (Visit 8).

For subjects who had a positive neutralizing antibody response at the Follow-up (Visit 8) (or last study visit at which immunogenicity was assessed if the Follow-up (Visit 8) immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-mepolizumab antibodies at least 4 months after the last dose of study drug.

Amended text:

**Follow-up:** Following completion of Visit 6, subjects will enter into the Follow-up phase which will consist of two additional visits at weeks 16 (Visit 7) and 20 (Visit 8).For subjects who had a positive neutralizing antibody response at the Follow-up (Visit 8) (or last study visit at which immunogenicity was assessed if the Follow-up (Visit 8) immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-mepolizumab antibodies at least 4 months after the last dose of study drug.

Study visits will have a window of ± 3 days; except for Visit 5 which should be scheduled ± 1 day.

A subject will be regarded as having completed Part A if they complete all phases of Part A (Pre-Screening/Screening/Run-in, Treatment, and Follow-up). Subjects who complete Part A will participate for approximately 22 weeks.

**Long-Term Safety / Pharmacodynamic Phase (Part B)**

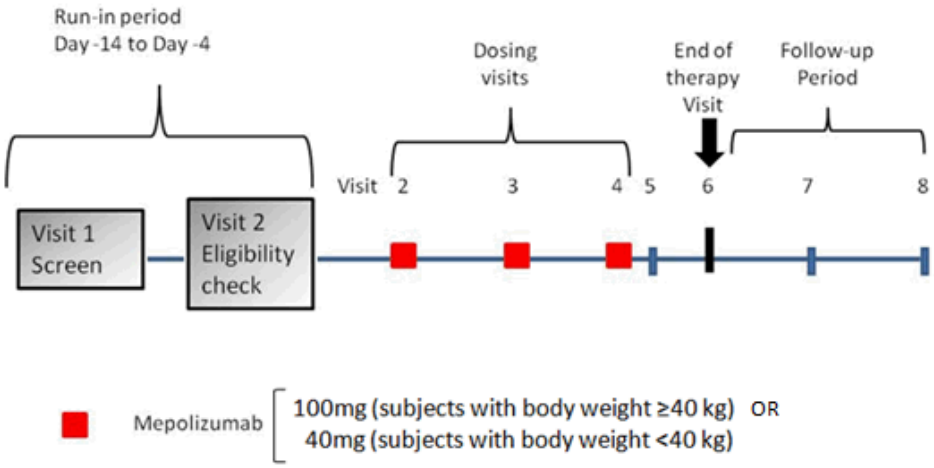
At the end of Part A, a benefit/risk assessment will be performed by the Investigator and if this assessment supports continued therapy with mepolizumab the subject can continue into Part B, with approval from GSK, following the Part A Follow-up (Visit 8).

Study visits in Part B will have a window of ± 5 days. The total duration of Part B is approximately 60 weeks.

**Section 4.1, Overall Design ; Section 4.2 Treatment Arms and Duration**

Original text:

## Overall Design




## Treatment Arms and Duration

Enrolled subjects in this study will be assigned to receive one of the following treatments:

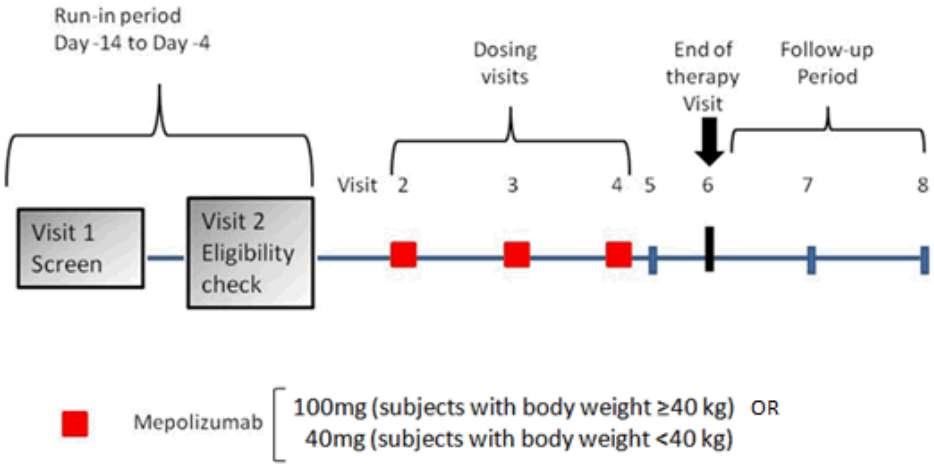
| Treatment Arm | SC dose |
|---|---|
| Mepolizumab 40 mg SC upper arm or thigh | Mepolizumab 40 mg SC<br>For subjects <40 kg bodyweight at Visit 2 (Week 0) |
| Mepolizumab 100 mg SC upper arm or thigh | Mepolizumab 100mg SC<br>For subjects ≥40 kg bodyweight at Visit 2 (Week 0) |

The total duration of the study will be 22 weeks and will include a run-in period of 1-2 weeks, a treatment period of 12 weeks and a follow-up phase of 8 weeks. A subject will be considered having completed the study if the subject completes all phases of the study including the follow-up phase (Visit 8). A subject will be defined as evaluable if the subject received all 3 planned doses of mepolizumab and has completed all pharmacokinetic and pharmacodynamic assessments through to study Visit 6.

Amended text:

## Overall Design

### Pharmacokinetic/Pharmacodynamic Phase (Part A)




This is a multi-centre, open-label study that will assess the pharmacokinetics pharmacodynamics of three 4-weekly doses of mepolizumab, either 40 or 100mg depending on subject bodyweight, administered SC to subjects with severe eosinophilic asthma aged 6-11 years.

### Long-Term Safety / Pharmacodynamic Phase (Part B)

This is a long-term safety / pharmacodynamic phase in which extended treatment will be offered on an optional basis to those subjects eligible for continued treatment. Subjects will receive either 40 or 100mg depending on subject bodyweight, administered subcutaneously at 4-weekly intervals for a total of 52 weeks.

## Treatment Arms and Duration

### Pharmacokinetic/Pharmacodynamic Phase (Part A)

Enrolled subjects in this study will be assigned to receive one of the following treatments:

| **Treatment Arm** | **SC dose** |
|---|---|
| Mepolizumab 40 mg SC upper arm or thigh | Mepolizumab 40 mg SC<br>For subjects <40 kg bodyweight at Visit 2 (Week 0) |
| Mepolizumab 100 mg SC upper arm or thigh | Mepolizumab 100mg SC<br>For subjects ≥40 kg bodyweight at Visit 2 (Week 0) |

**Part A Pre-Screening/Screening/Run-in**: Subjects will attend an initial Pre-screening visit to assess their willingness and eligibility to participate in the study. The Pre-screening visit will include: informed consent, demography, exacerbations and concomitant medications. Visit 1(Screening) will include a physical exam, screening laboratory tests, screening ECG and other assessments to determine suitability to participate in this study. The Pre-screening visit may be conducted at the same clinic visit as Visit 1 (Screening). Subjects meeting the Visit 1(Screening) eligibility criteria will enter a Run-in period of up to 2 weeks to allow for receipt and review of the lab results and ECG.

**Part A Treatment:** Those subjects meeting all of the inclusion/exclusion criteria by Visit 2 will receive mepolizumab 40 or 100 mg SC, depending on subject bodyweight (40 mg for subjects <40 kg and 100 mg for subjects ≥ 40 kg). Subjects will receive their first dose of mepolizumab at Visit 2 and enter into the Treatment phase of the study. Subjects shall be observed for a minimum of 60 minutes in the clinic following each injection. Those subjects who enter the run-in period but do not meet all inclusion/exclusion criteria will be deemed Run-in failures and will not be dosed in the study. The reason for any Run-in failure will be recorded in the eCRF.

During the Part A Treatment phase, all subjects will receive mepolizumab 40 or 100 mg SC, depending on subject bodyweight measured at Visit 2, at week 0 (Visit 2), week 4 (Visit 3) and week 8 (Visit 4) which will provide therapeutic coverage through to week 12 (Visit 6/End of Therapy Visit). Visit 6 will mark the end of the treatment phase.

Subjects will visit the clinic at week 9 (Visit 5) to allow for measurement of the approximate peak mepolizumab concentration.

**Part A Follow-up:** Following completion of Visit 6, subjects will enter into the Follow-up phase which will consist of two additional visits at weeks 16 (Visit 7) and 20 (Visit 8).

The total duration of Part A will be 22 weeks and will include a run-in period of 1-2 weeks, a treatment period of 12 weeks and a follow-up phase of 8 weeks. A subject will be considered having completed Part A if the subject completes all phases including the follow-up phase (Visit 8). A subject will be defined as evaluable for Part A if the subject received all 3 planned doses of mepolizumab and has completed all pharmacokinetic and pharmacodynamic assessments through to study Visit 6

## Long-Term Safety / Long Term Pharmacodynamic Phase (Part B)

| Treatment Arm | SC dose |
|---|---|
| Mepolizumab 40mg SC upper arm or thigh | Mepolizumab 40 mg SC<br>For subjects <40 kg bodyweight at Visit 9 (Week 20). From visit 10, subjects should be weighed at each visit until bodyweight reaches 40kg when the dose should be adjusted to 100mg. From this time onwards, the dose will not be adjusted again. |
| Mepolizumab 100mg SC upper arm or thigh | Mepolizumab 100mg SC<br>For subjects bodyweight at Visit 9 (Week 20) or from the time that bodyweight reaches 40 kg |

Following Part A subjects will be evaluated for eligibility to continue into Part B of this study. For those subjects determined to be eligible and for whom appropriate informed consent/assent has been obtained there will be a Long-Term Safety / Pharmacodynamic Phase (Part B). Part B will include Treatment and Follow-up phases.

**Part B Treatment:** Those subjects meeting all of the Part B eligibility criteria by Visit 9 will receive mepolizumab 40 or 100 mg SC, depending on subject bodyweight at Visit 9 (40 mg for subjects <40 kg and 100 mg for subjects ≥ 40 kg). Subjects shall be observed for a minimum of 60 minutes in the clinic following injection at Visit 9 and at subsequent visits subjects should be monitored according to standard practice at the site. From Visit 10 onwards subjects will receive the same dose of mepolizumab at 4-weekly intervals. Subjects with bodyweight <40 kg at Visit 9 should be weighed at each visit and have their dose adjusted once their bodyweight exceeds 40 kg. Once a subject starts treatment with the 100mg dose, the dose will not be adjusted further even if the subject's bodyweight should drop below 40kg.

**Part B Follow-up:** Following completion of Visit 22, subjects will enter into the Follow-up phase which will consist of an additional visit at week 80 (Visit 23).

**Section 4.4, Design Justification**

Additional text:

No long-term data (up to 52 weeks) documenting the safety and tolerability of mepolizumab in children aged 6 to 11 years with severe eosinophilic asthma are currently available. As it is expected that treatment with mepolizumab in this population may be long-term it is essential that such data be collected. Extended treatment with mepolizumab during Part B of this protocol also permits an assessment of the durability of the pharmacodynamic response to mepolizumab in this population.

**Section 4.5.1, Table Assessment of Risk, Mitigation Strategy:**

Original text:

In addition to normal institutional practices, subjects will be observed for a minimum of 60 minutes in the clinic following each injection.

Amended text:

In addition to normal institutional practices, subjects will be observed for a minimum of 60 minutes in the clinic following each injection up-to and including Visit 9. From Visit 10 onwards, monitoring post-injection should be according to the standard procedure at each site.

Original text:

Safety assessments to be conducted as outlined in protocols.

Amended text:

Daily monitoring of SAE by Serious Adverse Events (SAE) Co-ordinator (project Medical Monitor); regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team.

Safety assessments to be conducted as outlined in protocols.

**Section 5.3, Eligibility Criteria for Part B**

Additional Text:

## Eligibility Criteria for Part B

- The subject has completed all study assessments up-to and including Visit 8 and received all 3 doses of IP in Part A.
- The PI has performed a benefit/risk assessment and this assessment supports continued therapy with mepolizumab. The subject's parents (or guardian) have given consent and the subject has given assent for continued treatment

**Section 6.3, Dosage and Administration**

Original text:

## Dosage and Administration

Enrolled subjects in this study will be dosed with the following treatment:

| **Treatment Arm** | **SC dose** |
|---|---|
| Mepolizumab 40 mg SC upper arm or thigh | Mepolizumab 40 mg SC<br>For subjects < 40 kg bodyweight at Visit 2 (Week 0) |
| Mepolizumab 100 mg SC upper arm or thigh | Mepolizumab 100mg SC<br>For subjects ≥ 40 kg bodyweight at Visit 2 (Week 0) |

Site staff member assigned to the study will be required to prepare the appropriate medication according to the study subject's treatment assignment. Subjects eligible to enter the study will be assigned to treatment based on bodyweight at Visit 2. Assigned dose will remain the same irrespective of bodyweight changes during the treatment phase.

Amended text:

## Dosage and Administration

### Pharmacokinetic/Pharmacodynamic Phase (Part A)

Enrolled subjects in this study will be dosed with the following treatment:

| **Treatment Arm** | **SC dose** |
|---|---|
| Mepolizumab 40 mg SC upper arm or thigh | Mepolizumab 40 mg SC<br>For subjects < 40 kg bodyweight at Visit 2 (Week 0) |
| Mepolizumab 100 mg SC upper arm or thigh | Mepolizumab 100mg SC<br>For subjects ≥ 40 kg bodyweight at Visit 2 (Week 0) |

## Long-Term Safety / Long-Term Pharmacodynamic Phase (Part B)

| Treatment Arm | SC dose |
|---|---|
| Mepolizumab 40mg SC upper arm or thigh | Mepolizumab 40 mg SC<br>For subjects <40 kg bodyweight at Visit 9 (Week 20) |
| Mepolizumab 100mg SC upper arm or thigh | Mepolizumab 100mg SC<br>For subjects bodyweight at Visit 9 (Week 20) or from the time that bodyweight reaches 40 kg) |

**Preparation of Investigational Product (Part A and Part B)**

Site staff member assigned to the study will be required to prepare the appropriate medication according to the study subject's treatment assignment. Subjects eligible to enter the study will be assigned to treatment based on bodyweight at Visit 2. Assigned dose will remain the same irrespective of bodyweight changes during the treatment phase.

**Section 6.8, Treatment After Completion of Part A**

Original Text:

## Treatment after the End of the Study

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

Subjects who are considered to be at risk of experiencing a life-threatening exacerbation of their asthma or whose functional health status will become significantly worse on regular basis if returned to standard of care may be eligible for an OLE study. If the subject is likely to benefit from continued mepolizumab treatment, as judged by the investigator and agreed by GSK, the subject will be offered the opportunity to enrol in an extended treatment study with mepolizumab following the Follow-up (Visit 8).

Amended Text:

## Treatment after the Completion of Part A

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

At the end of Part A, a benefit/risk assessment will be performed by the Investigator and if this assessment supports continued therapy with mepolizumab and GSK has given approval, the subject will be offered the opportunity to enrol in Part B following the Part

A Follow-up visit (Visit 8). Part B will continue for 52 weeks of additional mepolizumab treatment.

At the end of Part B, subjects will return to usual care and will be prescribed appropriate alternative asthma therapy, as required.

**Section 7, Study Assessments and Procedures:**

Addition of Time & Events Table 4 for Part B:

Additional text:

**Table 4 Time and Events Table Long-Term Safety / Pharmacodynamic Phase (Part B)**

| Procedure | Eligibility Check / First Dose | | | | | | | | | | | | | Exit Visit | Follow-up | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | |
| Week of Study (visit window ± 5 days) | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | 80 | |
| | | | | | | | | | | | | | | | | |
| **Subject Screen** | | | | | | | | | | | | | | | | |
| Informed consent | X[1] | | | | | | | | | | | | | | | |
| Inclusion and exclusion criteria | X[1] | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| **Safety Assessments** | | | | | | | | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hematology (including eosinophils) | X | | | X | | | X | | | X | | | X | X | X | X |
| Clinical Chemistry | X | | | X | | | X | | | X | | | X | X | | X |
| 12-lead ECG | | | | | | | | | | | | | | X | | X |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Bodyweight | X | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | | | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Cardiovascular events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Liver events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | | | | | | | | | | | | | | |
| **Laboratory Assessments** | | | | | | | | | | | | | | | | |
| Urinalysis | X[1] | | | | | X | | | | | | | | X | | X |
| Pregnancy Test | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U |

| Procedure | Eligibility Check / First Dose | | | | | | | | | | | | | Exit Visit | Follow-up | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | |
| Week of Study (visit window ± 5 days) | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | 80 | |
| Blood sample for immunogenicity | | | | | | | X | | | | | | X | | X[6] | X[5] |
| | | | | | | | | | | | | | | | | |
| **Outcomes Assessments** | | | | | | | | | | | | | | | | |
| FEV1 | X[1] | | | X | | | X | | | X | | | X | X | X | X |
| ACQ-7 | X[1] | | | X | | | X | | | X | | | X | X | X | X |
| C-ACT | X[1] | | | X | | | X | | | X | | | X | X | X | X |
| Assessment of exacerbation | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | | | | | | | | | | | | | | |
| **Investigational Product** | | | | | | | | | | | | | | | | |
| Mepolizumab SC dose administered | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| | | | | | | | | | | | | | | | | |
| **Study Administration** | | | | | | | | | | | | | | | | |
| Email to GSK Operational Lead | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Complete eCRF | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

1. Bodyweight will be measured at Visit 9 and at each visit until such time as the subject reaches 40kg in weight. Subjects with bodyweight ≥40Kg at Visit 9 will not be weighed again during Part B.

**Section 7.5, Immunogenicity**

Original Text:

## Immunogenicity

Blood samples will be collected for the determination of anti-mepolizumab antibodies, prior to dosing at Visit 2 (Week 0), and subsequently at Visit 7 (Week 16), and at Visit 8 (Week 20).

Amended Text:

## Immunogenicity

Blood samples will be collected for the determination of anti-mepolizumab antibodies, prior to dosing at Visit 2 (Week 0), and subsequently at Visit 7 (Week 16), and at Visit 8 (Week 20).

For subjects who had a positive neutralizing antibody response at the Follow-up (Visit 8) (or last study visit at which immunogenicity was assessed if the Follow-up (Visit 8) immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-mepolizumab antibodies at least 4 months after the last dose of study drug in Part A.

In Part B, immunogenicity samples will be collected prior to dosing at Visit 15 (week 44), Visit 21 (week 68) and at Follow-up Visit 23 (week 80).

**Section 7.6, Forced Expiratory Volume (FEV1)**

Original Text:

## Forced Expiratory Volume-1 ($FEV_1$)

To permit investigator staff completion of the ACQ-7 questionnaire (Section 7.7 below) spirometry will be conducted, using the site's own equipment at the visits specified in the Time and Events schedule (Table 3). The spirometer should meet American Thoracic Society standards and produce a printout of all data generated, which should be stored in the subject's notes. The spirometer should be calibrated in accordance with the manufacturer's instructions and a calibration log maintained. Spirometry must be performed at the same time (±1 hour) of the Visit 2 spirometry. Subjects should try to withhold short-acting beta-2-agonists (SABAs) for ≥6 hours and LABAs for ≥12 hours prior to clinic visit, if possible. Assessments to be recorded will include $FEV_1$, and FVC. For predicted $FEV_1$ values, reference is made to the multi-ethnic reference values for spirometry for the 3-95-yr age range: using the Global Lung Function Initiative 2012 equations and look-up tables (Quanjer, 2012). A link to a simple online tool for calculating the percent predicted $FEV_1$ is provided in the Study Reference Manual.

Amended Text:

## Forced Expiratory Volume-1 ($FEV_1$)

To permit investigator staff completion of the ACQ-7 questionnaire (Section 7.7 below) spirometry will be conducted, using the site's own equipment at the visits specified in the Time and Events schedule (Table 3 and Table 4). The spirometer should meet American Thoracic Society standards and produce a printout of all data generated, which should be stored in the subject's notes. The spirometer should be calibrated in accordance with the manufacturer's instructions and a calibration log maintained. Spirometry must be performed at the same time (±1 hour) of the Visit 2 spirometry. Subjects should try to withhold short-acting beta-2-agonists (SABAs) for ≥6 hours and LABAs for ≥12 hours prior to clinic visit, if possible. Assessments to be recorded will include $FEV_1$, and FVC. For predicted $FEV_1$ values, reference is made to the multi-ethnic reference values for spirometry for the 3-95-yr age range: using the Global Lung Function Initiative 2012 equations and look-up tables (Quanjer, 2012). A spreadsheet calculator will be provided for calculating percent predicted $FEV_1$

**Section 9.2, Sample Size Considerations**

Additional paragraph:

Patients who complete Part A and who meet the eligibility criteria for Part B will be allowed to participate in Part B and no specific sample size requirements are defined.

**Section 9.3 Data Analysis Considerations**

Original Text:

## Data Analysis Considerations

### Analysis Populations

#### Intent to Treat Population

All subjects receiving at least one dose of study medication will be included in the safety population.

#### Pharmacokinetic Population

All subjects receiving at least one dose of mepolizumab and having at least one blood sample with measurable mepolizumab plasma concentration taken will be included in the pharmacokinetic population.

#### Pharmacodynamic Population (Blood Eosinophils)

All subjects receiving at least one dose of mepolizumab and having at least one blood sample taken for blood eosinophil count post dosing will be included in the pharmacodynamic population.

Interim Analysis

No interim analysis is planned.

Amended Text:

## Data Analysis Considerations

### Analysis Populations Part A

#### Safety Population Part A

All subjects receiving at least one dose of study medication beginning at Visit 2 will be included in the safety population for Part A analyses.

#### Pharmacokinetic Population Part A

All subjects receiving at least one dose of mepolizumab beginning at Visit 2 and having at least one blood sample taken at Visit 3 or thereafter with measurable mepolizumab plasma concentration will be included in the pharmacokinetic population for Part A analyses.

#### Pharmacodynamic Population (Blood Eosinophils) Part A

All subjects receiving at least one dose of mepolizumab beginning at Visit 2 and having at least one blood sample taken for blood eosinophil count post dosing at Visit 2 will be included in the pharmacodynamic population (blood eosinophils) for Part A analyses.

#### Pharmacodynamic Population (Outcome Assessments) Part A

All subjects receiving at least one dose of mepolizumab beginning at Visit 2 and having at least one assessment of pharmacodynamic outcomes (ACQ, ACT, asthma exacerbation, or $FEV_{1,}$) post dosing at Visit 2 will be included in the pharmacodynamic population (outcomes) for Part A analyses.

#### Safety Population Part B

All subjects receiving at least one dose of study medication beginning at Visit 9 will be included in the safety population for Part B analyses.

#### Pharmacodynamic Population (Blood Eosinophils) Part B

All subjects receiving at least one dose of mepolizumab beginning at Visit 9 and having at least one blood sample taken for blood eosinophil count post dosing at Visit 9 will be included in the pharmacodynamic population (blood eosinophils) for Part B analyses.

#### Pharmacodynamic Population (Outcome Assessments) Part B

All subjects receiving at least one dose of mepolizumab beginning at Visit 9 and having at least one assessment of pharmacodynamic outcomes (ACQ, ACT, asthma

exacerbation, or $FEV_{1,}$) post dosing at Visit 9 will be included in the pharmacodynamic population (outcomes) for Part B analyses.

### Interim Analysis

A full interim analysis is planned at the completion of the Pharmacokinetic/Pharmacodynamic Phase (Part A) of this study. All eCRF data will be monitored, queried, and a soft-database lock will be performed on all subject data through Visit 8 following last subject achieving Visit 8. A statistical output will be prepared in accordance with all study objective and endpoints for Part A.

**Section 9.5, Key Elements of Analysis Plan (Part B):**

Additional Text:

## Key Elements of Analysis Plan (Part B)

### Primary Analysis

The incidence in adverse events, frequency of positive anti-mepolizumab antibodies, and clinically significant changes in laboratory parameters and vital signs will be summarised using descriptive statistics.

### Secondary Analyses

Blood eosinophil count, the primary pharmacodynamic endpoint, will be log transformed prior to analysis and will also be summarised using descriptive statistics.

Secondary endpoints including ACQ-7, C-ACT will be summarised using descriptive statistics, Confidence intervals will be presented when appropriate. The analysis schema will be outlined in the RAP.

**Section 10.7, Provision of Study Results to Investigators**

Original Text:

A manuscript will be progressed for publication in the scientific literature.

Amended Text:

One or more manuscripts will be progressed for publication in the scientific literature.

## Protocol Amendment 03

**Section1, Synopsis, Treatment Arms and Duration, Part A:**

Original Text:

**Part A Treatment:** Those subjects meeting all of the inclusion/exclusion criteria by Visit 2 will receive mepolizumab 40 or 100 mg SC, depending on subject bodyweight (40 mg for subjects <40 kg and 100 mg for subjects ≥ 40 kg). Subjects will receive their first dose of mepolizumab at Visit 2 and enter into the Treatment phase of the study. Subjects shall be observed for a minimum of 60 minutes in the clinic following each injection. Those subjects who enter the run-in period but do not meet all inclusion/exclusion criteria will be deemed Run-in failures and will not be dosed in the study. The reason for any Run-in failure will be recorded in the eCRF.

During the Part A Treatment phase, all subjects will receive mepolizumab 40 or 100 mg SC, depending on subject bodyweight, at week 0 (Visit 2), week 4 (Visit 3) and week 8 (Visit 4) which will provide therapeutic coverage through to week 12 (Visit 6/End of Therapy Visit). Visit 6 will mark the end of the treatment phase.

Amended Text:

**Part A Treatment:** Those subjects meeting all of the inclusion/exclusion criteria by Visit 2 will receive mepolizumab 40 or 100 mg SC, depending on subject bodyweight (40 mg for subjects <40 kg and 100 mg for subjects ≥ 40 kg). Subjects will receive their first dose of mepolizumab at Visit 2 and enter into the Treatment phase of the study. Subjects shall be observed for a minimum of 60 minutes in the clinic following each injection. Safety monitoring of subjects will occur during SC administration and for 1 hour after the three administrations in Part A and then follow monitoring policies for the center in Part B. Such monitoring will include general safety monitoring including monitoring for both systemic hypersensitivity (i.e., allergic/IgE-mediated and non-allergic) and local site reactions. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of mepolizumab, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the patient 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.

Those subjects who enter the run-in period but do not meet all inclusion/exclusion criteria will be deemed Run-in failures and will not be dosed in the study. The reason for any Run-in failure will be recorded in the eCRF.

During the Part A Treatment phase, all subjects will receive mepolizumab either 40mg (subjects <40kg at Visit 2) or 100 mg SC (subjects ≥40kg at Visit 2) at week 0 (Visit 2), week 4 (Visit 3) and week 8 (Visit 4) which will provide therapeutic coverage through to week 12 (Visit 6/End of Therapy Visit). Visit 6 will mark the end of the treatment phase.

**Section1, Synopsis, Treatment Arms and Duration, Part B:**

Original Text:

**Part B Treatment:** Those subjects meeting the eligibility criteria for the long-term phase of the study at Visit 9 will receive mepolizumab 40 or 100 mg SC, (depending on subject bodyweight measured at Visit 9; 40 mg for subjects <40 kg and 100 mg for subjects ≥ 40 kg). Subjects shall be observed for a minimum of 60 minutes in the clinic following injection at Visit 9 and at subsequent visits subjects should be monitored according to standard practice at the site. From Visit 10 onwards subjects will receive the same dose of mepolizumab at 4-weekly intervals for a total of 48 weeks. Subjects with bodyweight <40 kg at Visit 9 should be weighed at each subsequent visit and have their dose adjusted once their bodyweight exceeds 40 kg.

Amended Text:

**Part B Treatment:** Those subjects meeting the eligibility criteria for the long-term phase of the study at Visit 9 will receive mepolizumab 40 or 100 mg SC, (depending on subject bodyweight measured at Visit 9; 40 mg for subjects <40 kg and 100 mg for subjects ≥ 40 kg). Subjects should be monitored post-SC administration according to standard practice at the site. From Visit 10 onwards subjects will receive mepolizumab at 4-weekly intervals for a total of 48 weeks. Subjects with bodyweight <40 kg at Visit 9 should be weighed at each subsequent visit and have their dose adjusted to 100mg once their bodyweight reaches 40 kg. Subjects weighing ≥40kg at Visit 9 will receive the 100mg dose at all subsequent treatment visits and will not be weighed again.

**Section 4 Study Design, Part A Treatment:**

Original Text:

**Treatment:** Those subjects meeting all of the inclusion/exclusion criteria by Visit 2 will receive mepolizumab 40 or 100 mg SC, depending on subject bodyweight (40 mg for subjects <40 kg and 100 mg for subjects ≥ 40 kg). Subjects will receive their first dose of mepolizumab at Visit 2 and enter into the Treatment phase of the study. Subjects shall be observed for a minimum of 60 minutes in the clinic following each injection. Those subjects who enter the run-in period but do not meet all inclusion/exclusion criteria will be deemed Run-in failures and will not be dosed in the study. The reason for any Run-in failure will be recorded in the eCRF.

During the Treatment phase, all subjects will receive mepolizumab 40 or 100 mg SC, depending on subject bodyweight, at week 0 (Visit 2), week 4 (Visit 3) and week 8 (Visit 4). These doses should provide therapeutic coverage through to week 12 (Visit 6/End of Therapy Visit). Visit 6 will mark the end of the treatment phase.

Amended Text:

**Treatment:** Those subjects meeting all of the inclusion/exclusion criteria by Visit 2 will receive mepolizumab 40 or 100 mg SC, depending on subject bodyweight (40 mg for subjects <40 kg and 100 mg for subjects ≥ 40 kg). Subjects will receive their first dose of

mepolizumab at Visit 2 and enter into the Treatment phase of the study. Subjects shall be observed for a minimum of 60 minutes in the clinic following each injection. Safety monitoring of subjects will occur during SC administration and for 1 hour after the three administrations in Part A and then follow monitoring policies for the center in Part B. Such monitoring will include general safety monitoring including monitoring for both systemic hypersensitivity (i.e., allergic/IgE-mediated and non-allergic) and local site reactions. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of mepolizumab, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the patient 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.

Those subjects who enter the run-in period but do not meet all inclusion/exclusion criteria will be deemed Run-in failures and will not be dosed in the study. The reason for any Run-in failure will be recorded in the eCRF.

During the Treatment phase, all subjects will receive mepolizumab either 40mg SC (subjects <40kg at Visit 2) or 100 mg SC (subjects ≥40kg at Visit 2) at week 0 (Visit 2), week 4 (Visit 3) and week 8 (Visit 4). These doses should provide therapeutic coverage through to week 12 (Visit 6/End of Therapy Visit). Visit 6 will mark the end of the treatment phase.

**Section 4 Study Design, Part A Follow-up:**

Original Text:

**Follow-up:** Following completion of Visit 6, subjects will enter into the Follow-up phase which will consist of two additional visits at weeks 16 (Visit 7) and 20 (Visit 8).For subjects who had a positive neutralizing antibody response at the Follow-up (Visit 8) (or last study visit at which immunogenicity was assessed if the Follow-up (Visit 8) immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-mepolizumab antibodies at least 4 months after the last dose of study drug.

Amended Text:

**Follow-up:** Following completion of Visit 6, subjects will enter into the Follow-up phase which will consist of two additional visits at weeks 16 (Visit 7) and 20 (Visit 8).For subjects who had a positive anti-mepolizumab antibody response at the Follow-up (Visit 8) (or last study visit at which immunogenicity was assessed if the Follow-up (Visit 8) immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-mepolizumab antibodies at least 4 months after the last dose of study drug in Part A or upon completion of Part A, whichever is later.

**Section 4 Study Design Long Term treatment:**

Original Text:

**Long-Term Treatment:** Those subjects meeting the eligibility criteria for the long-term phase of the study at Visit 9 will receive mepolizumab 40 or 100 mg SC, (depending on subject bodyweight measured at Visit 9; 40 mg for subjects <40 kg and 100 mg for subjects ≥ 40 kg). Subjects shall be observed for a minimum of 60 minutes in the clinic following injection at Visit 9 and at subsequent visits subjects should be monitored according to standard practice at the site.

Amended Text:

**Long-Term Treatment:** Those subjects meeting the eligibility criteria for the long-term phase of the study at Visit 9 will receive mepolizumab 40 or 100 mg SC, (depending on subject bodyweight measured at Visit 9; 40 mg for subjects <40 kg and 100 mg for subjects ≥ 40 kg). Subjects should be monitored post-SC administration according to standard practice at the site.

**Section 4.1 Overall Design, Part B:**

Original Text:

This is a long-term safety / pharmacodynamic phase in which extended treatment will be offered on an optional basis to those subjects eligible for continued treatment. Subjects will receive either 40 or 100mg depending on subject bodyweight, administered subcutaneously at 4-weekly intervals for a total of 52 weeks.

Amended Text:

This is a long-term safety / pharmacodynamic phase in which extended treatment for a further 52 weeks will be offered on an optional basis to those subjects eligible for continued treatment. Subjects will receive either 40 or 100mg depending on subject bodyweight, administered SC every 4 weeks to subjects with severe eosinophilic asthma aged 6-11 years. At the end of the 52 weeks extended treatment in Part B, subjects will have an Exit Visit 4 weeks after last dose and a Follow-Up visit 12 weeks after last dose.

**Section 4.2, Treatment Arms and Duration:**

Original Text:

## Pharmacokinetic/Pharmacodynamic Phase (Part A)

Enrolled subjects in this study will be assigned to receive one of the following treatments:

| **Treatment Arm** | **SC dose** |
|---|---|
| Mepolizumab 40 mg SC upper arm or thigh | Mepolizumab 40 mg SC<br>For subjects <40 kg bodyweight at Visit 2 (Week 0) |
| Mepolizumab 100 mg SC upper arm or thigh | Mepolizumab 100mg SC<br>For subjects ≥40 kg bodyweight at Visit 2 (Week 0) |

**Part A Pre-Screening/Screening/Run-in**: Subjects will attend an initial Pre-screening visit to assess their willingness and eligibility to participate in the study. The Pre-screening visit will include: informed consent, demography, exacerbations and concomitant medications. Visit 1(Screening) will include a physical exam, screening laboratory tests, screening ECG and other assessments to determine suitability to participate in this study. The Pre-screening visit may be conducted at the same clinic visit as Visit 1 (Screening). Subjects meeting the Visit 1(Screening) eligibility criteria will enter a Run-in period of up to 2 weeks to allow for receipt and review of the lab results and ECG.

**Part A Treatment:** Those subjects meeting all of the inclusion/exclusion criteria by Visit 2 will receive mepolizumab 40 or 100 mg SC, depending on subject bodyweight (40 mg for subjects <40 kg and 100 mg for subjects ≥ 40 kg). Subjects will receive their first dose of mepolizumab at Visit 2 and enter into the Treatment phase of the study. Subjects shall be observed for a minimum of 60 minutes in the clinic following each injection. Those subjects who enter the run-in period but do not meet all inclusion/exclusion criteria will be deemed Run-in failures and will not be dosed in the study. The reason for any Run-in failure will be recorded in the eCRF.

During the Part A Treatment phase, all subjects will receive mepolizumab 40 or 100 mg SC, depending on subject bodyweight measured at Visit 2, at week 0 (Visit 2), week 4 (Visit 3) and week 8 (Visit 4) which will provide therapeutic coverage through to week 12 (Visit 6/End of Therapy Visit). Visit 6 will mark the end of the treatment phase.

Subjects will visit the clinic at week 9 (Visit 5) to allow for measurement of the approximate peak mepolizumab concentration.

**Part A Follow-up:** Following completion of Visit 6, subjects will enter into the Follow-up phase which will consist of two additional visits at weeks 16 (Visit 7) and 20 (Visit 8).

The total duration of Part A will be 22 weeks and will include a run-in period of 1-2 weeks, a treatment period of 12 weeks and a follow-up phase of 8 weeks. A subject will be considered having completed Part A if the subject completes all phases including the follow-up phase (Visit 8). A subject will be defined as evaluable for Part A if the subject received all 3 planned doses of mepolizumab and has completed all pharmacokinetic and pharmacodynamic assessments through to study Visit 6.

### Long-Term Safety / Long Term Pharmacodynamic Phase (Part B)

| **Treatment Arm** | **SC dose** |
|---|---|
| Mepolizumab 40mg SC upper arm or thigh | Mepolizumab 40 mg SC<br>For subjects <40 kg bodyweight at Visit 9 (Week 20). From visit 10, subjects should be weighed at each visit until bodyweight reaches 40kg when the dose should be adjusted to 100mg. From this time onwards, the dose will not be adjusted again. |
| Mepolizumab 100mg SC upper arm or thigh | Mepolizumab 100mg SC<br>For subjects bodyweight at Visit 9 (Week 20) or from the time that bodyweight reaches 40 kg |

Following Part A subjects will be evaluated for eligibility to continue into Part B of this study. For those subjects determined to be eligible and for whom appropriate informed consent/assent has been obtained there will be a Long-Term Safety / Pharmacodynamic Phase (Part B). Part B will include Treatment and Follow-up phases.

**Part B Treatment:** Those subjects meeting all of the Part B eligibility criteria by Visit 9 will receive mepolizumab 40 or 100 mg SC, depending on subject bodyweight at Visit 9 (40 mg for subjects <40 kg and 100 mg for subjects ≥ 40 kg). Subjects should be monitored post-SC administration according to standard practice at the site. From Visit 10 onwards subjects will receive the same dose of mepolizumab at 4-weekly intervals. Subjects with bodyweight <40 kg at Visit 9 should be weighed at each visit and have their dose adjusted once their bodyweight exceeds 40 kg. Once a subject starts treatment with the 100mg dose, the dose will not be adjusted further even if the subject's bodyweight should drop below 40kg.

**Part B Follow-up:** Following completion of Visit 22, subjects will enter into the Follow-up phase which will consist of an additional visit at week 80 (Visit 23).

Amended Text:

## Pharmacokinetic/Pharmacodynamic Phase (Part A)

Enrolled subjects in this study will be assigned to receive one of the following treatments:

| **Treatment Arm** | **SC dose** |
|---|---|
| Mepolizumab 40 mg SC upper arm or thigh | Mepolizumab 40 mg SC<br>For subjects <40 kg bodyweight at Visit 2 (Week 0) |
| Mepolizumab 100 mg SC upper arm or thigh | Mepolizumab 100mg SC<br>For subjects ≥40 kg bodyweight at Visit 2 (Week 0) |

The total duration of Part A will be 22 weeks and will include a run-in period of 1-2 weeks, a treatment period of 12 weeks and a follow-up phase of 8 weeks.

## Long-Term Safety / Long Term Pharmacodynamic Phase (Part B)

| **Treatment Arm** | **SC dose** |
|---|---|
| Mepolizumab 40mg SC upper arm or thigh | Mepolizumab 40 mg SC<br>For subjects <40 kg bodyweight at Visit 9 (Week 20). From visit 10, subjects should be weighed at each visit until bodyweight reaches 40kg when the dose should be adjusted to 100mg. From this time onwards, the dose will not be adjusted again. |
| Mepolizumab 100mg SC upper arm or thigh | Mepolizumab 100mg SC<br>For subjects bodyweight at Visit 9 (Week 20) or from the time that bodyweight reaches 40 kg |

Following completion of Part A subjects will be evaluated for eligibility to continue into Part B of this study. For those subjects determined to be eligible and for whom appropriate informed consent/assent has been obtained there will be a Long-Term Safety / Pharmacodynamic Phase (Part B). The total duration of Part B is approximately 60 weeks.

**Section 4.3: Type and Number of Subjects:**

Original Text:

Approximately 40 male or female subjects with severe eosinophilic asthma, aged 6 to 11 years inclusive at screening (Visit 1), will be screened to achieve approximately 28 eligible subjects entering the Part A treatment phase to allow availability of 20 evaluable subjects, with a minimum of six subjects enrolled in the < 40 kg bodyweight group. An evaluable subject is defined to be a subject who has received all three doses of mepolizumab and has all PK and PD assessments completed through to Visit 6 (week 12).

Amended Text:

Approximately 40 male or female subjects with severe eosinophilic asthma, aged 6 to 11 years inclusive at screening (Visit 1), will be screened to achieve approximately 28 eligible subjects entering the Part A treatment phase to allow availability of 20 evaluable subjects, with a minimum of six subjects enrolled in the < 40 kg bodyweight group. An evaluable subject is defined to be a subject who has received all three doses of mepolizumab and has all PK and PD assessments completed through to Visit 6 (week 12).

Sample size is not determined for Part B. All subjects who completed Part A and meet the eligibility criteria for Part B will be allowed to participate in Part B.**Section 5.1: Inclusion Criteria for Part A:**

Original Text:

4. A well-documented requirement for regular treatment with inhaled corticosteroid (≥400 µg/day fluticasone propionate (DPI) or equivalent daily) in the 12 months prior to Visit 1 with or without maintenance oral corticosteroids (OCS).

Amended Text:

4. A well-documented requirement for regular treatment with inhaled corticosteroid (>200 µg/day fluticasone propionate (DPI) or equivalent daily) with or without maintenance oral corticosteroids (OCS). The ICS dose should represent medium or high dose in children aged 6-11 years of age [GINA, 2015].

**Section 5.1: Inclusion Criteria for Part A:**

Original Text:

7. Previously confirmed history of two or more exacerbations requiring treatment with systemic CS (intramuscular (IM), intravenous, or oral), in the 12 months prior to visit 1, despite the use of high-dose inhaled corticosteroids (ICS). For subjects receiving maintenance CS, the CS treatment for the exacerbations must have been a two-fold increase or greater in the dose.

Amended Text:

7. Previously confirmed history of two or more exacerbations requiring treatment with systemic CS (intramuscular (IM), intravenous, or oral), in the 12 months prior to visit 1, despite the use of inhaled corticosteroids (ICS). For subjects receiving maintenance OCS treatment for the exacerbations must have been a two-fold increase or greater in the CS dose.

**Section 5.1: Inclusion Criteria for Part A:**

Original Text:

9. Male or female: Females of childbearing potential must commit to consistent and correct use of an acceptable method of contraception (see Appendix 7) for the duration of the trial and for 4 months after the last dose of investigational product. A urine pregnancy test is required of girls of childbearing potential. This test will be performed at the initial screening visit (Visit 1) and will be performed at each scheduled study visit prior to the administration of investigational product, and during the Early Withdrawal and Follow-up Visits.

Amended Text:

9. Male or female: Females of childbearing potential must commit to consistent and correct use of an acceptable method of contraception (see Appendix 7) for the duration of the trial and for 4 months after the last dose of investigational product. A urine pregnancy test is required of girls of childbearing potential. This test will be performed at the initial screening visit (Visit 1) and will be performed at each scheduled treatment visit prior to the administration of investigational product, and during the Exit Visit, Early Withdrawal and Follow-up Visits.

**Section 5.1: Inclusion Criteria Part A**

Original Text:

6. $FEV_1$: Persistent airflow obstruction at either visit 1 or Visit 2 ($FEV_1$ performed prior to first dose of study medication) as indicated by:

    - A pre-bronchodilator FEV1 <110% predicted OR
    - FEV1:FVC ratio < 0.8

Amended Text:

6. $FEV_1$: Persistent airflow obstruction at either visit 1 or Visit 2 ($FEV_1$ performed prior to first dose of study medication) as indicated by:

    - A pre-bronchodilator FEV1 <110% predicted (Quanjer, 2012) OR
    - FEV1:FVC ratio < 0.8

**Section 5.2: Exclusion Criteria for Part A:**

Additional exclusion criterion:

5. A positive Hepatitis B Surface Antigen or Hepatitis C antibody at Visit 1

**Section 5.5: Withdrawal/Stopping Criteria**

Original Text:

Subjects are also free to withdraw consent to participate in the study at anytime. Every effort should be made to have them return to the clinic for an Exit Visit (See Table 3 and Table 4) and to return all study related materials. In those instances where the subject specifies the reason for withdrawal of consent, this information will be captured in the eCRF.

A subject should only be designated as lost to follow-up if the site is unable to establish contact with the subject after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc).

For both Part A and Part B of this study an Exit Visit should be conducted within 4 weeks of the last dose received. In the event a subject withdraws at, or during, a scheduled visit, an Exit Visit is not required. However, all study procedures scheduled at an Exit Visit must be performed at this visit instead. A Follow-up Visit should be scheduled 12 weeks after the last dose of investigational product.

Any data collected up until the point of withdrawal will be used in the analyses. For those subjects completing the follow-up visit, any safety data collected post withdrawal through follow-up will be summarised.

Amended Text:

Subjects are also free to withdraw consent to participate in the study at anytime. Every effort should be made to have them return to the clinic for an Early Withdrawal Visit (See Table 3 and Table 4) and to return all study related materials. In those instances where the subject specifies the reason for withdrawal of consent, this information will be captured in the eCRF.

A subject should only be designated as lost to follow-up if the site is unable to establish contact with the subject after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc).

For both Part A and Part B of this study an Exit Visit should be conducted within 4 weeks of the last dose received. In the event that a subject withdraws at, or during, a scheduled visit, an Early Withdrawal Visit should be performed at this visit instead. A Follow-up Visit should then be scheduled 12 weeks after the last dose of investigational product (Visit 8 or Visit 23 for subjects withdrawing from study Parts A or B, respectively)

Any data collected up until the point of withdrawal will be used in the analyses.

**Section 6.2: Dosage and Administration:**

Original Text:

| **Treatment Arm** | **SC dose** |
|---|---|
| Mepolizumab 40mg SC upper arm or thigh | Mepolizumab 40 mg SC<br>For subjects <40 kg bodyweight at Visit 9 (Week 20) |
| Mepolizumab 100mg SC upper arm or thigh | Mepolizumab 100mg SC<br>For subjects bodyweight at Visit 9 (Week 20) or from the time that bodyweight reaches 40 kg) |

Site staff member assigned to the study will be required to prepare the appropriate medication according to the study subject's treatment assignment. Subjects eligible to enter the study will be assigned to treatment based on bodyweight at Visit 2. Assigned dose will remain the same irrespective of bodyweight changes during the treatment phase.

Prior to administration, each vial of mepolizumab will need to be reconstituted and swirled gently to enable complete dissolution of the product. Detailed instructions can be found within the Study Reference Manual (SRM). Subjects assigned to the 40 mg treatment group will receive 0.4 mL of reconstituted mepolizumab. Subjects assigned to the 100 mg treatment group will receive 1.0 mL of reconstituted mepolizumab. Injected volume may be split between two injection sites for subjects receiving 100 mg (1.0 mL) and given as 2x0.5mL injections. Investigator should consider the use of a local anaesthetic at the injections sites.

All subjects in this open-label, non-randomized study entering the treatment phase will be assigned to a unique treatment number in accordance with the schedule generated by Clinical Statistics, prior to the start of the study.

Amended Text:

| **Treatment Arm** | **SC dose** |
|---|---|
| Mepolizumab 40mg SC upper arm or thigh | Mepolizumab 40 mg SC<br>For subjects with bodyweight <40 kg at Visit 9 (Week 20) and at any subsequent visits |
| Mepolizumab 100mg SC upper arm or thigh | Mepolizumab 100mg SC<br>For subjects with bodyweight ≥40kg at Visit 9 (Week 20) or from the visit at which bodyweight reaches 40 kg |

Site staff member assigned to the study will be required to prepare the appropriate medication according to the study subject's treatment assignment. Subjects eligible to enter the study will be assigned to treatment based on bodyweight at Visit 2. Assigned dose will remain the same irrespective of bodyweight changes during the treatment phase of Part A.

Prior to administration, each vial of mepolizumab will need to be reconstituted and swirled gently to enable complete dissolution of the product. Detailed instructions can be found within the Study Reference Manual (SRM). Subjects assigned to the 40 mg treatment group will receive 0.4 mL of reconstituted mepolizumab. Subjects assigned to the 100 mg treatment group will receive 1.0 mL of reconstituted mepolizumab. Injected volume may be split between two injection sites for subjects receiving 100 mg (1.0 mL) and given as 2x0.5mL injections. Investigator should consider the use of a local anaesthetic at the injections sites.

**Section 4: Study Design:**

Original Text:

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 (Table 3), are essential and required for study conduct.

Amended Text:

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 (Table 3 and Table 4), are essential and required for study conduct.

Section 6.8 Treatment After the Completion of Part A and Part B

Original wording

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

At the end of Part A, a benefit/risk assessment will be performed by the Investigator and if this assessment supports continued therapy with mepolizumab and GSK has given approval, the subject will be offered the opportunity to enrol in Part B following the Part A Follow-up visit (Visit 8). Part B will continue for 52 weeks of additional mepolizumab treatment.

Amended wording:

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

At the end of Part A, a benefit/risk assessment will be performed by the Investigator and if this assessment supports continued therapy with mepolizumab the subject will be offered the opportunity to enrol in Part B following the Part A Follow-up visit (Visit 8). Part B will continue for 52 weeks of additional mepolizumab treatment.

**Section 6.9.1: Permitted Medications and Non-Drug Therapies:**

Original Text:

All concomitant medications taken during the study will be recorded on the electronic Case Report Form (eCRF). The minimum requirement is that drug name and all dates and times of administration are to be recorded.

Amended Text:

All concomitant medications taken during the study will be recorded on the electronic Case Report Form (eCRF). The minimum requirement is that drug name and all dates ~~and times~~ of administration are to be recorded.

**Section 6.9.1: Permitted Medications and Non-Drug Therapies:**

Original Text:

All concomitant medications taken during the study will be recorded on the electronic Case Report Form (eCRF). The minimum requirement is that drug name and all dates and times of administration are to be recorded.

- Existing stable asthma therapy (inhaled fluticasone propionate (DPI) or equivalent, total daily dose greater than or equal to 400 mcg or equivalent daily) will be permitted during the run-in and active treatment period.
- Current treatment with an additional controller medication for at least 3 months [e.g., long-acting beta-2-agonist (LABA), leukotriene receptor antagonist (LTRA), or theophylline].
- Short acting beta 2 agonist inhalation aerosol (albuterol/salbutamol) will be permitted for symptomatic relief of asthma symptoms.
- Low potency topical corticosteroids (≤1% hydrocortisone).
- Acetaminophen. .

Other concomitant medication may be considered on a case by case basis by the GSK Medical Monitor.

Amended Text:

All concomitant medications taken during the study will be recorded on the electronic Case Report Form (eCRF). Asthma medications taken during the 12 months prior to Visit 1 should be recorded in the eCRF. The minimum requirement is that drug name and all dates of administration are to be recorded. Permitted medications include:

- Existing stable asthma therapy (inhaled fluticasone propionate (DPI) or equivalent, total daily dose greater than or equal to 200 mcg or equivalent daily) will be permitted during the run-in and active treatment period.
- Current treatment with an additional controller medication [e.g., long-acting beta-2-agonist (LABA), leukotriene receptor antagonist (LTRA), or theophylline] will be permitted during the run-in and active treatment period..
- Short acting beta 2 agonist inhalation aerosol (albuterol/salbutamol) will be permitted for symptomatic relief of asthma symptoms. Albuterol/salbutamol will be provided locally (except for US sites where GSK Global Supply Organisation will supply the rescue medication) and dispensed at each visit from Screening Visit 1, as required.
- Oral corticosteroids
- Low potency topical corticosteroids (≤1% hydrocortisone).
- Acetaminophen.

Other concomitant medication may be considered on a case by case basis by the GSK Medical Monitor.

No changes in the dose or regimen of baseline ICS and/or additional controller medication are permitted during the run-in period.

**Section 7: Table 3 Time and Events Table:**

Original Text:

| Procedure | Pre-Screen[1] | Screening | Treatment Period | | | | Exit Visit[3] | Follow-up | | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7[7] | 8[8] | |
| **Week of Study** (visit window ± 3 days, ±1 day Visit 5)) | Prior to or same day as Visit 1 | (up to 14 days prior to Visit 2) | 0 | 4 | 8 | 9 | 12 | 16 | 20 | |
| | | | | | | | | | | |
| **Subject Screen** | | | | | | | | | | |
| Informed consent | X | | | | | | | | | |
| Inclusion and exclusion criteria | | X | X | | | | | | | |
| Demography | X | | | | | | | | | |
| Medical history, including bronchodilator reversibility history[4] | | X | | | | | | | | |
| Past and current medical | | X | | | | | | | | |

| Procedure | Pre-Screen[1] | Screening | Treatment Period | | | | Exit Visit[3] | Follow-up | | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7[7] | 8[8] | |
| **Week of Study** (visit window ± 3 days, ±1 day Visit 5)) | Prior to or same day as Visit 1 | (up to 14 days prior to Visit 2) | 0 | 4 | 8 | 9 | 12 | 16 | 20 | |
| conditions | | | | | | | | | | |
| Asthma exacerbation history | | X | | | | | | | | |
| | | | | | | | | | | |
| **Safety Assessments** | | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X |
| Hematology (including eosinophils) | | X | X | X | X | X | X | X | X | X |
| Clinical Chemistry | | X | | X | X | | X | | X | X |
| 12-lead ECG | | X | | X | | | X | | | X |
| Vital signs | | X | X | X | X | X | X | X | X | X |
| Bodyweight | | | X | | | | | | | |
| Brief physical examination | | X | | | | | | | | |
| Adverse events | | X | X | X | X | X | X | X | X | X |
| Cardiovascular events | | X | X | X | X | X | X | X | X | X |
| Liver events | | X | X | X | X | X | X | X | X | X |
| | | | | | | | | | | |
| **Laboratory Assessments** | | | | | | | | | | |
| Urinalysis | | X | | | | | | | X | X |
| Pregnancy Test | | U | U[5] | U[5] | U[5] | | U | U | U | U |
| HBsAg and hepatitis C antibody | | X[6] | | | | | | | | |
| Serum IgE (total and specific) | | | X[5] | | | | | | | |
| PK blood sample | | | | X[5] | X[5] | X | X | X | X | X |
| IL5 serum sample | | | X[5] | | | | X | | | |
| Blood sample for immunogenicity | | | X[5] | | | | | X[7] | X[2] | X |
| | | | | | | | | | | |
| **Outcomes Assessments** | | | | | | | | | | |
| FEV1 | | X | X | X | X | | X | X | X | X |
| ACQ-7 | | | X | X | X | | X | X | X | X |
| C-ACT | | | X | X | X | | X | X | X | X |
| Assessment of exacerbation | X | X | X | X | X | X | X | X | X | X |
| | | | | | | | | | | |
| **Investigational Product** | | | | | | | | | | |
| Mepolizumab SC dose administered | | | X | X | X | | | | | |
| | | | | | | | | | | |
| **Study Administration** | | | | | | | | | | |
| Email to GSK Operational Lead | X | X | X | X | X | X | X | X | X | X |
| Complete eCRF | X | X | X | X | X | X | X | X | X | X |

9. Pre-screen must be completed prior to or on the same day as Screen Visit.
10. For subjects who had a positive anti-mepolizumab antibody response at the 12 week post-last-dose follow-up assessment an attempt will be made to obtain a serum sample for anti-mepolizumab antibodies at least 4 months after the last dose of study agent or upon completion of the study, whichever is later.
11. Exit visit may be completed 3 to 5 weeks post last dose. If more than 5 weeks has passed since the last dose, only perform Follow-up Visit.
12. Therapy history to include a detailed review of prior biologics received for treatment of asthma, including prior investigational anti-IL5 or anti-IL13 preparations.
13. During the treatment period, all lab samples and procedures should be obtained prior to study treatment administration.
14. A positive Hepatitis B Surface Antigen and Hepatitis C antibody is exclusionary
15. This immunogenicity sample must always be collected 12 weeks (± 7 days) post-last-dose of study treatment; therefore, for subjects who withdraw from study treatment early, this sample must be collected 12 weeks (± 7 days) after their confirmed last dose of study treatment (i.e., prior to Visit 8). In the event that this sample collection date coincides with an Early Withdrawal Visit, only one immunogenicity sample should be collected.
16. For subjects continuing into the long-term extension phase Part B, Visit 9 should be conducted on the same day as Visit 8 once all of the visit 8 assessments have been completed. .

**Table 4 Time and Events Table Long-Term Safety / Pharmacodynamic Phase (Part B)**

| Procedure | Eligibility Check / First Dose | | | | | | | | | | | | | Exit Visit | Follow-up | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | |
| Week of Study (visit window ± 5 days) | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | 80 | |
| | | | | | | | | | | | | | | | | |
| **Subject Screen** | | | | | | | | | | | | | | | | |
| Informed consent | X[1] | | | | | | | | | | | | | | | |
| Inclusion and exclusion criteria | X[1] | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| **Safety Assessments** | | | | | | | | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hematology (including eosinophils) [2] | X | | | X | | | X | | | X | | | X | X | X | X |
| Clinical Chemistry[2] | X | | | X | | | X | | | X | | | X | X | | X |
| 12-lead ECG | | | | | | | | | | | | | | X | | X |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Bodyweight | X | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | | | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Cardiovascular events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Liver events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | | | | | | | | | | | | | | |
| **Laboratory Assessments[2]** | | | | | | | | | | | | | | | | |
| Urinalysis | X[1] | | | | | X | | | | | | | | X | | X |
| Pregnancy Test | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U |
| Blood sample for immunogenicity[2] | | | | | | | X | | | | | | X | | X | X |
| | | | | | | | | | | | | | | | | |
| **Outcomes Assessments** | | | | | | | | | | | | | | | | |
| FEV1 | X[1] | | | X | | | X | | | X | | | X | X | X | X |
| ACQ-7 | X[1] | | | X | | | X | | | X | | | X | X | X | X |
| C-ACT | X[1] | | | X | | | X | | | X | | | X | X | X | X |
| Assessment of exacerbation | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| Procedure | Eligibility Check / First Dose | | | | | | | | | | | | | Exit Visit | Follow-up | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | |
| Week of Study (visit window ± 5 days) | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | 80 | |
| | | | | | | | | | | | | | | | | |
| **Investigational Product** | | | | | | | | | | | | | | | | |
| Mepolizumab SC dose administered | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| | | | | | | | | | | | | | | | | |
| **Study Administration** | | | | | | | | | | | | | | | | |
| Email to GSK Operational Lead | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Complete eCRF | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

4. Bodyweight will be measured at Visit 9 and at each visit until such time as the subject reaches 40kg in weight. Subjects with bodyweight ≥40Kg at Visit 9 will not be weighed again during Part B.

All laboratory samples should be collected prior to the administration of study medication

Amended text:

| Procedure | Pre-Screen[1] | Screening | Treatment Period | | | | Exit Visit[3] | Follow-up | | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7[7] | 8[8] | |
| **Week of Study** (visit window ± 3 days, ±1 day Visit 5)) | Prior to or same day as Visit 1 | (up to 14 days prior to Visit 2) | 0 | 4 | 8 | 9 | 12 | 16 | 20 | |
| | | | | | | | | | | |
| **Subject Screen** | | | | | | | | | | |
| Informed consent | X | | | | | | | | | |
| Inclusion and exclusion criteria | | X | X | | | | | | | |
| Demography | X | | | | | | | | | |
| Medical history, including bronchodilator reversibility history[4] | | X | | | | | | | | |
| Past and current medical conditions | | X | | | | | | | | |
| Asthma exacerbation history | | X | | | | | | | | |
| | | | | | | | | | | |
| **Safety Assessments** | | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X |
| Hematology (including eosinophils) | | X | X | X | X | X | X | X | X | X |
| Clinical Chemistry | | X | | X | X | | X | | X | X |
| 12-lead ECG | | X | | X | | | X | | | X |
| Vital signs | | X | X | X | X | X | X | X | X | X |
| Bodyweight | | | X | | | | | | | |
| Brief physical examination | | X | | | | | | | | |
| Adverse events | | X | X | X | X | X | X | X | X | X |
| Cardiovascular events | | X | X | X | X | X | X | X | X | X |
| Liver events | | X | X | X | X | X | X | X | X | X |
| | | | | | | | | | | |
| **Laboratory Assessments** | | | | | | | | | | |
| Urinalysis | | X | | | | | | | X | X |
| Pregnancy Test | | U | U[5] | U[5] | U[5] | | U | U | U | U |
| HBsAg and hepatitis C antibody | | X[6] | | | | | | | | |
| Serum IgE (total and specific) | | | X[5] | | | | | | | |
| PK blood sample | | | | X[5] | X[5] | X | X | X | X | X |
| IL5 serum sample | | | X[5] | | | | X | | | |
| Blood sample for immunogenicity[2,7] | | | X[5] | | | | | X | X[2] | X |
| | | | | | | | | | | |
| **Outcomes Assessments** | | | | | | | | | | |
| FEV1 | | X | X | X | X | | X | X | X | X |
| ACQ-7 | | | X | X | X | | X | X | X | X |
| C-ACT | | | X | X | X | | X | X | X | X |

| Procedure | Pre-Screen[1] | Screening | Treatment Period | | | | Exit Visit[3] | Follow-up | | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7[7] | 8[8] | |
| **Week of Study** (visit window ± 3 days, ±1 day Visit 5)) | Prior to or same day as Visit 1 | (up to 14 days prior to Visit 2) | 0 | 4 | 8 | 9 | 12 | 16 | 20 | |
| Assessment of exacerbation | X | X | X | X | X | X | X | X | X | X |
| | | | | | | | | | | |
| **Investigational Product** | | | | | | | | | | |
| Mepolizumab SC dose administered | | | X | X | X | | | | | |
| | | | | | | | | | | |
| **Study Administration** | | | | | | | | | | |
| Email to GSK Operational Lead | X | X | X | X | X | X | X | X | X | X |
| Complete eCRF | X | X | X | X | X | X | X | X | X | X |

1. Pre-screen must be completed prior to or on the same day as Screen Visit.
2. For subjects who had a positive anti-mepolizumab antibody response at the 12 week post-last-dose follow-up assessment (Visit 8) (or last study visit at which immunogenicity was assessed if the Follow-up (Visit 8) immunogenicity sample is not available) an attempt will be made to obtain a serum sample for anti-mepolizumab antibodies at least 4 months after the last dose of study drug in Part A or upon completion of Part A, whichever is later.
3. Exit visit should be performed as close as possible to the planned week 12 visit date.
4. Therapy history to include a detailed review of prior biologics received for treatment of asthma, including prior investigational anti-IL5 or anti-IL13 preparations.
5. During the treatment period, all lab samples and procedures should be obtained prior to study treatment administration.
6. A positive Hepatitis B Surface Antigen and Hepatitis C antibody is exclusionary
7. This immunogenicity sample must always be collected 12 weeks (± 7 days) post-last-dose of study treatment; therefore, for subjects who withdraw from study treatment early, this sample must be collected 12 weeks (± 7 days) after their confirmed last dose of study treatment (i.e., prior to Visit 8). In the event that this sample collection date coincides with an Early Withdrawal Visit, only one immunogenicity sample should be collected.
8. Visit 8 to be performed 12 weeks post last dose. For subjects continuing into the long-term extension phase Part B, Visit 9 should be conducted on the same day as Visit 8 once all of the visit 8 assessments have been completed. Assessments performed at Visit 8 that are also listed for Visit 9 should not be duplicated if Visit 8 and Visit 9 are performed on the same day.

## Table4 Time and Events Table Long-Term Safety / Pharmacodynamic Phase (Part B)

~~3. Exit visit may be completed 2 to 4 weeks post last dose. If more than 6 weeks has passed since the last dose, only perform Follow-up Visit.~~

| Procedure | Eligibility Check / First Dose | Treatment Period | | | | | | | | | | | | Exit Visit | Follow-up | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | |
| Week of Study (visit window ± 5 days) | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | 80 | |
| | | | | | | | | | | | | | | | | |
| **Subject Screen** | | | | | | | | | | | | | | | | |
| Informed consent | X[1] | | | | | | | | | | | | | | | |
| Inclusion and exclusion criteria | X[1] | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| **Safety Assessments** | | | | | | | | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hematology (including eosinophils) [2] | X | | | X | | | X | | | X | | | X | X | X | X |
| Clinical Chemistry[2] | X | | | X | | | X | | | X | | | X | X | | X |
| 12-lead ECG | | | | | | | | | | | | | | X | | X |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Bodyweight | X | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | | | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Cardiovascular events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Liver events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | | | | | | | | | | | | | | |
| **Laboratory Assessments[2]** | | | | | | | | | | | | | | | | |
| Urinalysis | X[1] | | | | | X | | | | | | | | X | | X |
| Pregnancy Test | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U |
| Blood sample for immunogenicity[2] | | | | | | | X | | | | | | X | | X | X |
| | | | | | | | | | | | | | | | | |
| **Outcomes Assessments** | | | | | | | | | | | | | | | | |

| Procedure | Eligibility Check / First Dose | Treatment Period | | | | | | | | | | | | Exit Visit | Follow-up | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | |
| Week of Study (visit window ± 5 days) | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | 80 | |
| FEV1 | X[1] | | | X | | | X | | | X | | | X | X | X | X |
| ACQ-7 | X[1] | | | X | | | X | | | X | | | X | X | X | X |
| C-ACT | X[1] | | | X | | | X | | | X | | | X | X | X | X |
| Assessment of exacerbation | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | | | | | | | | | | | | | | |
| **Investigational Product** | | | | | | | | | | | | | | | | |
| Mepolizumab SC dose administered | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| | | | | | | | | | | | | | | | | |
| **Study Administration** | | | | | | | | | | | | | | | | |
| Email to GSK Operational Lead | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Complete eCRF | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

1. Bodyweight will be measured at Visit 9 and at each visit until such time as the subject reaches 40kg in weight. Subjects with bodyweight ≥40Kg at Visit 9 will not be weighed again during Part B.
2. All laboratory samples should be collected prior to the administration of study medication

**Section 7.5 Immunogenicity**

**Original Text:**

Blood samples will be collected for the determination of anti-mepolizumab antibodies, prior to dosing at Visit 2 (Week 0), and subsequently at Visit 7 (Week 16), and at Visit 8 (Week 20).

For subjects who had a positive neutralizing antibody response at the Follow-up (Visit 8) (or last study visit at which immunogenicity was assessed if the Follow-up (Visit 8) immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-mepolizumab antibodies at least 4 months after the last dose of study drug in Part A.

In Part B, immunogenicity samples will be collected prior to dosing at Visit 15 (week 44), Visit 21 (week 68) and at Follow-up Visit 23 (week 80).

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

**Amended Text:**

Blood samples will be collected for the determination of anti-mepolizumab antibodies, prior to dosing at Visit 2 (Week 0), and subsequently at Visit 7 (Week 16), at Visit 8 (Week 20) and Early Withdrawal.

For subjects who had a positive anti-mepolizumab antibody response at the Follow-up (Visit 8) (or last study visit at which immunogenicity was assessed if the Follow-up (Visit 8) immunogenicity sample is not available), an attempt will be made to obtain a serum sample for anti-mepolizumab antibodies at least 4 months after the last dose of study drug in Part A or upon completion of Part A, whichever is later.

In Part B, immunogenicity samples will be collected prior to dosing at Visit 15 (week 44), Visit 21 (week 68) and at Follow-up Visit 23 (week 80) and Early Withdrawal.

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

**Section 7.6: Forced Expiratory Volume-1 ($FEV_1$):**

**Original Text:**

A spreadsheet calculator will be provided for calculating percent predicted $FEV_1$

**Amended Text:**

See the Study Reference Manual (SRM) for further details

**Section 7.7: Asthma Control Questionnaire-7 (ACQ-7):**

Original text:

The ACQ has a multidimensional construct assessing symptoms (5 items administered by clinic staff to the child using the interviewer administer format) and rescue bronchodilator use (query to child or parent), and FEV1% (1 item) completed by clinic staff (Appendix 6).

Amended Text:

The ACQ-IA has a multidimensional construct assessing symptoms (5 items administered by clinic staff to the child using the interviewer administer format) and rescue bronchodilator use (query to child or parent), and FEV1% (1 item) completed by clinic staff (Appendix 6).

**Section 7.8: Childhood Asthma Control Test (C-ACT):**

Original text:

The Childhood Asthma Control Test (C-ACT) assesses asthma control in children 4-11 years of age (Liu, 2007, Liu, 2010). The ACT will be completed on paper. The C-ACT should be completed prior to other study procedures to ensure that responses are not influenced by interactions with study site staff. The C-ACT is a 7-question, 2-part questionnaire, with items one through 4 to be completed by the child (with assistance from a caregiver, as needed) and items 5 to 7 to be completed by the caregiver (Appendix 10). All items are assessed using a five point descriptive scale. The descriptive response options are assigned scores from 1-5 with higher scores representing higher levels of asthma control. A total sum score based upon responses to all items is calculated to provide an overall measure of asthma control. The C-ACT should be completed prior to other study procedures to ensure that responses are not influenced by interactions with study site staff.

Amended Text:

The Childhood Asthma Control Test (C-ACT) assesses asthma control in children 4-11 years of age (Liu, 2007, Liu, 2010). The ACT will be completed on paper. The C-ACT should be completed prior to other study procedures to ensure that responses are not influenced by interactions with study site staff. The C-ACT is a 7-question, 2-part questionnaire, with items one through 4 to be completed by the child (with assistance from a caregiver, as needed) and items 5 to 7 to be completed by the caregiver (Appendix 10). A total sum score based upon responses to all items is calculated to provide an overall measure of asthma control.

**Section 9.2 Sample Size Considerations:**

Original Text:

The sample size was determined by the number of subjects needed for the PK and PD evaluations based on previous PK/PD studies. A pediatric population-PK trial simulation (GSK Document Number 2014N223495_00) was used to determine the Root Mean Square Error (RMSE, i.e. standard deviation) in estimated exposure ($AUC_{(0\text{-inf})}$ ) as a function of sample size, pharmacokinetic sampling scheme and model assumptions. Based on 1000 trial simulations per scenario, a sample size of 16-32 subjects is sufficient to maintain precision in exposure estimation (and hence bodyweight-adjusted clearance) below 20%, (as compared with the guideline 40%), providing five pharmacokinetic samples (including one close to Tmax) are collected and four parameters are fixed from adult values in the population-PK model.

Amended Text:

The sample size was determined by the number of subjects needed for the PK and PD evaluations of Part A of the study, based on previous PK/PD studies. A pediatric population-PK trial simulation (GSK Document Number 2014N223495_00) was used to determine the Root Mean Square Error (RMSE, i.e. standard deviation) in estimated exposure ($AUC_{(0\text{-inf})}$ ) as a function of sample size, pharmacokinetic sampling scheme and model assumptions. Based on 1000 trial simulations per scenario, a sample size of 16-32 subjects is sufficient to maintain precision in exposure estimation (and hence bodyweight-adjusted clearance) below 20%, (as compared with the guideline 40%), providing five pharmacokinetic samples (including one close to Tmax) are collected and four parameters are fixed from adult values in the population-PK model.

**Section 9.2.1 Sample Size Assumptions**

Original Text:

No sample size assumptions are assumed beyond the demonstrated comparability between adult pharmacokinetic parameters and those observed in children aged 2-17 years in an intravenous study of hyper-eosinophilic esophagitis.

Amended text:

No sample size assumptions are assumed beyond the demonstrated comparability between adult pharmacokinetic parameters and those observed in an intravenous study in children aged 2-17 years with eosinophilic esophagitis.

**Section 9.3.1.1 Safety Population Part A:**

Original Text:

All subjects receiving at least one dose of study medication beginning at Visit 2 will be included in the safety population for Part A analyses.

Amended Text:

All subjects receiving at least one dose of mepolizumab beginning at Visit 2 will be included in the safety population for Part A analyses.

**Section 9.3.1.5 Safety Population Part B:**

Original Text:

All subjects receiving at least one dose of study medication beginning at Visit 9 will be included in the safety population for Part B analyses.

Amended Text:

All subjects receiving at least one dose of mepolizumab beginning at Visit 9 will be included in the safety population for Part B analyses.

**Section 9.5.2 Secondary Analyses:**

**Original Text:**

Blood eosinophil count, the primary pharmacodynamic endpoint, will be log transformed prior to analysis and will also be summarised using descriptive statistics.

Secondary endpoints including ACQ-7, c-ACT will be summarised using descriptive statistics, Confidence intervals will be presented when appropriate. The analysis schema will be outlined in the RAP.

**Amended Text:**

Blood eosinophil count will be log transformed prior to analysis and will also be summarised using descriptive statistics.

Section 9.5.3: Exploratory Analyses:

Exploratory endpoints including ACQ-7, C-ACT and number of exacerbations will be summarised using descriptive statistics. Confidence intervals will be presented when appropriate. The analysis schema will be outlined in the RAP.

## Protocol Amendment 04

Section 5.1: Inclusion Criteria for Part A:

Original Text:

4. A well-documented requirement for regular treatment with inhaled corticosteroid (>200 µg/day fluticasone propionate (DPI) or equivalent daily) with or without maintenance oral corticosteroids (OCS). The ICS dose should represent medium or high dose in children aged 6-11 years of age [GINA, 2015].

Amended Text:

4. A well-documented requirement for regular treatment with inhaled corticosteroid (>200 µg/day fluticasone propionate (DPI) or equivalent daily) in the 12 months prior to Visit 1 with or without maintenance oral corticosteroids (OCS). The ICS dose should represent medium or high dose in children aged 6-11 years of age [GINA, 2015].

## Protocol Amendment 05

Section 1: Protocol Synopsis, Rationale:

Original Text:

Following the main study (Part A), subjects will be evaluated for eligibility to continue into the optional long-term extension phase (Part B) of this study. For those subjects determined to be eligible and for whom appropriate informed consent/assent has been obtained there will be the option of continuing to receive treatment with mepolizumab during a Long-Term Safety / Pharmacodynamic Phase (Part B) which will include Treatment and Follow-up phases. Part B will provide data to assess the long-term safety and tolerability of mepolizumab in this paediatric population and will also provide data to assess the durability of the pharmacodynamic response to mepolizumab.

Amended Test:

Following the main study (Part A), subjects will be evaluated for eligibility to continue into the optional long-term extension phase (Part B) of this study. For those subjects determined to be eligible and for whom appropriate informed consent/assent has been obtained there will be the option of continuing to receive treatment with mepolizumab during a Long-Term Safety / Pharmacodynamic Phase (Part B) which will include Treatment and Follow-up phases (Part B Follow-up is not required for subjects transitioning to the long term access program at the end of Part B). Part B will provide data to assess the long-term safety and tolerability of mepolizumab in this paediatric population and will also provide data to assess the durability of the pharmacodynamic response to mepolizumab.

Section 1: Protocol Synopsis, Objective(s)/Endpoint(s), Long Term Safety/Long Term Pharmacodynamic Phase (Part B):

Original Test:

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To assess the long-term (52 weeks) safety and tolerability of mepolizumab when administered subcutaneously to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Incidence of Adverse Events<br>• Frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies<br>• Incidence of clinically significant changes in vital sign measurements |

| Objectives | Endpoints |
|---|---|
| | • Incidence of clinically significant changes in clinical laboratory parameters |
| **Secondary** | |
| • To characterize the long-term (52 weeks) durability of pharmacodynamics of mepolizumab administered subcutaneously to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Change from Week 20 (Visit 9) in absolute blood eosinophil count at weeks 32, 44, 56, 68, 72 and 80. |
| • **Exploratory** | |
| • To assess the number of asthma exacerbations that occur during the long-term (52 weeks) part of the study following subcutaneous administration of mepolizumab to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Incidence of asthma exacerbations |
| • To characterize the long-term (52 weeks) asthma control following subcutaneous administration of mepolizumab to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Change from Week 20 (Visit 9) in ACQ-7 and C-ACT at weeks 32, 44, 56, 68, 72 and 80. |

*Subjects who reach their 12th birthday during Part A may participate in Part B

Amended Text:

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To assess the long-term (52 weeks) safety and tolerability of mepolizumab when administered subcutaneously to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Incidence of Adverse Events<br>• Frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies<br>• Incidence of clinically significant changes in vital sign measurements<br>• Incidence of clinically significant changes in clinical laboratory parameters |
| **Secondary** | |
| • To characterize the long-term (52 weeks) durability of | • Change from Week 0 (Visit 2) in absolute blood eosinophil count at |

| Objectives | Endpoints |
|---|---|
| pharmacodynamics of mepolizumab administered subcutaneously to subjects aged 6 to 11* years old with severe eosinophilic asthma | weeks 32, 44, 56, 68, 72 and 80**. |
| • **Exploratory** | |
| • To assess the number of asthma exacerbations that occur during the long-term (52 weeks) part of the study following subcutaneous administration of mepolizumab to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Incidence of asthma exacerbations |
| • To characterize the long-term (52 weeks) asthma control following subcutaneous administration of mepolizumab to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Change from Week 0 (Visit 2) in ACQ-7 and C-ACT at weeks 32, 44, 56, 68, 72 and 80**. |

*Subjects who reach their 12th birthday during Part A may participate in Part B

**Week 80 is not applicable to subjects transitioning to the long-term access program

Section 1: Protocol Synopsis, Objective(s)/Endpoint(s), Overall Design, Long Term Safety/Long Term Pharmacodynamic Phase (Part B):

Original Text:

This is a long-term safety / pharmacodynamic phase in which extended treatment for a further 52 weeks will be offered on an optional basis to those subjects eligible for continued treatment. Subjects will receive either 40 or 100mg depending on subject bodyweight, administered SC every 4 weeks to subjects with severe eosinophilic asthma aged 6-11 years. At the end of the 52 weeks extended treatment in Part B, subjects will have an Exit Visit 4 weeks after last dose and a Follow-Up visit 12 weeks after last dose.

Amended Text:

This is a long-term safety / pharmacodynamic phase in which extended treatment for a further 52 weeks will be offered on an optional basis to those subjects eligible for continued treatment. Subjects will receive either 40 or 100mg depending on subject bodyweight, administered SC every 4 weeks to subjects with severe eosinophilic asthma aged 6-11 years. At the end of the 52 weeks extended treatment in Part B, subjects will have an Exit Visit 4 weeks after last dose. Subjects not transitioning to the long-term access program will also have a Follow-Up visit 12 weeks after last dose.

Section 1: Protocol Synopsis, Objective(s)/Endpoint(s), Treatment Arms and Duration, Long Term Safety/Long Term Pharmacodynamic Phase (Part B), Part B Follow-up:

Original Text:

**Part B Follow-up:** Following completion of Visit 22, subjects will enter into the Follow-up phase which will consist of one additional follow-up visit at week 80 (Visit 23).

Amended Text:

**Part B Follow-up:** Following completion of Visit 22, subjects not transitioning to the long term access program will enter into the Follow-up phase which will consist of one additional follow-up visit at week 80 (Visit 23).

Section 3, Objective(s) and Endpoint(s), Long Term Safety/Long term Pharmacodynamic Phase (Part B):

Original Text:

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To assess the long-term (52 weeks) safety and tolerability of mepolizumab when administered subcutaneously to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Incidence of Adverse Events<br>• Frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies<br>• Incidence of clinically significant changes in vital sign measurements<br>• Incidence of clinically significant changes in clinical laboratory parameters |
| **Secondary** | |
| • To characterize the long-term (52 weeks) durability of pharmacodynamics of mepolizumab administered subcutaneously to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Change from Week 20 (Visit 9) in absolute blood eosinophil count at weeks 32, 44, 56, 68, 72 and 80. |
| • **Exploratory** | |
| • To assess the number of asthma exacerbations that occur during the long-term (52 weeks) part of the study following subcutaneous administration of mepolizumab to subjects aged 6 to | • Incidence of asthma exacerbations |

| Objectives | Endpoints |
|---|---|
| 11* years old with severe eosinophilic asthma<br><br>• To characterize the long-term (52 weeks) asthma control following subcutaneous administration of mepolizumab to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Change from Week 20 (Visit 9) in ACQ-7 and C-ACT at weeks 32, 44, 56, 68, 72 and 80. |

*Subjects who reach their 12th birthday during Part A may continue into Part B

Amended Text:

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To assess the long-term (52 weeks) safety and tolerability of mepolizumab when administered subcutaneously to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Incidence of Adverse Events<br>• Frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies<br>• Incidence of clinically significant changes in vital sign measurements<br>• Incidence of clinically significant changes in clinical laboratory parameters |
| **Secondary** | |
| • To characterize the long-term (52 weeks) durability of pharmacodynamics of mepolizumab administered subcutaneously to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Change from Week 0 (Visit 2) in absolute blood eosinophil count at weeks 32, 44, 56, 68, 72 and 80**. |
| • **Exploratory** | |
| • To assess the number of asthma exacerbations that occur during the long-term (52 weeks) part of the study following subcutaneous administration of mepolizumab to subjects aged 6 to 11* years old with severe eosinophilic asthma | • Incidence of asthma exacerbations |
| • To characterize the long-term (52 weeks) asthma control following subcutaneous administration of | • Change from Week 0 (Visit 2) in ACQ-7 and C-ACT at weeks 32, 44, 56, 68, 72 and 80**. |

| Objectives | Endpoints |
|---|---|
| mepolizumab to subjects aged 6 to 11* years old with severe eosinophilic asthma | |

*Subjects who reach their 12th birthday during Part A may continue into Part B

** Week 80 is not applicable to subjects transitioning to the long-term access program

Section 4, Study Design:

Original Text:

This study will consist of two phases: Part A will consist of Pre-Screening/Screening/Run-in, Treatment, and Follow-up. Part B will consist of Long-Term Treatment and Follow-up.

Amended Text:

This study will consist of two phases: Part A will consist of Pre-Screening/Screening/Run-in, Treatment, and Follow-up. Part B will consist of Long-Term Treatment and Follow-up. The Part B follow-up phase is not required for subjects transitioning to the long term access program.

Section 4, Study Design, Long Term Safety/Pharmacodynamic Phase (Part B), Follow-up:

Original Text:

**Follow-up:** Following completion of Visit 22, subjects will enter into the Follow-up phase which will consist of one additional follow-up visit at week 80 (Visit 23).

Study visits in Part B will have a window of ± 5 days. The total duration of Part B is approximately 60 weeks. A subject will be regarded as having completed Part B if they complete all phases of Part B (Long-Term Treatment and Follow-up).

Amended Text:

**Follow-up:** Following completion of Visit 22, subjects not transitioning to the long term access program will enter into the Follow-up phase which will consist of one additional follow-up visit at week 80 (Visit 23).

Study visits in Part B will have a window of ± 5 days. The total duration of Part B is approximately 60 weeks (52 weeks for subjects transitioning to the long-term access program). A subject not transitioning to the long-term access program will be regarded as having completed Part B if they complete all phases of Part B (Long-Term Treatment

and Follow-up). A subject transitioning to the long-term access program will be regarded as having completed Part B if they complete the Treatment Phase of Part B.

Section 4.1, Overall Design, Long Term Safety/Pharmacodynamic Phase (Part B):

Original Text:

This is a long-term safety / pharmacodynamic phase in which extended treatment for a further 52 weeks will be offered on an optional basis to those subjects eligible for continued treatment. Subjects will receive either 40 or 100mg depending on subject bodyweight, administered SC every 4 weeks to subjects with severe eosinophilic asthma aged 6-11 years. At the end of the 52 weeks extended treatment in Part B, subjects will have an Exit Visit 4 weeks after last dose and a Follow-Up visit 12 weeks after last dose.

Amended Text:

This is a long-term safety / pharmacodynamic phase in which extended treatment for a further 52 weeks will be offered on an optional basis to those subjects eligible for continued treatment. Subjects will receive either 40 or 100mg depending on subject bodyweight, administered SC every 4 weeks to subjects with severe eosinophilic asthma aged 6-11 years. At the end of the 52 weeks extended treatment in Part B, subjects will have an Exit Visit 4 weeks after last dose. Subjects not transitioning to the long term access program will have a Follow-Up visit 12 weeks after last dose.

Section 4.2, Treatment Arms and Duration, Long Term Safety/Pharmacodynamic Phase (Part B):

Original Text:

Following completion of Part A subjects will be evaluated for eligibility to continue into Part B of this study. For those subjects determined to be eligible and for whom appropriate informed consent/assent has been obtained there will be a Long-Term Safety / Pharmacodynamic Phase (Part B). The total duration of Part B is approximately 60

Amended text:

Following completion of Part A subjects will be evaluated for eligibility to continue into Part B of this study. For those subjects determined to be eligible and for whom appropriate informed consent/assent has been obtained there will be a Long-Term Safety / Pharmacodynamic Phase (Part B). The total duration of Part B is approximately 60 weeks (52 weeks for subjects transitioning to the long-term access program).

Section 4.4, Design Justification:

Original Text:

A treatment phase duration of 12 weeks is considered sufficient to support the primary PK and PD endpoint of the study. A dose ranging PK/PD study (MEA114092) of mepolizumab administered intravenously (75 mg) or subcutaneously (12.5, 125 and 250

mg) with a similar duration was conducted in adult asthmatic subjects with elevated blood eosinophil levels. Concordance in the blood eosinophil reduction at 75 mg IV between this study and the 12-month duration phase 2/3 study (Pavord, 2012) confirms suitability of the 12 weeks duration treatment for the chosen endpoint. Furthermore, comparable blood eosinophil count reduction was observed at 75 mg IV and 100 mg SC in a phase 3 study (MEA115588) with consistent blood eosinophil reduction observed from 12 weeks onwards. These data support conducting a study of 12 weeks duration and will allow comparison with adult/adolescent data to support the extrapolation of the safety and efficacy data observed in adults/adolescents in the severe asthma phase 3 program to the 6-11 pediatric population. Subjects will be followed-up for a total of 12 weeks after the last dose, which is consistent with the follow-up duration in adult studies.

Amended Text:

A treatment phase duration of 12 weeks is considered sufficient to support the primary PK and PD endpoint of the study. A dose ranging PK/PD study (MEA114092) of mepolizumab administered intravenously (75 mg) or subcutaneously (12.5, 125 and 250 mg) with a similar duration was conducted in adult asthmatic subjects with elevated blood eosinophil levels. Concordance in the blood eosinophil reduction at 75 mg IV between this study and the 12-month duration phase 2/3 study (Pavord, 2012) confirms suitability of the 12 weeks duration treatment for the chosen endpoint. Furthermore, comparable blood eosinophil count reduction was observed at 75 mg IV and 100 mg SC in a phase 3 study (MEA115588) with consistent blood eosinophil reduction observed from 12 weeks onwards. These data support conducting a study of 12 weeks duration and will allow comparison with adult/adolescent data to support the extrapolation of the safety and efficacy data observed in adults/adolescents in the severe asthma phase 3 program to the 6-11 pediatric population. Subjects will be followed-up for a total of 12 weeks after the last dose in Part A, which is consistent with the follow-up duration in adult studies.

Section 5.6, Subject and Study Completion:

Original text:

A completed subject is one who has completed all phases of the study including the follow-up visit.

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

Amended Text:

In Part A, a completed subject is one who has completed all phases of the study including the Part A follow-up visit. In Part B, for subjects not transitioning to the long-term access program, a completed subject is one who has completed all phases of Part B (including the Part B follow-up visit) and for subjects transitioning to the long term access program a completed subject is one who has completed the Treatment Phase of Part B.

Section 6.8, Treatment After the Completion of Part A and Part B:

Original Text:

At the end of Part B, subjects will return to usual care and will be prescribed appropriate alternative asthma therapy, as required.

Amended Text:

At the end of Part B, when feasible, subjects will transition to a long term access program. At the end of the Treatment Phase of Part B, subjects that are not able to transition to the long term access program will return to usual care and will be prescribed appropriate alternative asthma therapy, as required.

Section 7, Study Assessments and Procedures, Table 3:

Original Text:

| Procedure | Pre-Screen[1] | Screening | Treatment Period | | | | Exit Visit[3] | Follow-up | | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8[8] | |
| **Week of Study** (visit window ± 3 days, ±1 day Visit 5)) | Prior to or same day as Visit 1 | (up to 14 days prior to Visit 2) | 0 | 4 | 8 | 9 | 12 | 16 | 20 | |
| | | | | | | | | | | |
| **Subject Screen** | | | | | | | | | | |
| Informed consent | X | | | | | | | | | |
| Inclusion and exclusion criteria | | X | X | | | | | | | |
| Demography | X | | | | | | | | | |
| Medical history, including bronchodilator reversibility history[4] | | X | | | | | | | | |
| Past and current medical conditions | | X | | | | | | | | |
| Asthma exacerbation history | | X | | | | | | | | |
| | | | | | | | | | | |
| **Safety Assessments** | | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X |
| Hematology (including eosinophils) | | X | X | X | X | X | X | X | X | X |
| Clinical Chemistry | | X | | X | X | | X | | X | X |
| 12-lead ECG | | X | | X | | | X | | | X |
| Vital signs | | X | X | X | X | X | X | X | X | X |
| Bodyweight | | | X | | | | | | | |
| Brief physical examination | | X | | | | | | | | |
| Adverse events | | X | X | X | X | X | X | X | X | X |
| Cardiovascular events | | X | X | X | X | X | X | X | X | X |
| Liver events | | X | X | X | X | X | X | X | X | X |
| | | | | | | | | | | |
| **Laboratory** | | | | | | | | | | |

| Procedure | Pre-Screen[1] | Screening | Treatment Period | | | | Exit Visit[3] | Follow-up | | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8[8] | |
| **Week of Study** (visit window ± 3 days, ±1 day Visit 5)) | Prior to or same day as Visit 1 | (up to 14 days prior to Visit 2) | 0 | 4 | 8 | 9 | 12 | 16 | 20 | |
| **Assessments** | | | | | | | | | | |
| Urinalysis | | X | | | | | | | X | X |
| Pregnancy Test | | U | U[5] | U[5] | U[5] | | U | U | U | U |
| HBsAg and hepatitis C antibody | | X[6] | | | | | | | | |
| Serum IgE (total and specific) | | | X[5] | | | | | | | |
| PK blood sample | | | | X[5] | X[5] | X | X | X | X | X |
| IL5 serum sample | | | X[5] | | | | X | | | |
| Blood sample for immunogenicity[2,7] | | | X[5] | | | | | X | X[2] | X |
| | | | | | | | | | | |
| **Outcomes Assessments** | | | | | | | | | | |
| FEV1 | | X | X | X | X | | X | X | X | X |
| ACQ-7 | | | X | X | X | | X | X | X | X |
| C-ACT | | | X | X | X | | X | X | X | X |
| Assessment of exacerbation | X | X | X | X | X | X | X | X | X | X |
| | | | | | | | | | | |
| **Investigational Product** | | | | | | | | | | |
| Mepolizumab SC dose administered | | | X | X | X | | | | | |
| | | | | | | | | | | |
| **Study Administration** | | | | | | | | | | |
| Email to GSK Operational Lead | X | X | X | X | X | X | X | X | X | X |
| Complete eCRF | X | X | X | X | X | X | X | X | X | X |

1. Pre-screen must be completed prior to or on the same day as Screen Visit.
2. For subjects who had a positive anti-mepolizumab antibody response at the 12 week post-last-dose follow-up assessment (Visit 8) (or last study visit at which immunogenicity was assessed if the Follow-up (Visit 8) immunogenicity sample is not available) an attempt will be made to obtain a serum sample for anti-mepolizumab antibodies at least 4 months after the last dose of study drug in Part A or upon completion of Part A, whichever is later.
3. Exit visit should be performed as close as possible to the planned week 12 visit date.
4. Therapy history to include a detailed review of prior biologics received for treatment of asthma, including prior investigational anti-IL5 or anti-IL13 preparations.
5. During the treatment period, all lab samples and procedures should be obtained prior to study treatment administration.
6. A positive Hepatitis B Surface Antigen and Hepatitis C antibody is exclusionary
7. This immunogenicity sample must always be collected 12 weeks (± 7 days) post-last-dose of study treatment; therefore, for subjects who withdraw from study treatment early, this sample must be collected 12 weeks (± 7 days) after their confirmed last dose of study treatment (i.e., prior to Visit 8). In the event that this sample collection date coincides with an Early Withdrawal Visit, only one immunogenicity sample should be collected.
8. Visit 8 to be performed 12 weeks post last dose. For subjects continuing into the long-term extension phase Part B, Visit 9 should be conducted on the same day as Visit 8 once all of the visit 8 assessments have been completed. Assessments performed at Visit 8 that are also listed for Visit 9 should not be duplicated if Visit 8 and Visit 9 are performed on the same day.

Amended Text:

| Procedure | Pre-Screen[1] | Screening | Treatment Period | | | | Exit Visit[3] | Follow-up | | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8[8] | |
| **Week of Study** (visit window ± 3 days, ±1 day Visit 5)) | Prior to or same day as Visit 1 | (up to 14 days prior to Visit 2) | 0 | 4 | 8 | 9 | 12 | 16 | 20 | |
| | | | | | | | | | | |
| **Subject Screen** | | | | | | | | | | |
| Informed consent | X | | | | | | | | | |
| Inclusion and exclusion criteria | | X | X | | | | | | | |
| Demography | X | | | | | | | | | |
| Medical history, including bronchodilator reversibility history[4] | | X | | | | | | | | |
| Past and current medical conditions | | X | | | | | | | | |
| Asthma exacerbation history | | X | | | | | | | | |
| | | | | | | | | | | |
| **Safety Assessments** | | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X |
| Hematology (including eosinophils) | | X | X | X | X | X | X | X | X | X |
| Clinical Chemistry | | X | | X | X | | X | | X | X |
| 12-lead ECG | | X | | X | | | X | | | X |
| Vital signs | | X | X | X | X | X | X | X | X | X |
| Bodyweight | | | X | | | | | | | |
| Brief physical examination | | X | | | | | | | | |
| Adverse events | | X | X | X | X | X | X | X | X | X |
| Cardiovascular events | | X | X | X | X | X | X | X | X | X |
| Liver events | | X | X | X | X | X | X | X | X | X |
| | | | | | | | | | | |
| **Laboratory Assessments** | | | | | | | | | | |
| Urinalysis | | X | | | | | | | X | X |
| Pregnancy Test | | U | U[5] | U[5] | U[5] | | U | U | U | U |
| HBsAg and hepatitis C antibody | | X[6] | | | | | | | | |
| Serum IgE (total) | | | X[5] | | | | | | | |
| PK blood sample | | | | X[5] | X[5] | X | X | X | X | X |
| IL5 serum sample | | | X[5] | | | | X | | | |
| Blood sample for immunogenicity[2,7] | | | X[5] | | | | | X | X[2] | X |
| | | | | | | | | | | |
| **Outcomes Assessments** | | | | | | | | | | |
| FEV1 | | X | X | X | X | | X | X | X | X |
| ACQ-7 | | | X | X | X | | X | X | X | X |
| C-ACT | | | X | X | X | | X | X | X | X |
| Assessment of | X | X | X | X | X | X | X | X | X | X |

| Procedure | Pre-Screen[1] | Screening | Treatment Period | | | | Exit Visit[3] | Follow-up | | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Number** | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8[8] | |
| **Week of Study** (visit window ± 3 days, ±1 day Visit 5)) | Prior to or same day as Visit 1 | (up to 14 days prior to Visit 2) | 0 | 4 | 8 | 9 | 12 | 16 | 20 | |
| exacerbation | | | | | | | | | | |
| | | | | | | | | | | |
| **Investigational Product** | | | | | | | | | | |
| Mepolizumab SC dose administered | | | X | X | X | | | | | |
| | | | | | | | | | | |
| **Study Administration** | | | | | | | | | | |
| Email to GSK Operational Lead | X | X | X | X | X | X | X | X | X | X |
| Complete eCRF | X | X | X | X | X | X | X | X | X | X |

1. Pre-screen must be completed prior to or on the same day as Screen Visit.
2. For subjects who had a positive anti-mepolizumab antibody response at the 12 week post-last-dose follow-up assessment (Visit 8) (or last study visit at which immunogenicity was assessed if the Follow-up (Visit 8) immunogenicity sample is not available) an attempt will be made to obtain a serum sample for anti-mepolizumab antibodies at least 4 months after the last dose of study drug in Part A or upon completion of Part A, whichever is later.
3. Exit visit should be performed as close as possible to the planned week 12 visit date.
4. Therapy history to include a detailed review of prior biologics received for treatment of asthma, including prior investigational anti-IL5 or anti-IL13 preparations.
5. During the treatment period, all lab samples and procedures should be obtained prior to study treatment administration.
6. A positive Hepatitis B Surface Antigen and Hepatitis C antibody is exclusionary
7. This immunogenicity sample must always be collected 12 weeks (± 7 days) post-last-dose of study treatment; therefore, for subjects who withdraw from study treatment early, this sample must be collected 12 weeks (± 7 days) after their confirmed last dose of study treatment (i.e., prior to Visit 8). In the event that this sample collection date coincides with an Early Withdrawal Visit, only one immunogenicity sample should be collected.
8. Visit 8 to be performed 12 weeks post last dose. For subjects continuing into the long-term extension phase Part B, Visit 9 should be conducted on the same day as Visit 8 once all of the visit 8 assessments have been completed. Assessments performed at Visit 8 that are also listed for Visit 9 should not be duplicated if Visit 8 and Visit 9 are performed on the same day.

Section 7, Study Assessments and Procedures, Table 4:

Original Text:

| Procedure | Eligibility Check / First Dose | Treatment Period | | | | | | | | | | | | Exit Visit | Follow-up | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | |
| Week of Study (visit window ± 5 days) | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | 80 | |
| | | | | | | | | | | | | | | | | |
| **Subject** | | | | | | | | | | | | | | | | |

| Procedure | Eligibility Check / First Dose | Treatment Period | | | | | | | | | | | | Exit Visit | Follow-up | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | |
| Week of Study (visit window ± 5 days) | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | 80 | |
| **Screen** | | | | | | | | | | | | | | | | |
| Informed consent | X[1] | | | | | | | | | | | | | | | |
| Inclusion and exclusion criteria | X[1] | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| **Safety Assessments** | | | | | | | | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hematology (including eosinophils)[2] | X | | | X | | | X | | | X | | | X | X | X | X |
| Clinical Chemistry[2] | X | | | X | | | X | | | X | | | X | X | | X |
| 12-lead ECG | | | | | | | | | | | | | | X | | X |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Bodyweight | X | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | | | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Cardiovascular events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Liver events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | | | | | | | | | | | | | | |
| **Laboratory Assessments[2]** | | | | | | | | | | | | | | | | |
| Urinalysis | X[1] | | | | | X | | | | | | | | X | | X |
| Pregnancy Test | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U |
| Blood sample for immunogenicity[2] | | | | | | | X | | | | | | X | | X | X |
| | | | | | | | | | | | | | | | | |
| **Outcomes Assessments** | | | | | | | | | | | | | | | | |
| FEV1 | X[1] | | | X | | | X | | | X | | | X | X | X | X |
| ACQ-7 | X[1] | | | X | | | X | | | X | | | X | X | X | X |
| C-ACT | X[1] | | | X | | | X | | | X | | | X | X | X | X |
| Assessment | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| Procedure | Eligibility Check / First Dose | Treatment Period | | | | | | | | | | | | Exit Visit | Follow-up | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | |
| Week of Study (visit window ± 5 days) | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | 80 | |
| of exacerbation | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| **Investigational Product** | | | | | | | | | | | | | | | | |
| Mepolizumab SC dose administered | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| | | | | | | | | | | | | | | | | |
| **Study Administration** | | | | | | | | | | | | | | | | |
| Email to GSK Operational Lead | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Complete eCRF | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

1. Bodyweight will be measured at Visit 9 and at each visit until such time as the subject reaches 40kg in weight. Subjects with bodyweight ≥40Kg at Visit 9 will not be weighed again during Part B.
2. All laboratory samples should be collected prior to the administration of study medication

Amended Text:

| Procedure | Eligibility Check / First Dose | Treatment Period | | | | | | | | | | | | Exit Visit | Follow-up[3] | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | |
| Week of Study (visit window ± 5 days) | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | | |
| | | | | | | | | | | | | | | | | |
| **Subject Screen** | | | | | | | | | | | | | | | | |
| Informed consent | X[1] | | | | | | | | | | | | | | | |
| Inclusion and exclusion | X[1] | | | | | | | | | | | | | | | |

| Procedure | Eligibility Check / First Dose | Treatment Period | | | | | | | | | | | | Exit Visit | Follow-up[3] | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | |
| Week of Study (visit window ± 5 days) | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | | |
| criteria | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| **Safety Assessments** | | | | | | | | | | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hematology (including eosinophils)[2] | X | | | X | | | X | | | X | | | X | X | X | X |
| Clinical Chemistry[2] | X | | | X | | | X | | | X | | | X | X | | X |
| 12-lead ECG | | | | | | | | | | | | | | X | | X |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Bodyweight | X | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | X[1] | | | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Cardiovascular events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Liver events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| | | | | | | | | | | | | | | | | |
| **Laboratory Assessments[2]** | | | | | | | | | | | | | | | | |
| Urinalysis | X[1] | | | | | X | | | | | | | | X | | X |
| Pregnancy Test | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U | U |
| Blood sample for immunogenicity[2] | | | | | | | X | | | | | | X | | X | X |
| | | | | | | | | | | | | | | | | |
| **Outcomes Assessments** | | | | | | | | | | | | | | | | |
| FEV1 | X[1] | | | X | | | X | | | X | | | X | X | X | X |
| ACQ-7 | X[1] | | | X | | | X | | | X | | | X | X | X | X |
| C-ACT | X[1] | | | X | | | X | | | X | | | X | X | X | X |
| Assessment | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| Procedure | Eligibility Check / First Dose | Treatment Period | | | | | | | | | | | | Exit Visit | Follow-up[3] | Early Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | |
| Week of Study (visit window ± 5 days) | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 56 | 60 | 64 | 68 | 72 | | |
| of exacerbation | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| **Investigational Product** | | | | | | | | | | | | | | | | |
| Mepolizumab SC dose administered | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| | | | | | | | | | | | | | | | | |
| **Study Administration** | | | | | | | | | | | | | | | | |
| Email to GSK Operational Lead | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Complete eCRF | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

1. Bodyweight will be measured at Visit 9 and at each visit until such time as the subject reaches 40kg in weight. Subjects with bodyweight ≥40Kg at Visit 9 will not be weighed again during Part B.
2. All laboratory samples should be collected prior to the administration of study medication
3. The 12-week post-dose follow-up visit (Visit 23) is not required for subjects transitioning to the long-term access program.

Section 7.2.6, Clinical Safety Laboratory Assessments:

Original Text:

All blood samples which will be taken prior to each administration of study medication will be sent to a central laboratory for analysis (details provided in the SRM). Standard reference ranges will be used.

Amended Text:

All blood samples which will be taken prior to each administration of study medication will be sent to a central laboratory for analysis (details provided in the $Q^2$ Solutions Investigator Manual). Standard reference ranges will be used.

Section 7.3, Pharmacokinetics:

Original Text

Blood samples for analysis of mepolizumab plasma concentration will be obtained as per the Part A Time and Events table (Table 3). Samples obtained at visit 3 and 4 must be drawn prior to mepolizumab 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.

Amended text:

Blood samples for analysis of mepolizumab plasma concentration will be obtained as per the Part A Time and Events table (Table 3). Samples obtained at visit 3 and 4 must be drawn prior to mepolizumab 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 $Q^2$ Solutions Investigator Manual.

Section 7.5, Immunogenicity:

Original Text:

In Part B, immunogenicity samples will be collected prior to dosing at Visit 15 (week 44), Visit 21 (week 68) and at Follow-up Visit 23 (week 80) and Early Withdrawal.

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

Amended Text:

In Part B, immunogenicity samples will be collected prior to dosing at Visit 15 (week 44), Visit 21 (week 68) and, when applicable, at Follow-up Visit 23 (week 80) and Early Withdrawal.

Details for sample collection and processing may be found in the $Q^2$ Solutions Investigator Manual.

Section 9.2, Sample Size Considerations:

Original Text:

With regards to the pre-planned secondary analysis, the trial simulations also showed that for the proposed sample size and sampling scheme, 80% of simulated trials yielded a bodyweight-adjusted clearance with 90% confidence limits falling within the bounds 0.8 – 1.25 of the adult value (0.29 L/day). This precision is deemed sufficient for extrapolation purposes from adults to pediatric subjects aged 6 to 11 years supported by this study (GSK Document Number 2014N223495_00).

Amended Text:

With regards to the pre-planned secondary analysis, the trial simulations also showed that for the proposed sample size and sampling scheme, 80% of simulated trials yielded a bodyweight-adjusted apparent clearance with 90% confidence limits falling within the bounds 0.8 – 1.25 of the adult apparent clearance value (CL/F of 0.29 L/day). This precision is deemed sufficient for extrapolation purposes from adults to pediatric subjects aged 6 to 11 years supported by this study (GSK Document Number 2014N223495_00).

Section 9.4.2, Secondary Analyses:

Original Text:

The comparison of bodyweight-adjusted clearance between the 6-11 year olds and adults will be made by comparing the point estimate and 90% CI of bodyweight-adjusted clearance in this study with the historic value in adults of 0.29 L/day along with a proposed 80-125% interval around this estimate (i.e., 0.23-0.36 L/day).

Amended Text:

The comparison of bodyweight-adjusted clearance between the 6-11 year olds and adults will be made by comparing the point estimate and 90% CI of bodyweight-adjusted clearance in this study with the historic value in adults of 0.22 L/day (corresponding to an apparent clearance of 0.29 L/day assuming an absolute bioavailability of 75%) along with a proposed 80-125% interval around this estimate (i.e., 0.18-0.28 L/day).

Section 12.1, Appendix 1: Abbreviations and Trademarks:

Original text:

| | |
|---|---|
| ACQ-7 | Asthma Control Questionnaire-7 |
| ADA | Anti-drug Antibody |
| AE | Adverse Event |
| ALT | Alanine aminotransferase (SGPT) |
| AST | Aspartate aminotransferase (SGOT) |
| AUC | Area under concentration-time curve |
| $AUC_{(0\text{-inf})}$ | Area under concentration time curve to infinity |
| β-HCG | Beta-Human Chorionic Gonadotropin |
| BUN | Blood urea nitrogen |
| C-ACT | Childhood Asthma Control Test |
| CC | Cubic Centimeter |
| CI | Confidence Interval |
| CL | Systemic clearance of parent drug |
| Cmax | Maximum observed concentration |
| CDC | Centers for Disease Control (US) |
| $CO_2$ | Carbon dioxide |
| CPK | Creatine phosphokinase |
| CPSR | Clinical Pharmacology Study Report |
| eCRF | Electronic Case Report Form |
| CS | Corticosteroids |
| CV | Cardiovascular |
| DCSI | Developmental Core Safety Information |
| DPI | Dry Powder Inhaler |
| ECG | Electrocardiogram |
| ED | Emergency Department |
| EGD | Esophagogastroduodenoscopy |
| EoE | Eosionophilic Esophagitis |
| FAAN | Food Allergy and Anaphylaxis Network |
| $FEV_1$ | Forced Expiratory Volume in 1 second |
| FVC | Forced Vital Capacity |
| GCP | Good Clinical Practice |
| GCSP | Global Clinical Safety and Pharmacovigilence |
| GGT | Gamma glutamyltransferase |
| GINA | Global Initiative for Asthma |
| GSK | GlaxoSmithKline |
| HBsAg | Hepatitis B surface antigen |
| hCG | Human chorionic gonadotropin |
| HES | Hypereosinophilic syndrome |
| HR | Heart rate |
| IB | Investigator’s Brochure |

| | |
|---|---|
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ICS | Inhaled Corticosteroids |
| ID50/90 | 50% or 90% Inhibition of Maximum Effect |
| IEC | Independent Ethics Committee |
| IgG | Immunoglobulin |
| IL-5 | Interleukin 5 |
| IM | Intramuscular |
| $I_{max}$ | Maximum Inhibition Model |
| IP | Investigational Product |
| IRB | Institutional Review Board |
| IUD | Intrauterine Device |
| IV | Intravenous |
| kg | Kilogram |
| LABA | Long acting inhaled β2 adrenoceptor agonist |
| LRTA | Leukotriene Receptor Antagonist |
| µg | Microgram |
| µL | Microliter |
| mAb | Monoclonal Antibody |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| MCV | Mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligrams |
| mL | Milliliter |
| MSDS | Material Safety Data Sheet |
| Nab | Neutralizing Antibody |
| NIAID | National Institute of Allergy and Infectious Diseases (US) |
| NIH | National Institute of Health (US) |
| OCS | Oral Corticosteroids |
| OLE | Open label extension |
| PD | Pharmacodynamic |
| PK | Pharmacokinetic |
| Pop-PK | Population Pharmacokinetics |
| QT | The QT interval is measured from the beginning of the QRS complex to the end of the T wave |
| QTc | QT duration corrected for heart rate |
| RAP | Reporting and Analysis Plan |
| SAE | Serious adverse event(s) |
| SAS | Statistical Analysis Software |
| SC | subcutaneous |
| SGOT | Serum glutamic-oxaloacetic transaminase |
| SGPT | Serum glutamic pyruvic transaminase |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |

| | |
|---|---|
| SRM | Study Reference Manual |
| SRT | Safety Review Team |
| SUSAR | Suspected, Unexpected, Serious Adverse drug Reaction |
| t½ | Terminal phase half-life |
| Tmax | Time of occurrence of Cmax |
| TTS | Study Specific Technical Agreement Memo |
| µL | Microliter |
| ULN | Upper limit of normal |
| UK | United Kingdom |
| US | United States |
| Vc | Central Volume of Distribution |
| WBC | White blood cells |
| Vss | Steady State Volume of Distribution |

Amended Text:

| | |
|---|---|
| ACQ-7 | Asthma Control Questionnaire-7 |
| ADA | Anti-drug Antibody |
| AE | Adverse Event |
| ALT | Alanine aminotransferase (SGPT) |
| AST | Aspartate aminotransferase (SGOT) |
| AUC | Area under concentration-time curve |
| $AUC_{(0\text{-}inf)}$ | Area under concentration time curve to infinity |
| β-HCG | Beta-Human Chorionic Gonadotropin |
| BUN | Blood urea nitrogen |
| C-ACT | Childhood Asthma Control Test |
| CC | Cubic Centimeter |
| CI | Confidence Interval |
| CL | Systemic clearance of parent drug |
| CL/F | Apparent clearance after extravascular (e.g., subcutaneous) administration |
| Cmax | Maximum observed concentration |
| CDC | Centers for Disease Control (US) |
| $CO_2$ | Carbon dioxide |
| CPK | Creatine phosphokinase |
| CPSR | Clinical Pharmacology Study Report |
| eCRF | Electronic Case Report Form |
| CS | Corticosteroids |
| CV | Cardiovascular |
| DCSI | Developmental Core Safety Information |
| DPI | Dry Powder Inhaler |
| ECG | Electrocardiogram |
| ED | Emergency Department |
| EGD | Esophagogastroduodenoscopy |
| EoE | Eosionophilic Esophagitis |

| | |
|---|---|
| FAAN | Food Allergy and Anaphylaxis Network |
| $FEV_1$ | Forced Expiratory Volume in 1 second |
| FVC | Forced Vital Capacity |
| GCP | Good Clinical Practice |
| GCSP | Global Clinical Safety and Pharmacovigilence |
| GGT | Gamma glutamyltransferase |
| GINA | Global Initiative for Asthma |
| GSK | GlaxoSmithKline |
| HBsAg | Hepatitis B surface antigen |
| hCG | Human chorionic gonadotropin |
| HES | Hypereosinophilic syndrome |
| HR | Heart rate |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ICS | Inhaled Corticosteroids |
| ID50/90 | 50% or 90% Inhibition of Maximum Effect |
| IEC | Independent Ethics Committee |
| IgG | Immunoglobulin |
| IL-5 | Interleukin 5 |
| IM | Intramuscular |
| $I_{max}$ | Maximum Inhibition Model |
| IP | Investigational Product |
| IRB | Institutional Review Board |
| IUD | Intrauterine Device |
| IV | Intravenous |
| kg | Kilogram |
| LABA | Long acting inhaled β2 adrenoceptor agonist |
| LRTA | Leukotriene Receptor Antagonist |
| µg | Microgram |
| µL | Microliter |
| mAb | Monoclonal Antibody |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| MCV | Mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligrams |
| mL | Milliliter |
| MSDS | Material Safety Data Sheet |
| Nab | Neutralizing Antibody |
| NIAID | National Institute of Allergy and Infectious Diseases (US) |
| NIH | National Institute of Health (US) |
| OCS | Oral Corticosteroids |
| OLE | Open label extension |
| PD | Pharmacodynamic |

| | |
|---|---|
| PK | Pharmacokinetic |
| Pop-PK | Population Pharmacokinetics |
| QT | The QT interval is measured from the beginning of the QRS complex to the end of the T wave |
| QTc | QT duration corrected for heart rate |
| RAP | Reporting and Analysis Plan |
| SAE | Serious adverse event(s) |
| SAS | Statistical Analysis Software |
| SC | subcutaneous |
| SGOT | Serum glutamic-oxaloacetic transaminase |
| SGPT | Serum glutamic pyruvic transaminase |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SRM | Study Reference Manual |
| SRT | Safety Review Team |
| SUSAR | Suspected, Unexpected, Serious Adverse drug Reaction |
| t½ | Terminal phase half-life |
| Tmax | Time of occurrence of Cmax |
| TTS | Study Specific Technical Agreement Memo |
| µL | Microliter |
| ULN | Upper limit of normal |
| UK | United Kingdom |
| US | United States |
| Vc | Central Volume of Distribution |
| WBC | White blood cells |
| Vss | Steady State Volume of Distribution |

Section 12.2, Appendix 2: Liver Safety Required Actions Follow-Up and Assessments, Footnote 5:

Original Text:

5. 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.

Amended Text:

5. 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 $Q^2$ Solutions Investigator Manual.

Section 12.3.6, Reporting of SAEs to GSK:

Original Text:

- 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 SAE coordinator

Amended Text:

- If the electronic system is unavailable, the site will use the paper SAE data collection tool and fax it to the SAE coordinator within 24 hours.