TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A multi-center, randomized, double-blind, placebo controlled, parallel group study to compare cessation versus continuation of long-term mepolizumab treatment in patients with severe eosinophilic asthma (201810)

Compound Number: SB-240563

Development Phase: IIIB

Effective Date: 07-JUL-2016

Protocol Amendment Number: 02

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2015N232375_00	2015-MAY-20	Original
2015N232375_01	2015-JUN-23	Republished
1. Added birth control requirement for 4 months after last dose 2. Corrected symptom score from ≥5 to 5 3. Language allows for inflammatory biomarkers to be tested at GSK 4. eDiary arrow adjusted to span from Visit B2 to the Exit Visit or EW/IP DISC 5. Estradiol, FSH, drug alcohol screens only conducted if clinically indicated 6. Added further explanation of Part D switch during a visit 7. Extended Part A to 2.5 years in text and Table 6 8. In Section 7.9.2, added a statement that recreational drug us is not allowed during the study 9. In Table 7, added a line for biomarker analysis 10. Added clarifying language to the disallowance of treatment gaps during 201312 and MEA115666		
2015N232375_02	2015-NOV-06	Amendment No. 1
1. Change of Secondary Medical Monitor 2. Simplified definition of "continuous mepolizumab treatment" 3. Clarified when a subject switches from Part C to Part D 4. Removed the process of withdrawing a subject due to unblinding 5. Several minor changes to the Time and Events table and corresponding text within the protocol to ensure subjects entering from MEA115666 and 201312 are consistently and correctly monitored 6. Removed Urinalysis testing 7. Updated contraception requirements		
2015N232375_03	2016-JUL-07	Amendment No. 2
1. Amended Section 5.6.1 Risk Assessment 2. Corrected numbering of Exclusion Criteria 3. Amended exclusion criterion No. 7 in Section 6.2: Exclusion Criteria 4. Amended Randomization Exclusion criterion No. 7 in Section 6.3.2: Randomization Exclusion Criteria. 5. Additional text added to Section 7.1 Investigational Product and Other Study Treatment 6. Amended Section 7.9.1 Permitted Medications and Non-Drug Therapies 7. Multiple changes to Section 7.9.2 Prohibited Medications and Non-Drug Therapies 8. Removed interactive response technology requirements from certain visits of the T&E tables 9. Added Physical Examination at Visit C1 in Time and Events table 10. Added Physical Examination to C1 visit		

11.	Updated Subject/Clinician Rating of Global Impression of Disease Severity and Response to Therapy
12.	Clarified unblinding risk when performing local laboratory testing
13.	Updated biomarker collection text
14.	Removed “Xolair” from the Trademark Information section

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SPONSOR SIGNATORY

PPD

7th July 2016

Steve Pascoe, MD
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MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): IND No. 006971, EudraCT No: 2015-002361-32

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 201810

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

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

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

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY 201810

Rationale

The efficacy of mepolizumab in severe asthma has been demonstrated over one year of continuous treatment in double-blinded studies. However, it is currently unknown whether chronic exposure is necessary for disease control. It was recently reported that discontinuation of mepolizumab after one year of treatment resulted in the increased presence of eosinophils and a corresponding increase in exacerbation frequency to pre-study levels, suggesting that a treatment response was not sustained after treatment discontinuation. Beyond one year of treatment, there is no data available on the sustainability of a treatment response following the discontinuation of mepolizumab.

Asthma management guidelines recommend stepping down therapy once control is achieved in an effort to find the patient's minimal effective treatment. Thus, it remains important to understand the duration of response to mepolizumab when treatment is withdrawn after longer-term exposure.

Objectives

Primary Objective

To evaluate whether patients with severe eosinophilic asthma who have received long-term treatment with mepolizumab (at least 3 years) need to maintain treatment with mepolizumab to continue to receive benefit.

Secondary Objective

To assess the safety and tolerability of mepolizumab continuation compared to placebo following long-term treatment with mepolizumab in patients with severe eosinophilic asthma.

Endpoints

Primary Endpoint

- Time to first clinically significant exacerbation

  Clinically significant exacerbations will be defined as worsening of asthma which requires use of systemic corticosteroids[1] and/or hospitalisation and/or emergency department (ED) visits.

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

Secondary Endpoints

- Ratio to baseline in blood eosinophil count at weeks 12, 24, 36 and 52
- Time to a decrease in asthma control, defined as an increase from baseline in Asthma Control Questionnaire-5 (ACQ-5) score of ≥ 0.5 units
- Time to first exacerbation requiring hospitalization or ED visit

Other Endpoints

- Time to first exacerbation requiring hospitalization
- Mean change from baseline in clinic pre-bronchodilator FEV_1 at weeks 12, 24, 36, 52
- Mean change from baseline in clinic post-bronchodilator FEV_1 at weeks 12, 24, 36, 52
- Mean change from baseline in daily salbutamol/albuterol use
- Mean change from baseline in daily asthma symptom scores
- Mean change from baseline in awakening at night due to asthma symptoms requiring rescue medication use
- Mean change from baseline in morning (AM) Peak Expiratory Flow (PEF)
- Time to worsening of asthma (subjects meeting at least 2 of the following 4 criteria for worsening of asthma for at least 2 consecutive days)
    - **AM PEF:** Decrease in AM PEF ≥30% compared with baseline (last 7 days of run-in Part B).
    - **Rescue Medication Use:** An increase of ≥50% in rescue medication compared with the average use for the previous week.
    - **Night time awakenings requiring rescue medication:** Awakening due to asthma symptoms requiring rescue medication
    - **Symptoms:** An asthma symptom score of 5
- Mean change from baseline in ACQ-5 score
- Proportion of patients experiencing a decrease in asthma control, defined as an increase from baseline in ACQ-5 score of ≥0.5 or more units
- Proportion of subjects with a clinically meaningful worsening of health-related quality of life measurements (St. George's Respiratory Questionnaire, SGRQ) at weeks 12, 24, 36 and 52 (defined as subjects who have a clinically relevant increase from baseline of ≥4 units in SGRQ score).
- Mean change from baseline in SGRQ score at week 12, 24, 36 and 52
- Subject/Clinician global impression of asthma severity rating at weeks 12, 24, 36 and 52

- Subject/Clinician rating of response to therapy at weeks 12, 24, 36 and 52
- Number of days in hospital due to asthma
- Unscheduled healthcare contacts/resource utilisation
- Days off of regular work/school

Safety Endpoints

- Adverse Events and Serious Adverse Events
- Clinical Laboratory parameters
- 12-lead ECG parameters
- Vital Signs

Overall Design

This is a 52-week, 2-arm, randomized, double-blind, parallel-group, multi-center study evaluating mepolizumab 100 mg and placebo administered subcutaneously (SC) every 4 weeks in subjects with severe eosinophilic asthma who have been treated with mepolizumab continuously in addition to standard of care therapy for at least 3 years. Subjects who participated in the open-label studies MEA115666 or 201312 and who have no treatment gaps of more than 12 weeks (84 days) between any two doses of mepolizumab in MEA115666 or 201312, will be eligible to participate in this study.

It is intended that the Follow up/Exit Visit or Early Withdrawal (EW) Visit for studies MEA115666 and 201312 will serve as the Pre-Screening/Screening Visit (Visit 0/Visit 1) for this study.

Part A and B: Variable and Fixed Open-Label Run-In Periods

At Visit 1 (Screening), eligible subjects will have their exposure period for mepolizumab treatment assessed:

- **Subjects with less than 3 years of mepolizumab treatment** will enter Part A of the study, a variable open-label run-in period on mepolizumab (100 mg SC every 4 weeks) of 4 to 132 weeks, in order for subjects to reach 3 years of exposure to mepolizumab.
    - Once the required 3 year exposure is reached, the subject will enter Part B of the study at Visit B1 and complete a fixed run-in period of 4 weeks (up to 8 weeks) during which open-label mepolizumab (100 mg SC every 4 weeks) is administered, in order to collect baseline information.

- **Subjects with at least 3 years of mepolizumab treatment** will directly enter Part B of the study. For these subjects, assessments for Visit 1 and Visit B1 should be conducted on the same day. No assessments should be duplicated.

Part C: Double-Blind Treatment Period

Upon completion of the fixed run-in period Part B, eligible subjects will be randomized 1:1 to the following double-blinded treatment arms at Visit C1:

- mepolizumab (100 mg) administered SC every 4 weeks
- placebo administered SC every 4 weeks

Part D: Optional Switch to Open-Label Mepolizumab

Subjects who experience a clinically significant asthma exacerbation during the double-blind treatment period Part C will require a prompt assessment by the investigator to determine if they should continue taking double-blind study treatment.

Subjects deemed to be unsuitable to continue double-blind study treatment by the Investigator should discontinue double-blind investigational product (IP) and complete a Discontinuation of IP Visit approximately 4 weeks following their last dose of double-blind IP.

Subjects discontinuing IP due to a clinically significant asthma exacerbation are eligible to enter optional Part D of the study and receive open-label mepolizumab in addition to their standard of care therapy for the remainder of the study, through Part D, to Visit D13. Subjects switching to Part D should complete the Discontinuation of IP Visit and their first Part D visit on the same day, corresponding to the week post-randomization. No assessments should be duplicated.

Switch to Part D between visits: For example, if a subject completed Visit C7 at Week 24 (and the subject received a dose of IP at Visit C7) and it is later determined that they should switch to Part D, the IP Discontinuation assessments and the first visit in Part D will be D8 at Week 28.

Switch to Part D during a visit: If a subject is in the process of completing a Part C visit, as long as they have not yet received a dose of IP, they may be switched to Part D at that same visit (e.g., a subject that is part way through Visit C7 at Week 24 and whose last dose of IP was at Visit C6, Week 20 can be switched to Part D and complete the IP Discontinuation assessments and Visit D7 at that same visit, Week 24).

An Exit Visit will be conducted 52 weeks after randomization (whether the subject is in Part C or Part D) in order to assess subject's efficacy parameters, immunogenicity status, and to conduct additional safety assessments.

Subjects who permanently discontinue study treatment in Part C or D of the study are NOT required to withdraw from the study. If a subject discontinues double blind study treatment during Part C and does not switch to Part D at their next visit (IP

Discontinuation Visit) after experiencing a clinically significant asthma exacerbation, the subject cannot enter Part D at a later visit.

Treatment Arms and Duration

Eligible subjects will participate in the study ranging from 56 to192 weeks, depending on the duration of Part A (0 to 132 weeks) and Part B (4 to 8 weeks). A summary of study phases is described in Table 1.

Table 1 Study Phases, Duration and Study Treatments

Study Phase	Phase Title	Duration	Treatment arms
Part A	Variable Open-Label Run-in	0 to 132 weeks	Open-label mepolizumab (100 mg SC) every 4 weeks
Part B	Fixed Open-Label Run-In	4 weeks (up to 8 weeks)	Open-label mepolizumab (100 mg SC) every 4 weeks
Part C	Double Blind Treatment Period	52 weeks	Subjects randomized 1:1 to double-blind study treatment: • mepolizumab (100 mg SC) every 4 weeks • placebo administered SC every 4 weeks
Optional Part D	Open-Label Switch	Up to 52-weeks post-randomization	Open-label mepolizumab (100 mg SC) every 4 weeks

Type and Number of Subjects

Subjects with severe eosinophilic asthma who completed the Follow Up/Exit Visit or EW Visit from either open-label study MEA115666 or 201312 will be eligible to participate in this study.

Approximately 375 subjects from studies MEA115666 and 201312 are expected to be screened in order for approximately 300 subjects to be randomized 1:1 to double-blind study treatment (150 per arm).

Sample Size and Analysis

With a sample size of 300 randomized subjects (150 per arm), it is estimated that statistical significance will be declared if the proportion of subjects with a clinically significant exacerbation following withdrawal of mepolizumab is 52.5% compared to 40% for those continuing to receive mepolizumab (hazard ratio = 0.686).

If the true hazard ratio is 0.55 (corresponding to a proportion with a clinically significant exacerbation following discontinuation of mepolizumab of 60.5%), then the study has a probability of 90% of observing a hazard ratio of < 0.686 and therefore the study has 90% power for declaring statistical significance on this endpoint.

Time to first clinically significant exacerbation will be compared between treatment groups using a Cox's proportional hazards model allowing for covariates of region, exacerbations in the year prior to randomization and use of baseline maintenance oral corticosteroids (OCS vs no OCS).

2. INTRODUCTION

Eosinophilic inflammation of the airways specifically plays a central role in the pathogenesis of asthma [Cohn, 2004]. Eosinophils are not normally present in healthy lungs, and are thought to play a major role in maintaining airway inflammation [Walsh; 2010; Wadsworth, 2011]. Studies in the severe asthma population have shown that more than half of these patients have persistent eosinophilic (>3% eosinophils) airway inflammation despite corticosteroid therapy [Wenzel, 2005; ENFUMOSA, 2003].

Of the inflammatory mediators postulated to contribute to the regulation of eosinophil trafficking and degranulation, interleukin-5 (IL-5) has been identified as the main cytokine to selectively regulate eosinophil function [Sumitas, 2011]. IL-5 specifically promotes the differentiation of eosinophils in the bone marrow and stimulates the release of eosinophils from the bone marrow into peripheral circulation [Sanderson, 1992; Collins, 1995]. Binding of IL-5 to eosinophil-expressing IL-5 receptors results in enhanced adhesion of eosinophils to endothelial cells and increased eosinophil survival and activation [Lopez, 1988].

Mepolizumab is a humanized anti-interleukin 5 (anti-IL5) antibody (IgG Kappa) that binds to and inactivates IL-5. Mepolizumab is currently under clinical development for the treatment of severe asthma.

2.1. Study Rationale

The efficacy of mepolizumab in severe asthma has been demonstrated over one year of continuous treatment in double-blinded studies. However, it is currently unknown whether chronic exposure is necessary for disease control. It was recently reported that discontinuation of mepolizumab after one year of treatment resulted in the increased presence of eosinophils and a corresponding increase in exacerbation frequency to pre-study levels, suggesting that a treatment response was not sustained after treatment discontinuation [Haldar, 2014]. Beyond one year of treatment, there is no data available on the sustainability of a treatment response following the discontinuation of mepolizumab.

Asthma management guidelines recommend stepping down therapy once control is achieved in an effort to find the patient's minimal effective treatment [GINA, 2015]. Thus, it remains important to understand the duration of response to mepolizumab when treatment is withdrawn after longer-term exposure.

2.2. Brief Background

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

The randomized, multi-centre, placebo-controlled exacerbation studies (MEA112997, MEA115588) and Oral Corticosteroid (OCS) Reduction Study (MEA115575) have demonstrated the efficacy of mepolizumab and support the use of mepolizumab 100 mg

SC every 4 weeks as an add-on therapy for the treatment of severe eosinophilic asthma. Compared with placebo, mepolizumab has been shown to:

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

Additional details of the pharmacology, efficacy and safety can be found in the Investigator Brochure (IB).

3. OBJECTIVES

3.1. Primary Objective

To evaluate whether patients with severe eosinophilic asthma who have received long-term treatment with mepolizumab (at least 3 years) need to maintain treatment with mepolizumab to continue to receive benefit.

3.2. Secondary Objective

To assess the safety and tolerability of mepolizumab continuation compared to placebo following long-term treatment with mepolizumab in patients with severe eosinophilic asthma.

4. ENDPOINTS

Primary Endpoint

- Time to first clinically significant exacerbation

  Clinically significant exacerbations will be defined as worsening of asthma which requires use of systemic corticosteroids[1] and/or hospitalisation and/or ED visits.

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

Secondary Endpoints

- Ratio to baseline in blood eosinophil count at weeks 12, 24, 36 and 52
- Time to a decrease in asthma control, defined as an increase from baseline in Asthma Control Questionnaire-5 (ACQ-5) score of ≥ 0.5 units
- Time to first exacerbation requiring hospitalization or ED visit

Other Endpoints

- Time to first exacerbation requiring hospitalization
- Mean change from baseline in clinic pre-bronchodilator FEV_1 at weeks 12, 24, 36, 52
- Mean change from baseline in clinic post-bronchodilator FEV_1 at weeks 12, 24, 36, 52
- Mean change from baseline in daily salbutamol/albuterol use
- Mean change from baseline in daily asthma symptom scores
- Mean change from baseline in awakening at night due to asthma symptoms requiring rescue medication use
- Mean change from baseline in morning (AM) Peak Expiratory Flow (PEF)
- Time to worsening of asthma (subjects meeting at least 2 of the following 4 criteria for worsening of asthma for at least 2 consecutive days)
    - **AM PEF:** Decrease in AM PEF ≥30% compared with baseline (last 7 days of run-in Part B)
    - **Rescue Medication Use:** An increase of ≥50% in rescue medication compared with the average use for the previous week
    - **Night time awakenings requiring rescue medication:** Awakening due to asthma symptoms requiring rescue medication
    - **Symptoms:** An asthma symptom score of 5
- Mean change from baseline in ACQ-5 score
- Proportion of patients experiencing a decrease in asthma control, defined as an increase from baseline in ACQ-5 score of ≥ 0.5 units
- Proportion of subjects with a clinically meaningful worsening of health-related quality of life measurements (SGRQ) at weeks 12, 24, 36 and 52 (defined as subjects who have a clinically relevant increase from baseline of ≥4 units in SGRQ score).
- Mean change from baseline in SGRQ score at week 12, 24, 36 and 52
- Subject/Clinician global impression of asthma severity rating at weeks 12, 24, 36 and 52

- Subject/Clinician rating of response to therapy at weeks 12, 24, 36 and 52
- Number of days in hospital due to asthma
- Unscheduled healthcare contacts/resource utilisation
- Days off of regular work/school

Safety Endpoints

- Adverse Events and Serious Adverse Events
- Clinical Laboratory parameters
- 12-lead ECG parameters
- Vital Signs

5. STUDY DESIGN

5.1. Overall Design

This is a 52-week, 2-arm, randomized, double-blind, parallel-group, multi-center study evaluating mepolizumab 100 mg and placebo administered SC every 4 weeks in subjects with severe eosinophilic asthma who have been treated with mepolizumab continuously in addition to standard of care therapy for at least 3 years.

Definition of Continuous Mepolizumab Treatment

Continuous treatment with mepolizumab is defined as no more than 2 consecutive missed doses, i.e. no treatment gaps of more than 12 weeks (84 days) between any two doses.

When deriving the period of continuous mepolizumab exposure, treatment from the following studies may be considered: MEA115666, MEA115588, MEA115575, MEA115661 and 201312. The earliest date of initiating mepolizumab treatment may be considered when deriving this total exposure, however if a gap of >84 days between any two doses of mepolizumab is experienced, this exposure period can no longer be considered ‘continuous’. If such an instance occurs the subject's period of continuous mepolizumab treatment will be derived from the first dose of mepolizumab following this gap in mepolizumab treatment.

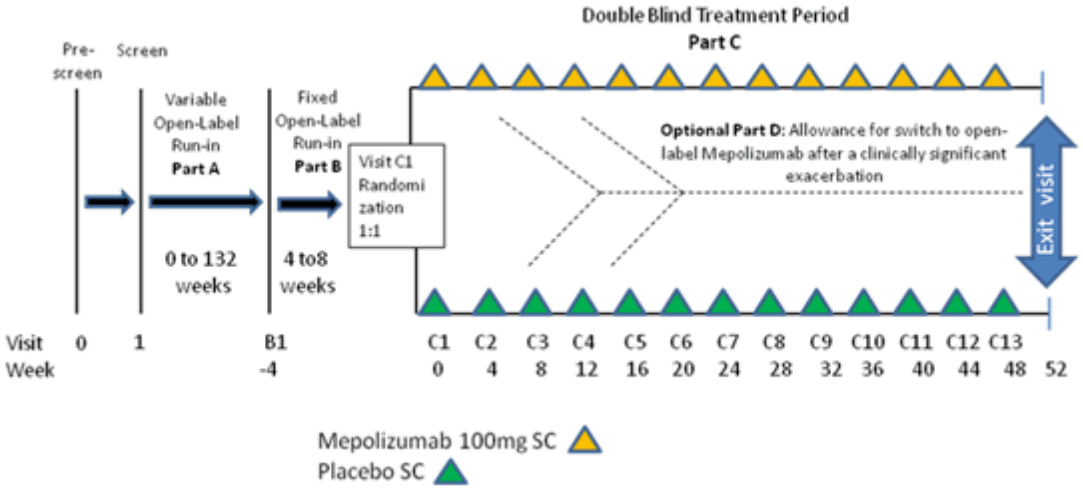
However, if a subject has experienced a gap of >12 weeks (84 days) between any two doses of mepolizumab within studies MEA115666 or 201312 this will exclude the subject from entry into 201810.

It is intended that the Follow Up/Exit Visit or Early Withdrawal (EW) for studies MEA115666 and 201312 will serve as the Pre-Screening/Screening Visit (Visit 0/Visit 1) for this study. For subjects who are unable to complete the Follow Up/Exit Visit or EW from their preceding study and Visit 1 for this study on the same day, a Pre-Screening

Visit (Visit 0) is included in order to obtain the signed informed consent, review concomitant medications, and perform an exacerbation review. In this case, Visit 1 must then be completed within 12 weeks (no more than 84 days) of the last dose in MEA115666/201312 to ensure continuous treatment with mepolizumab is maintained per inclusion criteria (Section 6.1). It is expected that in most cases, the Pre-Screening Visit and Screening Visit will be conducted on the same day.

A study schematic is shown in Figure 1. Assessments at each visit are summarised in the Time and Events Tables (Table 5, Table 6, Table 7 and Table 8).

Figure 1 Study Schematic



Subjects will remain on standard of care asthma therapy (controller therapy) throughout the study. Standard of care will consist of inhaled corticosteroids (ICS) and another controller, e.g. Long-Acting Beta$_2$-Agonists (LABA), with or without maintenance oral corticosteroids (OCS). Standard of care therapy may have been adjusted during the MEA115666 and 201312 studies and may be adjusted during the variable open-label run-in period (Part A) at the discretion of the investigator. During the fixed open-label run-in period (Part B) and the double-blind treatment period (Part C), subjects should maintain the stable dose and regimen of controller therapy established in Part A or studies MEA115666 and 201312.

Any change in controller regimen or dose in Part B and Part C (except for OCS use for the treatment of exacerbations) should be discussed with the medical monitor.

Albuterol/salbutamol will be provided to subjects for use on an as needed basis for relief of asthma symptoms from Visit 1 throughout the study.

Part A and B: Variable and Fixed Open-Label Run-In Periods

At Visit 1 (Screening), eligible subjects will have their exposure period for mepolizumab treatment assessed:

- **Subjects with less than 3 years of mepolizumab treatment** will enter Part A of the study, a variable open-label run-in period on mepolizumab (100 mg SC every 4 weeks) of 4 to 132 weeks, in order for subjects to reach 3 years of exposure to mepolizumab.
    - Once the required 3 year exposure is reached, the subject will enter Part B of the study at Visit B1 and complete a fixed run-in period of 4 weeks (up to 8 weeks) during which open-label mepolizumab (100 mg SC every 4 weeks) is administered, in order to collect baseline information.
- **Subjects with at least 3 years of mepolizumab treatment** will directly enter Part B of the study. For these subjects, assessments for Visit 1 and Visit B1 should be conducted on the same day. No assessments should be duplicated.

Part C: Double-Blind Treatment Period

Upon completion of the fixed run-in period Part B, eligible subjects will be randomized 1:1 to the following double-blind treatment arms at Visit C1:

- mepolizumab (100 mg) administered SC every 4 weeks
- placebo administered SC every 4 weeks

All subjects will be given a paper diary starting at Visit 1 through the Exit Visit or EW to record any medical problems experienced during the study, and any medication taken for those medical problems. Any unscheduled healthcare resource utilization (e.g.; physician visits, emergency department visits) due to asthma will also be recorded.

Subjects will complete a daily electronic diary (eDiary) during the fixed run-in Part B, double-blind treatment period Part C and open-label Part D. Subjects will be asked to provide the following information daily:

- AM Peak flow before rescue medication usage (L/min)
- Rescue medication use
- Nocturnal awakening due to asthma symptoms requiring rescue medication use
- Asthma symptoms
- Missed days of work/school due to asthma

Subjects will also be asked to provide the following information via eDiary weekly:

- Asthma Control Questionnaire-5 (ACQ-5)

Part D: Optional Switch to Open-Label Mepolizumab

Subjects who experience a clinically significant asthma exacerbation during the double-blind treatment period Part C will require a prompt assessment by the investigator to determine if they should continue taking double-blind study treatment.

Subjects deemed to be unsuitable to continue double-blind study treatment by the investigator should discontinue double-blind investigational product (IP) and complete a Discontinuation of IP Visit approximately 4 weeks following their last dose of double-blind IP.

Subjects discontinuing IP due to a clinically significant asthma exacerbation are eligible to enter optional Part D of the study and receive open-label mepolizumab in addition to their standard of care therapy for the remainder of the study, through Part D, to Visit D13. Subjects switching to Part D should complete the Discontinuation of IP Visit and their first Part D visit on the same day, corresponding to the week post-randomization. No assessments should be duplicated.

Switch to Part D between visits: For example, if a subject completed Visit C7 at Week 24 (and the subject received a dose of IP at Visit C7) and it is later determined that they should switch to Part D, the IP Discontinuation assessments and the first visit in Part D will be D8 at Week 28.

Switch to Part D during a visit: If a subject is in the process of completing a Part C visit, as long as they have not yet received a dose of IP, they may be switched to Part D at that same visit (e.g., a subject that is part way through Visit C7 at Week 24 and whose last dose of IP was at Visit C6, Week 20 can be switched to Part D and complete the IP Discontinuation assessments and Visit D7 at that same visit, Week 24).

Haematology samples will be collected for each of the subject's first 3 visits of Part D, and then according to designated Visits in Table 8.

An Exit Visit will be conducted 52 weeks after randomization (whether the subject is in Part C or Part D) in order to assess subject's efficacy parameters, immunogenicity status, and to conduct additional safety assessments.

Subjects who permanently discontinue study treatment in Part C or D of the study are NOT required to withdraw from the study. If a subject discontinues double blind study treatment during Part C and does not switch to Part D at their next visit (IP Discontinuation Visit) after experiencing a clinically significant asthma exacerbation, the subject cannot enter Part D at a later visit.

5.2. Study Phases, Duration and Treatment Arms

Eligible subjects will participate in the study ranging from 56 to192 weeks, depending on the duration of Part A (0 to 132 weeks) and Part B (4 to 8 weeks). A summary of study phases is described in Table 2.

Table 2 Study Phases, Duration and Study Treatments

Study Phase	Phase Title	Duration	Treatment arms
Part A	Variable Open-Label Run-In	0 to 132 weeks	Open-label mepolizumab (100 mg SC) every 4 weeks
Part B	Fixed Open-Label Run-In	4 weeks (up to 8 weeks)	Open-label mepolizumab (100 mg SC) every 4 weeks
Part C	Double Blind Treatment Period	52 weeks	Subjects randomized 1:1 to double-blind study treatment: • mepolizumab (100 mg SC) every 4 weeks • placebo administered SC every 4 weeks
Optional Part D	Open-Label Switch	Up to 52-weeks post-randomization.	Open-label mepolizumab (100 mg SC) every 4 weeks

5.3. Type and Number of Subjects

Subjects with severe eosinophilic asthma who completed the Follow Up/Exit Visit or EW Visit from either open-label study MEA115666 or 201312 will be eligible to participate in this study.

It is estimated that approximately 375 subjects with severe eosinophilic asthma from studies MEA115666 and 201312 are expected to be screened in order to randomize approximately 300 subjects 1:1 to double-blind study treatment (150 per arm). It is anticipated that approximately 120 subjects will experience a clinically significant exacerbation and meet the criteria for the Switch to Open-Label Mepolizumab treatment within Part D. The sample size calculations assume 20% of subjects will withdraw prior to the end of the double-blind treatment phase before experiencing an exacerbation. It is anticipated that approximately 120 subjects will complete the double-blind treatment period within Part C, Visit 13.

5.4. Design Justification

This study is designed to evaluate treatment response following withdrawal of mepolizumab after at least 3 years of treatment in patients with severe eosinophilic asthma comparing mepolizumab continuation with placebo over one year. All subjects should continue standard of care therapy throughout the study, and both mepolizumab and placebo arms will be dosed in addition to standard of care. Subjects who have participated in studies MEA115666 and 201312 are eligible to enroll, as they have been determined to be appropriate candidates for treatment with mepolizumab and will have a substantial duration of mepolizumab treatment. This will minimize the duration of study participation compared to enrolment of mepolizumab naive subjects.

A placebo controlled, double-blinded study is a well established means to compare the effect of treatment in two treatment arms. There are currently no alternative approved therapies for severe eosinophilic asthma and, therefore, the comparator arm will be placebo in addition to standard of care treatment. Standard of care will consist of ICS and another controller, e.g. LABA, with or without maintenance OCS. This is consistent with current standard of care treatment used in a severe asthma population [ATS, 2000; Chung, 2014].

A primary endpoint of time to first clinically significant exacerbation was selected as a robust measure to evaluate the return of disease activity following the discontinuation of mepolizumab treatment after long term use. Additional measures of exacerbation severity are also included. As this study is designed to evaluate withdrawal of treatment after long term use, it is anticipated that the rate of discontinuation from Part C may be high and therefore limit the ability to assess exacerbation rate. An optional switch to open- label mepolizumab is included in the study design (Part D) to collect additional safety data and to prevent loss to follow-up. A study duration of 52 weeks is considered adequate for the evaluation of exacerbations [EMA, 2013].

Part A is designed to ensure that all subjects have a duration of mepolizumab treatment of at least 3 years prior to randomization. The purpose of Part B is to collect baseline eDiary and safety information.

Eosinophil levels are an important proxy of IL-5 activity, the biological target of mepolizumab. Increasing levels of eosinophils after mepolizumab withdrawal after 1 year or treatment have previously shown to be correlated to increasing exacerbation frequency [Haldar, 2014]. Thus, it is important to measure eosinophils as a biomarker of mepolizumab activity in patients who are withdrawn from mepolizumab treatment after long-term treatment. To ensure the integrity of the blind, eosinophil levels will be blinded to both the Investigator/site staff and the study team during Part C and Part D.

The Asthma Control Questionnaire (ACQ-5) will be used to assist the investigator in assessing the subject's asthma status. The ACQ has been validated in several separate studies and the minimal clinically important difference value of ±0.5 has been established to demonstrate a significant clinical change in asthma status [Juniper, 2005].

5.5. Dose Justification

The dose selection is based on previous experience from a Phase 3 program, including two Phase 3 placebo-controlled studies (MEA115588 and MEA115575) that demonstrated the safety and efficacy of mepolizumab at a dose of 100 mg SC. Additionally, this is the same dose that subjects received in precursor studies MEA115666 and 201312. See the IB for additional information.

5.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with mepolizumab can be found in the IB/IB supplement. The following section (Table 3) outlines the risk assessment and mitigation strategy for this protocol:

5.6.1. Risk Assessment

- Across the mepolizumab development program, chronic dosing of mepolizumab up to 750 mg intravenous (IV) every 4 weeks has been associated with an adverse event (AE) profile similar to placebo (both dosed in addition to standard of care therapy), in the patient populations studied, including mild to moderate asthma and severe refractory asthma.
- The majority of reports of systemic non-allergic and allergic (i.e., hypersensitivity) reactions have been non-serious and resolved without sequelae following minimal supportive care. There have been rare reports of serious reactions.
- Anti-drug antibodies (ADA) have been observed infrequently and have not been associated with negative clinical outcomes; there has been no evidence of untoward or persistent neutralizing antibodies (NaB) at any dose.
- Infection rates have been similar across treatment groups. The data to date do not support an association between treatment with mepolizumab and an increased risk of clinically serious opportunistic or parasitic infections.
- Reports of malignancies have been similar between treatment groups in placebo-controlled trials. The known biology of IL-5 and eosinophils suggest that blocking the binding of IL-5 to its receptor with mepolizumab would not likely induce an immuno-suppressive effect that would impair host surveillance against malignancy.
- There is a risk of exacerbation in subjects randomized to placebo (in addition to their standard of care therapy). An increased exacerbation frequency was reported in subjects withdrawn from mepolizumab after one year of treatment [Haldar, 2014]. However, it is undetermined if certain patients will continue to receive treatment benefit after withdrawal of mepolizumab following long-term treatment.

Table 3 Risk Assessment and Mitigation Strategy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) mepolizumab		
Risk of Systemic Allergic and Non-allergic Reactions, including Anaphylaxis	Biopharmaceutical products administered subcutaneously may elicit systemic (e.g. hypersensitivity) and local site reactions. Reactions reported to date across the mepolizumab program are summarized in the IB; see 'Special Warnings and Special Precautions for Use' section located in Section 6 titled 'Summary of Data and Guidance for the Investigator'.	Daily monitoring of serious adverse events (SAEs) by medical monitor; regular systematic review of adverse event (AE)/SAE data from ongoing studies by a GSK safety review team. Specific case report form (CRF) pages utilized for targeted collection of reactions data. Use of Joint NIAID/FAAN 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (see Appendix 8). Safety monitoring of subjects is required during SC administration, in accordance with standard of care at the site.
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. Immunogenicity data reported to date across the mepolizumab development program are summarized in the IB; See 'Clinical	Blood samples are collected in clinical studies for detection of both ADA and NaB. Monitoring of subjects for immunogenic-related events will be done by the treating physician as per standard of care. Immunogenicity profile will be updated in the Mepolizumab IB as appropriate.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Immunogenicity' and a summary of immunogenicity findings in the 'Other Potentially Clinically Relevant Information for the Investigator' section titled 'Summary of Data and Guidance for the Investigator'.	
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 CV function. 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. No clinically relevant trends observed in ECG data in humans. 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	Subjects with uncontrolled, severe or clinically significant cardiovascular disease are excluded from study participation. Daily monitoring of SAEs by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team. CV monitoring for study includes: • ECG monitoring during the trial • 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	Summary of Data/Rationale for Risk	Mitigation Strategy
	System SOC).	
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. Murine data demonstrate that IL-5 antagonism is unlikely to influence cellular or humoral immunity, particularly in response to parasitic infections. 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. An integrated safety analysis of all placebo-controlled multiple dose asthma trials showed similar reports of infections, including serious and opportunistic, across treatment groups including placebo. Infections reported to date across the mepolizumab development program are summarized in the IB; see 'Special Precautions and Warnings' (for exclusion of subjects with underlying parasitic infections) and 'Undesirable Effects' (for very common infections of nasopharyngitis, upper respiratory tract infection (URTI), rhinitis and bronchitis reported in other patient populations) sections	Daily monitoring of SAEs by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team Standard safety assessments to be conducted as outlined in protocol

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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. No evidence of defective tumor surveillance in IL-5 or eosinophil-deficient mice. Direct assessment of the carcinogenic potential of long-term IL-5 blockade in rodent models not technically feasible. An integrated safety analysis of all placebo-controlled multiple dose asthma trials showed similar reports of malignancies across treatment groups including placebo. Malignancies reported to date across the mepolizumab development program are summarized in the IB.	Daily monitoring of SAEs by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team Standard safety assessments to be conducted as outlined in protocol
Placebo		
Inclusion of placebo arm	Mepolizumab has been shown to be an effective treatment for the reduction of exacerbations for patients with severe eosinophilic asthma. There is currently no pre-clinical or clinical evidence to suggest long-term continuation	Both mepolizumab and placebo double-blind study treatments will be dosed in addition to standard of care therapy including corticosteroid treatment (ICS or OCS) and a long-acting bronchodilator.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	of treatment benefit after withdrawal of mepolizumab [Haldar, 2014], however, this has not been prospectively evaluated in subjects after long-term treatment with mepolizumab.	Subjects will be provided with rescue albuterol/salbutamol throughout the study. Subject's condition will be assessed at clinic visits every 4 weeks. Subjects' symptoms and rescue medication usage will be tracked daily via eDiary. Subjects with increasing respiratory symptoms indicative of worsening of asthma will automatically be notified through the symptom diary to contact their investigator for further evaluation. Investigators will also receive alerts, and review eDiary data weekly. Additionally, to minimize the impact of significant worsening due to withdrawal of therapy over 52 weeks, subjects may optionally switch to open-label mepolizumab (Part D) per investigator discretion after experiencing one clinically significant asthma exacerbation.
Potential risk for rebound eosinophilia with associated clinical consequences	Early published data with Schering-Plough anti- IL5 mAb suggested potential for rebound eosinophilia and disease exacerbation when treatment was stopped [Kim, 2004; Gevaert, 2006]; however, no standard definition of rebound was used and criteria for reporting were variable. There have been no verbatim reports of	Daily monitoring of SAEs by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team Standard safety assessments to be conducted as outlined in protocol

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	'rebound' from completed clinical trials of subjects with asthma, atopic dermatitis and eosinophilic esophagitis. Furthermore, the data do not support an exaggerated return of symptoms after cessation of treatment.	
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)

5.6.2. Benefit Assessment

Data from earlier studies [Haldar, 2009; Nair, 2009; Pavord, 2012] attest to the clinical utility of mepolizumab in the treatment of severe eosinophilic asthma, as do the data from recently completed Phase III studies MEA115575 and MEA115588 [Bel, 2014; Ortega, 2014].

In this study, benefit considerations for a subject may include:

- Continuation to receive active drug during study conduct that may have clinical benefit, even for subjects randomized to placebo who may undergo switch to open-label mepolizumab after experiencing one clinically significant asthma exacerbation

- Contributing to the process of developing new therapies in an area of unmet need, and providing insight into the need for continuous therapy in order to receive clinical benefit

- Medical evaluations/assessments associated with study procedures

5.6.3. Overall Benefit:Risk Conclusion

Current data from mepolizumab preclinical and clinical development indicate the ability of mepolizumab to inhibit IL-5 leading to consistent reduction in blood eosinophils, with demonstration of clinical benefit in the treatment of conditions associated with eosinophilic inflammation, such as asthma. Data from the Phase III asthma programme with mepolizumab demonstrates, compared to placebo, a reduction in asthma exacerbations, improvements in asthma control and quality of life (as measured by the ACQ and SGRQ, respectively), improvements in lung function and a reduction in steroid use in those subjects on chronic OCS treatment. To date, the safety profile of mepolizumab compared to placebo has been favorable and AEs reported commonly are non-serious and manageable with minimal supportive care. Furthermore, evaluation of the post-treatment adverse event data from the severe asthma clinical program does not support an exaggerated return of symptoms after cessation of treatment.

Considering the measures taken to minimize risk to a subject participating in this study, the potential risks identified are justified by the anticipated benefits that may be afforded to a subject with severe asthma. Therefore, the Sponsor considers that investigation of the effect of cessation versus continuation of long-term mepolizumab treatment in patients with severe eosinophilic asthma is justified in study 201810 with a positive benefit/risk ratio.

6. SELECTION OF STUDY POPULATION, IP DISCONTINUATION AND WITHDRAWAL CRITERIA

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

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

6.1. Inclusion Criteria

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

1. **Informed Consent:** Prior to commencing any study related activities, subjects must be able and willing to provide written informed consent, and an assent for subjects under 18 years of age, at Visit 0 (or Visit 1 if these Visits are conducted on the same day).
2. **Continuous Mepolizumab Treatment during MEA115666 or 201312:** Participation through the Follow Up/Exit Visit or Early Withdrawal Visit and documented evidence of treatment with mepolizumab with no treatment gaps of more than 12 weeks (84 days) between any two doses within MEA115666 or 201312. (A treatment gap of more than 12 weeks [84 days] cannot occur between the end of MEA115666 or 201312 and Visit 1).
3. **Current Anti-Asthma Therapy:** Asthma is currently being treated with a controller medication and the subject has been on a controller medication for the past 12 weeks. Subjects will be expected to continue controller therapy for the duration of the study.
4. **Male or Eligible Female Subjects:**

   A female is eligible to enter and participate in the study if she is of:

   Non-child bearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is post-menopausal or surgically sterile). Surgically sterile females are defined as those with a documented hysterectomy and/or bilateral oophorectomy or tubal ligation. Post-menopausal females are defined as being amenorrhoeic for greater than 1 year with an appropriate clinical profile, e.g., age appropriate, > 45 years, in the absence of hormone replacement therapy.

   OR

   Child bearing potential, has a negative pregnancy test at screening, and agrees to acceptable contraceptive methods approved in their local country, when used consistently and correctly (i.e., in accordance with the approved product label and the instructions of the physician) for the duration of the study and for 4 months after the last study drug administration (see Appendix 5).

   A urine pregnancy test is required of all females of child-bearing potential at each scheduled study visit prior to the injection of study treatment, and at the Exit Visit, EW or Discontinuation of IP Visit.

5. **French subjects:** In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

6.2. Exclusion Criteria

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

1. **MEA115666 or 201312 IP Discontinuation:** Subjects withdrawn from IP or withdrawn from study participation from either MEA115666 or 201312 for safety reasons
2. **Health Status:** Clinically significant deterioration in health status at the completion of participation or EW from either the MEA115666 or 201312 trials which in the opinion of the investigator would make the subject unsuitable for participation in this study.
3. **Pregnancy:** Subjects who are pregnant or breastfeeding. Subjects should not be enrolled if they plan to become pregnant during the time of study participation.
4. **Cardiovascular:** Subjects who have severe or clinically significant cardiovascular disease uncontrolled with standard treatment. Including but not limited to:
    - known ejection fraction of <30% OR
    - severe heart failure meeting New York Heart Association Class IV classification OR
    - hospitalised in the 12 months prior to Visit 1 for severe heart failure meeting New York Heart Association Class III OR
    - angina diagnosed less than 3 months prior to Visit 1 or at Visit 1
5. **12-Lead ECG:** ECG which has a clinically significant abnormality observed at the Screening Visit as determined by the investigator. Subjects with the following abnormalities are excluded from study participation:
    - QTcF > 450 msec, or
    - QTcF >480 msec for subjects with Bundle Branch Block.
6. **Malignancy:** A current malignancy or previous history of cancer in remission for less than 12 months prior to screening (Subjects that had localized carcinoma of the skin which was resected for cure will not be excluded). [**Note for South Korea**: Korean subjects with a diagnosis of malignancy within 5 years are excluded].
7. **Other Monoclonal Antibodies**: Subjects who have received any monoclonal antibody within 5 half-lives of Visit 1.
8. **Adherence:** Subjects who have known evidence of lack of adherence within studies MEA115666 or 201312 (less than 80%) to controller medications, scheduled study visits and/or ability to follow physician's recommendations.
9. **Smoking status:** Current smokers

10. **Inability to read:** In the opinion of the Investigator, any subject who is unable to read and/or would not be able to complete a questionnaire.

6.3. Randomization Criteria

6.3.1. Randomization Inclusion Criteria

Subjects are eligible for randomization if ALL of the following are met:

1. **Continuous Mepolizumab Treatment:** Documented evidence of at least **3 years (156 weeks) of treatment with mepolizumab** with no treatment gaps of more than 12 weeks (84 days) between any two doses while treated with mepolizumab. See Section 5.1 for the definition of continuous mepolizumab treatment.
2. **eDiary Compliance:** Compliance with completion of the eDiary defined as:

   Symptom Scores: Completion of **symptom scores** on 4 or more days out of the last 7 days immediately preceding Visit C1.

   Rescue Medication Use: Completion of information relating to **rescue medication use** on 4 or more days out of the last 7 days immediately preceding Visit C1.

   PEF Measurements: Completion of **PEF measurements** on 4 or more days out of the last 7 days immediately preceding Visit C1.

   Night time awakenings requiring rescue medication: Completion of **night time awakenings** on 4 or more days out of the last 7 days immediately preceding Visit C1.

Subjects who fail this criterion in the run-in Part B may extend their run-in Part B by 4 weeks, and be re-educated on the importance of completion of eDiary daily entries.

3. **Maintenance Asthma Therapy:** No changes in the dose or regimen of baseline ICS and/or additional controller medication (except for OCS for the treatment of an exacerbation) during the fixed run-in period (Part B).

6.3.2. Randomization Exclusion Criteria

Subjects should not be randomized if ANY of the following are met:

1. **Health Status:** Clinically significant deterioration in health status during Part A or Part B which in the opinion of the investigator would make the subject unsuitable for participation in this study.
2. **12-Lead ECG as assessed at Visit B1:** ECG which has a clinically significant abnormality as assessed at Visit B1, as determined by the investigator. Subjects with the following abnormalities are excluded from further study participation:
   - QTcF > 450 msec, or

- QTcF >480 msec for subjects with Bundle Branch Block.

3. Liver function as assessed at Visit B1:

Alanine transaminase (ALT) >2x upper limit of normal (ULN); and

Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)

Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment).

NOTES:

- Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice, or cirrhosis.
- Chronic stable hepatitis B and C (e.g., presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment) are acceptable if subject otherwise meets entry criteria

4. **Pregnancy:** Positive pregnancy test
5. **Immunogenicity:** Positive neutralizing antibody status based on the last result obtained.
6. **Smoking status:** Current smokers
7. **Current Asthma Exacerbation:** Subjects with an asthma exacerbation (or asthma worsening) that has not resolved completely within 7 days of Visit C1. Subjects who experience an exacerbation (or asthma worsening) in the fixed run-in Part B which is not resolved within 7 days of Visit C1 may extend their run-in Part B by 4 weeks.

6.4. Pre-screen/Screen/Run-in Failures

Pre-screen/screen failures/run-in failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including, but not limited to Demography, Screen Failure details, Eligibility Criteria and Serious Adverse Events (see Section 8.4.1.5).

For the purposes of this study pre-screen/screen failures/run-in failures will be defined as follows:

- Subjects will be assigned a study number at the time of signing the informed consent (Pre-screen Visit). Subjects who do not progress to the Screening Visit will be deemed a pre-screen failure.

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

- Those subjects that enter Part A or Part B, but are not randomized, will be designated as run-in failures.

Subjects who fail to meet inclusion and exclusion criteria at Visit 1 will be considered screen failures and cannot be re-screened.

6.5. Study Withdrawal Prior to Randomization: Withdrawal during Part A or Part B

Subjects have the right to discontinue study participation before the end of the study. A subject may also be asked to discontinue study participation at the investigator's discretion or because the subject met the protocol defined stopping criteria detailed below.

Subjects in Parts A or B of the study MUST discontinue study participation if any of the following stopping criteria are met:

1. **Liver Chemistry**: Meets any of the protocol-defined liver chemistry stopping criteria (see Appendix 2).

   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

   If the liver chemistry stopping criteria are met by any subject participating in this study, treatment restart or re-challenge is not permitted.

2. **Pregnancy**: Positive pregnancy test
3. **Laboratory abnormality:** Evidence of clinically significant abnormality in the haematological or biochemical screen, which in the opinion of the investigator would make the subject unsuitable for participation in this study.
4. **Hepatitis Status:** Positive Hepatitis B Surface Antigen (HBsAg) screen conducted at Visit 1.
5. **ECG**: Discontinuation is required if any of the following ECG criteria are met during the study:
   - QTcF>500 msec or uncorrected QT>600 msec
   - Change from Visit 1 baseline: QTcF> 60msec

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

Visit 1 Baseline QTc with Bundle Branch Block	**Discontinuation QTc with Bundle Branch Block**
< 450 msec	> 500 msec
450 – 480 msec	≥ 530 msec [Note: QTc(F)>500 msec for Korean subjects]

Details on performing ECG assessments can be found in Section 8.4.5.

Subjects who discontinue open-label mepolizumab/withdraw from study participation during Part A or Part B should return to the clinic for an Early Withdrawal (EW) visit (Section 6.6.1) and to return any study materials approximately 4 weeks following their last dose of open-label mepolizumab. No additional follow-up is needed.

Subjects withdrawing from study participation in Part A or Part B, prior to randomization will be classified as **run-in failures,** as appropriate (Section 6.4).

6.6. Discontinuation of Investigational Product (IP) during Part C or Part D

Subjects in study Part C or D who have permanently discontinued double-blind or open-label IP are NOT required to withdraw from the study. Subjects have the right to permanently discontinue IP before the end of the study. A subject may also be asked to discontinue IP at the investigator's discretion or because the subject met the protocol defined IP discontinuation criteria detailed below. Subjects who discontinue IP, but remain in the study will be treated per local standard of care, according to the judgment of the investigator.

Subjects in Parts C or D of the study MUST discontinue IP permanently if either 1, 2 or 3 of the following stopping criteria are met:

1. **Liver Chemistry**: Meets any of the protocol-defined liver chemistry stopping criteria (see Appendix 2).

   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

   If the liver chemistry stopping criteria are met by any subject participating in this study, treatment restart or re-challenge is not permitted.

2. **Pregnancy**: Positive pregnancy test

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

   - QTcF>500 msec or uncorrected QT>600 msec
   - Change from Visit B1 baseline: QTcF> 60msec

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

Visit B1 Baseline QTc with Bundle Branch Block	**Discontinuation QTc with Bundle Branch Block**
< 450 msec	> 500 msec
450 – 480 msec	≥ 530 msec [Note: QTc(F)>500 msec for Korean subjects]

   Details on performing ECG assessments can be found in Section 8.4.5.

Subjects in Part C who meet IP discontinuation criteria 1, 2 or 3 will not be eligible to switch to open-label Part D.

Subjects who have permanently discontinued IP and have not withdrawn consent may continue in the study. Subjects wishing to remain in the study will complete an IP Discontinuation Visit (approximately 4 weeks after the last dose and may be at the same time as a scheduled visit) and continue to attend the clinic visits at the protocol designated time intervals and complete eDiary daily and weekly entries for important efficacy and safety assessments. However, if this is not possible then the investigator will encourage the subject to participate in as much of the study as they are willing (or able) to. Guidance is provided in the study reference manual (SRM) and can be used by the investigator to discuss and agree the appropriate level of ongoing study participation with subjects, after they have discontinued IP.

If the subject is unable to visit the clinic to complete any study assessments which require physical presence of the subject, visits will occur by telephone contact to review the following:

- Exacerbations
- Adverse Event (AE)/Serious Adverse Events (SAEs)
- Concomitant medications

Subjects discontinuing IP, but remaining in the study should continue to record on their paper diary any medical problems experienced during the study, and any medication taken for those medical problems.

6.6.1. IP Discontinuation Visit Assessments

The Investigator must make every effort to have the subject return to the clinic approximately 4 weeks after the subject permanently discontinues IP in order to complete the IP Discontinuation Visit. Evaluations and procedures as outlined in the Time and Events Tables (Table 5, Table 6, Table 7 and Table 8) should be completed and recorded in the eCRF as required.

6.6.2. Reasons for Discontinuation of IP

The primary reason for permanent discontinuation of IP will be recorded in the eCRF on the IP discontinuation form. Specific regard should be given to distinguishing permanent discontinuation of IP due to an adverse event from other reasons for permanent discontinuation of IP.

6.7. Study Withdrawal During Part C or Part D

6.7.1. Study Withdrawal Criteria

For this study there are no pre-determined protocol specific study withdrawal criteria (see Protocol Defined IP Discontinuation Criteria, Section 6.6).

6.7.2. Study Withdrawal Assessments

If a subject is withdrawn from the study for any reason, including but not limited to the Protocol Defined IP Discontinuation Criteria (Section 6.6), the Investigator must make every effort to have the subject to return to the clinic for an EW Visit approximately 4 weeks following the last dose to perform EW Visit assessments and to return all study-related materials. Assessments are described in the Time and Events Tables (Table 5, Table 6, Table 7 and Table 8).

Subjects who have previously discontinued IP and have already completed their IP Discontinuation Visit (approximately 4 weeks following the last dose) but then decide at a later date that they no longer wish to participate in the study, will be asked to return to the clinic to complete an EW Visit (approximately 4±1 weeks) to complete any EW assessments, as agreed by the subject and investigator, and to return any remaining study materials. No additional safety follow-up visit is required.

6.7.3. Reasons for Withdrawal

The primary reason for study withdrawal will be recorded in the eCRF. Specific regard should be given to distinguishing withdrawal due to an adverse event from other reasons for withdrawal.

6.7.4. Lost to Follow Up

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

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

6.8. Subject and Study Completion

A subject will be considered to have completed study treatment if he/she receives study treatment at Visit C13 or D13 (Week 48). A subject will be considered to have completed the study if they continue to participate in the study until the Exit Visit assessments have been completed (regardless of whether the subject completed the study treatment schedule).

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

7. STUDY TREATMENT

7.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

Mepolizumab (SB-240563) is a fully humanised IgG antibody (IgG1, kappa) with human heavy and light chain frameworks. Mepolizumab will be provided as a lyophilised cake in sterile vials for individual use. The vial will be reconstituted with Sterile Water for Injection, as described in the SRM.

The placebo in this study will be 0.9% sodium chloride solution and will be provided by the study site.

Trade label albuterol/salbutamol metered dose inhalers (MDIs) will be provided as rescue medication throughout the study. Albuterol/salbutamol will be sourced by GSK for centers in the United States of America. For all other centers it will be sourced locally where possible. Subjects will be dispensed an MDI at the time of Visit 1 to be used to primarily treat asthma symptoms on an as needed basis. The MDI should be replaced as needed, and collected at the Exit Visit or EW visit.

Safety monitoring of subjects is required during SC administration in accordance with standard of care at the site. Such monitoring will include general safety monitoring including monitoring for systemic (i.e., allergic/IgE-mediated and non-allergic) and local injection site reactions. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study treatment, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the subject including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the patient to another facility for additional care if appropriate.

7.2. Treatment Assignment

At the Randomization Visit (Visit C1) those subjects who meet the randomization eligibility criteria will be randomized in a 1:1 ratio to receive one of the following study treatments every 4 weeks in addition to their standard of care asthma treatment:

- Mepolizumab 100mg SC into the upper arm or thigh
- Placebo 0.9% sodium chloride SC into the upper arm or thigh

Subjects eligible to enter the study will be assigned to treatment randomly via an interactive response technology (IRT) system.

The randomization schedule will be generated using the GSK validated randomization software RandAll NG. The study will be randomized separately for each country. Subjects will be assigned to study treatment in accordance with the randomization schedule. Once a randomization number has been assigned to a subject, it cannot be reassigned to any other subject in the study.

7.3. Blinding

Study treatment will be prepared by a designated **unblinded** member of the study site staff (i.e. a qualified person who is independent of the protocol-defined study assessments) and will be administered by a designated **blinded** member of the site staff. Once prepared, mepolizumab and placebo will be identical in appearance. The blinding of all those involved in the evaluation of the study treatment (e.g. physician/nurse as well as the subject) shall be maintained at all times, therefore, procedures must be in-place at the study site to ensure that this blinding is maintained. Additionally, the site staff and central study team will be blinded to each subject's eosinophil count (including blood count differential) and IL-5 values within Part C and D.

With regards to the emergency unblinding of the study treatment assigned to a specific subject, the following will apply:

- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.

- Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
- If the treatment code assigned to a subject in Part C is unblinded to the subject, Investigator and/or the treating physician/blinded member of site staff, please consult the Study Reference Manual and GSK for guidance. Remediation will be assessed on a case by case basis to minimise the impact of any possible bias.
- The date and reason for the unblinding must be fully documented in the eCRF
- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

7.4. Packaging and Labeling

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

7.5. Preparation/Handling/Storage/Accountability

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

A description of the methods and materials required for the preparation of placebo or reconstitution of mepolizumab will be detailed in the unblinded staff manual which is available in the SRM.

A qualified **unblinded** site staff member assigned to the study will be required to prepare the appropriate study treatment according to the study subject's treatment assignment (see Section 7.2 for further details on treatment assignment):

- **Mepolizumab:** 1 mL of reconstituted mepolizumab (equivalent to 100 mg of mepolizumab) will be drawn into a 1 mL polypropylene syringe.
- **Placebo:** 1 mL of 0.9% sodium chloride solution will be drawn into a 1mL polypropylene syringe.

A **blinded** staff member will administer the study treatment into the subject's upper arm or thigh via SC injection.

- Under normal conditions of handling and administration, study treatment 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. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- 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.
- 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's unblinded site staff.
- In accordance with local regulatory requirements, the investigator's designated unblinded site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and the investigator or designated blinded site staff will document the amount administered to study subjects. The designated unblinded site staff will document the amount returned by blinded staff, and the amount received from and returned to GSK, when applicable. Product dispensing/accountability logs will be maintained by a designated unblinded member of the site staff throughout the study.

Further guidance and information for final disposition of unused study treatment are provided in the SRM.

7.6. Compliance with Study Treatment Administration

Mepolizumab and placebo will be administered via SC injection to subjects at the study site. Administration will be documented in the source documents and reported in the eCRF.

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

7.8. Treatment after the End of the Study

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

There are no plans to routinely provide mepolizumab following study completion, as mepolizumab is expected to be commercially available in the countries participating in this study.

7.9. Concomitant Medications and Non-Drug Therapies

Details of asthma-related medications taken from 12 weeks prior to the first dose of study medication (Visit 1), until the Exit Visit or EW, will be collected and recorded in the eCRF (except rescue medication, which is only recorded in the eDiary).

Details of non-asthma-related medications taken from the first dose of study medication (Visit 1) until the Exit Visit or EW, will be collected and recorded in the eCRF.

The minimum requirement for recording of concomitant medication is that the drug name and the start and stop dates of administration are recorded in the eCRF.

7.9.1. Permitted Medications and Non-Drug Therapies

Standard of care will consist of ICS and another controller, e.g. LABA, with or without maintenance OCS.

During the fixed open-label period (Part B) and the double-blind treatment period (Part C), subjects should maintain the stable dose and regimen of controller therapy established in Part A or in studies MEA115666 and 201312. Any change in controller regimen or dose in Part B and Part C (except for OCS use for the treatment of exacerbations) should be discussed with the medical monitor.

Additional asthma medications such as theophyllines or anti-leukotrienes will be permitted provided that they have been taken regularly (per label) in the 12 weeks prior to randomization (Visit C1). If uncertain whether a medication is permitted please confirm with the medical monitor.

Albuterol/salbutamol is permitted throughout the study, except in the 6 hour period prior to spirometry conducted at clinic visits. Study provided Albuterol/salbutamol should NOT be recorded in the eCRF, but will be captured in the eDiary.

LABAs or ICS/LABA fixed dose combinations should be withheld for ≥ 12 hours prior to spirometry, if possible.

Continuous Positive Airway Pressure (CPAP) for the treatment of obstructive sleep apnea is permitted, if initiated prior to the Screening Visit (Visit 1). This treatment must be captured in the eCRF.

7.9.2. Prohibited Medications and Non-Drug Therapies

The following medications are not permitted during the 201810 study:

Table 4 Medications not permitted during the study

Medications
Investigational drugs (other than mepolizumab)
Other monoclonal antibodies
Experimental anti-inflammatory drugs
Any medication with a significant immunosupressive effect. (some examples listed below)
• Methotrexate, troleandomycin, cyclosporin, azathioprine
• Oral gold
• Chemotherapy
• Regular systemic (oral or parenteral) corticosteroids for the treatment of conditions other than asthma
• Long acting depot, intramuscular injections of corticosteroids if used to treat a condition other than asthma

Additionally, Bronchial Thermoplasty and Radiotherapy are excluded for 12 months prior to Visit 1 and throughout the study.

Neither CPAP nor oxygen therapy may be initiated on or after Visit 1.

Recreational drug use is not allowed during the study.

If uncertain whether a medication is permitted please contact the medical monitor prior to administration to confirm if the medication is prohibited.

8. 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, Section 8.1.

8.1. Time and Events Tables

Table 5 Time and Events Table: Screening/Variable Open-Label Run-In Weeks 0 - 52 - Part A

PART A **Procedures**	**Pre-Screen[1]**	**Exit/EW Visit MEA115666 or 201312/ Screen[1]**	**Variable Open-Label Treatment Part A[2] (window is ± 1 week)**													EW Visit[5]
Visit	**0**	**1**	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**	**A10**	**A11**	**A12**	**A13**	
Week of Variable Run-In		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Written Informed Consent	X															
Demography		X														
Medical History		X														
Assess cardiac risk factors		X														
Smoking status		X														
Inclusion/Exclusion Criteria		X														
Safety Assessments[3]																
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination		X												X		X
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG		X						X						X		X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[3]																
Haematology		X						X						X		X
Chemistry (incl. LFT)		X						X						X		X
Pregnancy Test[4]		U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Immunogenicity		X												X		X
HbsAg and hepatitis C antibody		X														
Efficacy Assessments[3]																
Exacerbation review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Asthma Control Questionnaire-5		X			X			X			X			X		X

PART A **Procedures**	**Pre-Screen[1]**	**Exit/EW Visit MEA115666 or 201312/ Screen[1]**	**Variable Open-Label Treatment Part A[2] (window is ± 1 week)**													EW Visit[5]
Visit	**0**	**1**	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**	**A10**	**A11**	**A12**	**A13**	
Week of Variable Run-In		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Spirometry		X						X						X		X
Worksheets/Diary/IP/ eCRF																
Administer open-label mepolizumab		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense albuterol/salbutamol		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect albuterol/salbutamol			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense paper diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect/review paper diary			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	X															X
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. The Pre-Screen Visit and Screening Visit may occur on the same day.
2. Visits should be conducted every 4 weeks until the subject has reached 3 years of mepolizumab exposure.
3. Please see the SRM for details on which screening procedures to perform for subjects entering from 201312 and MEA115666. ALL procedures should be completed prior to dosing with open-label mepolizumab.
4. Urine pregnancy tests (U) should be conducted for women of child bearing potential.
5. EW = Early Withdrawal. Should be conducted 4 ± 1 weeks from the subject's last dose

Table 6 Time and Events Table: Screening/Variable Open-Label Run-In Weeks 56 - 132- Part A

PART A Procedures	Variable Open-Label Treatment Part A[1] (window is ± 1 week)													EW Visit[3]
Visit	**A14/A27**	**A15/A28**	**A16/A29**	**A17/A30**	**A18/A31**	**A19/A32**	**A20/A33**	**A21**	**A22**	**A23**	**A24**	**A25**	**A26**	
Week of Variable Run-In	**56/108**	**60/112**	**64/116**	**68/120**	**72/124**	**76/128**	**80/132**	**84**	**88**	**92**	**96**	**100**	**104**	
Safety Assessments														
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination												X		X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG					X							X		X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments														
Haematology					X							X		X
Chemistry (incl. LFT)					X							X		X
Pregnancy Test[2]	U	U	U	U	U	U	U	U	U	U	U	U	U	X
Immunogenicity												X		X
Efficacy Assessments														
Exacerbation review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Asthma Control Questionnaire-5		X			X			X				X		X
Spirometry					X							X		X
Worksheets/Diary/IP/eCRF														
Administer open-label mepolizumab	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense albuterol/salbutamol	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect albuterol/salbutamol	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense paper diary	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect/review paper diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT														X
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Visits should be conducted every 4 weeks until the subject has reached 3 years of mepolizumab exposure.
2. Urine pregnancy tests (U) should be conducted for women of child bearing potential.
3. EW = Early Withdrawal. Should be conducted 4 ± 1 weeks from the subject's last dose

Table 7 Time and Events Table: Fixed Run-In & Double-Blind Treatment Period – Parts B and C

PARTS B&C Procedures	Fixed Run-in Part B		EW from Part B[7]	Randomization	Double-Blind Treatment Part C (window is ± 1 week)												IPDISC/EW Visit [7]
Visit	**B1**	**B2[1]**	**Part B EW**	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**	**C13**	**Exit Visit**	
Week of Study	**-4 ± 1**	**-4 ± 1[1]**		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Smoking status				X														
Randomization Criteria				X														
Safety Assessments[2]																		
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X		X	X													X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X		X							X							X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[2]																		
Haematology	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry (incl. LFT)	X		X	X						X							X	X
Biomarkers				X	X	X	X	X	X	X							X	X
Pregnancy Test [3]	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Immunogenicity			X														X	X
Efficacy Assessments[2]																		
Subject/Clinician Global Impression Rating				X			X			X			X				X	X
Subject/Clinician Rating of Response to Therapy							X			X			X				X	X

PARTS B&C Procedures	Fixed Run-in Part B		EW from Part B[7]	Randomization	Double-Blind Treatment Part C (window is ± 1 week)												IPDISC/EW Visit [7]
Visit	**B1**	**B2[1]**	**Part B EW**	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**	**C13**	**Exit Visit**	
Week of Study	**-4 ± 1**	**-4 ± 1[1]**		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
SGRQ				X			X			X			X				X	X
Exacerbation review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry (pre- and post-albuterol/salbutamol)			X[8]	X			X			X			X				X	X
Healthcare resource utilization					X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review eDiary[4] (symptoms, rescue use, nocturnal awakenings, PEF, ACQ-5, missed days of work/school)	←																	→
Worksheets/Diary/IP/ eCRF[2]																		
Administer open-label mepolizumab[4]	X	X																
Administer double blind study treatment				X[5]	X	X	X	X	X	X	X	X	X	X	X	X		
Dispense albuterol/salbutamol	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Collect albuterol/salbutamol	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense paper diary	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Dispense eDiary	X																	
Collect eDiary			X														X	X[6]

PARTS B&C Procedures	Fixed Run-in Part B		EW from Part B[7]	Randomization	Double-Blind Treatment Part C (window is ± 1 week)													IPDISC/EW Visit [7]
Visit	**B1**	**B2[1]**	**Part B EW**	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**	**C13**	**Exit Visit**	
Week of Study	**-4 ± 1**	**-4 ± 1[1]**		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Collect/review paper diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT			X	X													X	X
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Visit B2 is only intended for subjects who experience an exacerbation in the run-in Part B which is not resolved within 7 days of Visit C1 or subjects who fail eDiary Compliance Criteria (Section 6.3).
2. All assessments to be completed prior to dosing.
3. Urine pregnancy tests (U) should be conducted every 4 weeks for women of child bearing potential.
4. Subjects eDiary entries should be reviewed by the site weekly during Part C
5. An unblinding card will be dispensed after Randomization at Visit C1.
6. The eDiary is only collected at an Early Withdrawal visit and not at IPDISC in Part C.
7. IPDISC/EW visit should be conducted 4 ± 1 weeks from the subject's last dose
8. Only *pre*-bronchodilator spirometry required at this visit.

Table 8 Time and Events Table: Optional Open-Label Switch to Mepolizumab – Part D

PART D Procedures	OPTIONAL Open-Label Switch to mepolizumab Part D[1] (window is ± 1 week)														IPDISC/EW Visit [8]
Visit	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D13**	**Exit Visit**	
Week of Study[2]	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Safety Assessments[3]															
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination														X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG							X							X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[3]															
Haematology[4]				X			X			X				X	X
Chemistry (incl. LFT)							X							X	X
Pregnancy Test [5]	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Immunogenicity														X	X
Efficacy Assessments[3]															
Exacerbation review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry				X			X			X				X	X
Worksheets/Diary/IP/ eCRF[3]															
Administer open-label mepolizumab	X	X	X	X	X	X	X	X	X	X	X	X	X		
Dispense albuterol/salbutamol	X	X	X	X	X	X	X	X	X	X	X	X	X		
Collect albuterol/salbutamol	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense paper diary	X	X	X	X	X	X	X	X	X	X	X	X	X		
Review eDiary[6] (symptoms, rescue use, nocturnal awakenings, PEF, ACQ-5, missed days of work/school)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect eDiary														X	X[7]

PART D **Procedures**	**OPTIONAL Open-Label Switch to mepolizumab Part D[1] (window is ± 1 week)**														**IPDISC/EW Visit [8]**
Visit	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D13**	**Exit Visit**	
Week of Study[2]	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Collect/review paper diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT														X	X
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. The combined treatment period (Part C) and any switch to open-label mepolizumab (Part D) should not exceed a total duration of 52 weeks.
2. Subjects may enter the Open-label Switch Part D at any point during Part C provided they meet switch criteria, starting with the week of study that the switch is made and continuing until week 52, discontinuation of IP or early withdrawal.
3. All assessments to be completed prior to dosing
4. Haematology samples will be collected for each of the subject's first 3 visits of Part D, and then according to designated Visits in Table 8
5. Urine pregnancy tests (U) should be conducted every 4 weeks for women of child bearing potential.
6. The eDiary should be reviewed at each visit. Weekly review is not required in Part D.
7. The eDiary is only collected at an Early Withdrawal or Exit visit.
8. IPDISC/EW visit should be conducted 4 ± 1 weeks from the subject's last dose

8.2. Screening and Critical Baseline Assessments

Informed consent/assent will be obtained at the Pre-screen Visit or Screening Visit (if Pre-screen and Screening Visits are performed on the same day).

8.2.1. Critical procedures performed at Screening (Visit 1)

If the MEA115666 or 201312 Exit Visit/EW and 201810 Screening Visit are conducted on different days (no more than 84 days apart), the Physical Exam, Immunogenicity assessment, and Spirometry do not need to be repeated at Screening. Other assessments should be conducted at the Screening Visit. Please see the Study Reference Manual (SRM) for full details.

- Review Inclusion/Exclusion criteria (see Section 6)
- Demographic information including gender, ethnic origin, race, year of birth
- Medical history including smoking status, history of sinusitis, nasal polyposis, aspirin allergy, courses of rescue corticosteroids
- Vital signs
- Physical exam
- Resting 12 lead ECG
- Therapy history (review concomitant medications from the previous 12 weeks prior to the first dose of study medication)
- Cardiovascular medical history/risk factors (as detailed in the eCRF) will be assessed at screening. This assessment must include a review of the subject responses to the cardiovascular assessment questions (see Appendix 6)
- Exacerbation review
- Smoking status
- Asthma Control Questionnaire (ACQ-5)
- Spirometry
- Laboratory tests:
  - Chemistry (including liver function test [LFT])
  - Haematology with differential
  - Immunogenicity
  - Hepatitis B Surface Antigen and hepatitis C antibody
  - Urine pregnancy test- for all females of child bearing potential (Follicle Stimulating Hormone [FSH] will be assessed to confirm child-bearing status, if clinically indicated)
- AE/SAE assessment

8.2.2. Critical procedures performed at entry to Part B (Visit B1)

- Vital signs
- Resting 12- lead ECG
- Physical examination
- Concomitant medication review
- Exacerbation review
- Laboratory tests:
  - Chemistry (including LFT)
  - Haematology with differential
  - Urine pregnancy test- for all females of child bearing potential
- AE/SAE assessment

8.2.3. Critical procedures performed at Randomization (Visit C1)

- History of previous intubations, asthma exacerbation history in previous year, asthma triggers
- Review of randomization criteria (see Section 6.3)
- Subject/Clinician global impression of asthma severity rating
- St. George's Respiratory Questionnaire (SGRQ)
- Vital signs
- Physical examination
- Spirometry (pre- and post-albuterol/salbutamol)
- Review/Collect eDiary data
- Exacerbation review
- Smoking status
- Concomitant medication assessment
- Laboratory tests:
  - Clinical Chemistry (including LFT)
  - Haematology with differential
  - Biomarker sample
  - Urine pregnancy test for all females of childbearing potential
- AE/SAE assessment

8.3. Efficacy

8.3.1. Efficacy Endpoints

Efficacy endpoints are listed in Section 4.

8.3.2. Efficacy Assessments

The timings of all efficacy assessments are documented in the Time and Events Schedules (Table 5, Table 6, Table 7 and Table 8).

8.3.2.1. Asthma Exacerbations

C***linically significant exacerbations*** of asthma are defined by:

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

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

Clinically significant exacerbations recorded in the eCRF by the Investigator or designee will be verified using eDiary data to confirm that the exacerbation was associated with changes in:

- AM peak flow (L/min)
- rescue medication use
- nocturnal awakening due to asthma symptoms requiring rescue medication use
- symptoms

In the case that an event described as a clinically significant exacerbation is not associated with deterioration in at least one of these objective eDiary parameters, the investigator will be asked to provide an explanation to support the decision for defining the event as an exacerbation. In those circumstances where the event cannot be supported by any objective assessment, the case will not be included as a protocol defined clinically significant exacerbation, but will be included as an investigator defined exacerbation. This verification process will be overseen by GSK clinical staff to ensure consistency. Additional details on the process for determination of clinically significant exacerbations can be found in the Reporting and Analysis Plan (RAP).

Details of each asthma exacerbation, including medications used to treat exacerbations should be recorded in the eCRF.

Asthma exacerbations should not be recorded as an Adverse Event unless they meet the definition of a Serious Adverse Event.

The time period for collection of exacerbation information in the eCRF will be from the time that the ICF is signed until the Exit Visit or EW.

8.3.2.1.1. Guideline for Assessing Multiple Exacerbations

Exacerbations which are separated by less than 7 days will be treated as a continuation of the same exacerbation.

8.3.2.2. eDiary Reporting, Worsening of Asthma and Alerts: Part B, C and D

Subjects should be instructed to bring their eDiary to each Clinic Visit in Part B, Part C and Part D.

The subject will be asked to record the following parameters **daily** in the eDiary from Visit B1 until the completion of Part C or Part D:

- Morning peak flow (best of three), before rescue medication usage (L/min).
- Asthma symptom score over the previous 24-hours using a 6-point scale (Appendix 7)
- Occasions of rescue medication usage over the previous 24-hours
- Frequency of awakening due to asthma symptoms requiring rescue medication use

8.3.2.2.1. eDiary Alerts Indicating Worsening of Asthma

For safety the following alerts, indicative of worsening asthma, will be programmed into the eDiary with instructions to contact the investigator if any of the alert criteria are met.

NOTE: An alert in itself will not qualify as a clinically significant exacerbation:

- Decrease in morning PEF ≥30% on at least two of three consecutive days, compared with baseline (last 7 days of run-in Part B)
- A symptom score of 5 for at least two of three consecutive days
- An increase of ≥50% in occasions of rescue medication on at least two of three consecutive days, compared with the average use for the previous week.
- Awakening due to asthma symptoms requiring rescue medication use for at least two of three consecutive nights.

Sites should review subject data weekly during Part C through a study specific web portal, and contact subjects for follow-up as appropriate. Additionally, eDiary data will be reviewed at each clinic visit in Parts C and D by the site staff throughout the treatment period to confirm an association between any exacerbation event and eDiary data.

8.3.2.2.2. eDiary Daily Entry: Missed Days of Work or School

Subjects who work for pay or go to school on a regular basis will record in the eDiary any full and part days of missed work or school due to asthma.

8.3.2.2.3. eDiary Weekly Entry: Asthma Control Questionnaire-5 (ACQ-5)

Subjects in Part B, Part C and Part D should complete the ACQ-5 on their eDiary once weekly.

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

8.3.2.2.4. eDiary Compliance

Subjects should be compliant in completing their daily eDiary entries between each pair of on-treatment visits. Subjects should be ≥80% compliant with completion of their eDiary. Subjects who are non-compliant (<80%) should be re-educated on the requirement for daily diary entry compliance, and this re-education should be documented in the subjects source notes.

8.3.2.3. Paper Diary

Subjects will be issued a paper worksheet to record adverse events, changes in concomitant medications and any visits to the hospital and/or emergency department during the study. Subjects will be asked to bring their worksheet to every study visit as it will be used to assist subject recall in discussions with the investigator, for site staff to then enter as appropriate in the eCRF.

8.3.2.4. Spirometry

Spirometry will be performed to assess FEV_1 and FVC using the sites own equipment as detailed in the Time and Events Tables (Table 5, Table 6, Table 7 and Table 8).

The spirometer should meet American Thoracic Society standards and produce a print out of all data generated, which should be stored in the subjects source notes. The spirometer should be calibrated per manufacturer's instructions and a calibration log maintained.

At least 3 acceptable and ideally, 2 repeatable spirometry manoeuvres (from a maximum of 8 attempts) should be achieved on each occasion that spirometry assessments are performed, in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) standards [Miller, 2005]. At each visit, spirometry assessments should be performed at the same time of day (± 2 hours) as the baseline assessment for that part of the study (i.e., the same time of day as Visit 1 for Part A, Visit B1 for Part B, Visit C1 for Part C). Subjects should withhold rescue albuterol/salbutamol for ≥ 6 hours and LABAs or ICS/LABA fixed dose combinations for ≥ 12 hours prior to spirometry, if possible.

Details on performing the spirometry assessments, as well as specific instructions on performing the spirometry manoeuvres, are documented in the SRM.

8.3.2.4.1. Pre- and Post-Albuterol/Salbutamol Spirometry

At all spirometry assessments conducted within Part B and Part C, both pre- and post-albuterol/salbutamol spirometry will be obtained.

Bronchodilator responsiveness testing will be completed as follows:

- Following pre-albuterol/salbutamol spirometry, the subject will self-administer 4 puffs of albuterol/salbutamol via MDI. Spirometry efforts should be obtained approximately 10 to 30 minutes after albuterol/salbutamol administration.

8.3.2.5. Paper-based Asthma Control Questionnaire-5 (Part A only)

Subjects in Part A of the study will complete the ACQ-5 at specified clinic visits (Table 5 and Table 6) on paper, and their responses will be entered by site staff into the eCRF.

Note: In parts B, C and D the ACQ-5 will be completed by subjects using their eDiary (Section 8.3.2.2.3).

8.3.2.6. St. George's Respiratory Questionnaire (SGRQ)

The St. George's Respiratory Questionnaire is a well established instrument, comprising 50 questions designed to measure Quality of Life in patients with diseases of airway obstruction, measuring symptoms, impact, and activity. The questions are designed to be self-completed by the subject, taking on average 20 minutes [Jones, 1992] with a recall over the past 4 weeks. It has been used successfully in studies of chronic obstructive pulmonary disease (COPD) and asthma subjects and has been translated and validated for use in most major languages. Research has demonstrated that it is sensitive to change, and interpretation of the results has been enhanced by determination of the score change necessary to achieve a clinically meaningful improvement in quality of life [Jones, 2002].

Additional instructions for the completion of SGRQ are provided in the SRM.

8.3.2.7. Subject/Clinician Rating of Global Impression of Disease Severity and Response to Therapy

The Global Impressions of Disease Severity and Response to Therapy should be the first procedure completed by the subject and clinician (Primary or Sub Investigators) at the specified study visit. To avoid biasing responses, the subjects should not be told the results of diagnostic tests prior to completing the questionnaires and these questionnaires should be completed before any procedures are performed on the subject to avoid influencing the subject's and Investigator's response.

Additional instructions will be found in the SRM.

Global Impression of Disease Severity: The investigator (or designee) and subject will complete a Global Impression of Disease Severity question at Randomisation and visits described in Table 7. This single global question will ask subjects and clinicians to rate the subject's asthma severity on a four-point scale (mild, moderate, severe, very severe).

Response to Therapy: The investigator (or designee) and subject will also be asked to rate the subject's response to therapy at specified visits (Table 7). This is an overall evaluation of response to treatment, *as compared to Visit C1*. This will be conducted separately by the investigator (or designee) and the subject using a seven-point rating scale as follows:

1 = significantly improved
2 = moderately improved
3 = mildly improved
4 = no change
5 = mildly worse
6 = moderately worse
7 = significantly worse

8.3.2.8. Healthcare Resource Utilization

All unscheduled asthma-related visits to a physician's office, visits to urgent care, visits to the emergency department, and hospitalizations associated with the subject's asthma will be recorded in the eCRF.

At Visits C2 through the Part C Exit Visit or EW, the resource utilization worksheet used by the patient to record all health care contacts experienced since the last visit will be presented to the investigator (or designated coordinator). The investigator (or designated coordinator) should ask the subject if any of the health care contacts that are recorded on the worksheet were due to asthma. The investigator can refer to his/her records to verify or supplement information given by the subject, if necessary.

If any unscheduled healthcare contact is due to an asthma exacerbation, then the Asthma Exacerbation section of the eCRF must be completed.

Details regarding completion of the Healthcare Utilization worksheet are located in the SRM.

8.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Tables (Section 8.1).

See Section 4 for details of the safety endpoints to be assessed in the study.

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

The definitions of an AE or SAE can be found in Appendix 4.

Adverse Events include systemic (i.e., allergic/IgE-mediated and non-allergic) and injection site reactions reported throughout all study treatment periods. If the investigator considers that there is a reasonable possibility that the Systemic reaction (e.g., Hypersensitivity) or Local injection site reaction event is related to investigational product, then additional information about the type of reaction and whether it meets anaphylaxis criteria will be collected in the eCRF.

NOTE: 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 8). Information will be also collected from subjects to help with the assessment of potential localised injection site reactions.

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

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

- AEs will be collected from the Screening visit (Visit 1), until the Exit Visit or EW (see Section 8.4.1.3), at the timepoints specified in the Time and Events Tables (Section 8.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- 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 concomitant medication will be recorded from the time a subject consents to participate in the study up to and including any Exit Visit or EW.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 4.
- 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 4

8.4.1.2. Method of Detecting AEs and SAEs

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

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”

- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

8.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as related to the identified and potential risks described in Table 3) 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 6.7.4). Further information on follow-up procedures is given in Appendix 4.

8.4.1.4. Cardiovascular and Death Events

8.4.1.4.1. Cardiovascular Events

Cardiovascular-related AEs and SAEs that will require the investigator to complete event specific pages in the eCRF are listed in Section 13.4.3.

Cardiovascular events information should be recorded on the corresponding eCRF pages within one week of when the AE/SAE(s) are first reported. Please refer to Appendix 4 for timelines for reporting AE/SAEs.

8.4.1.4.2. Death Events

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

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

Please refer to Appendix 4 for timelines for reporting SAEs.

8.4.1.5. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.4.2. Pregnancy

- Details of all pregnancies in female subjects will be collected after the start of dosing (Visit 1) until the Exit Visit or EW

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.

- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

8.4.3. Physical Exams

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

8.4.4. Vital Signs

- As detailed in the Time and Events Schedules (Table 5, Table 6, Table 7 and Table 8) vital signs will be measured in a semi-supine position after 5 minutes rest and will include systolic and diastolic blood pressure and heart rate.
- Vital signs assessments will be taken **before** measurement of any clinic lung function tests or ECGs at the specified time point.

8.4.5. Electrocardiogram (ECG)

- Twelve-lead ECGs will be obtained at each time point specified in the Time and Events Schedules (Table 5, Table 6, Table 7 and Table 8).
- ECG machines that automatically calculate the heart rate and measure PR, QRS, QT, and QTc intervals will be provided by GSK via a designated central laboratory.
    - The *same* QT correction formula *must* be used for *each individual subject* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled.
    - For example, as a subject is eligible for the study based on QTcF, then QTcF must be used for discontinuation of this individual subject as well.
    - Once the QT correction formula has been chosen for a subject's eligibility, the *same formula* must continue to be used for that subject *for all QTc data*

being collected for data analysis. Safety ECGs and other non-protocol specified ECGs are an exception.

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

- ECG measurements will be made after the subject has rested in the supine position for 5 minutes. The ECG should be obtained after the vital signs assessments but 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.
- Paper ECG traces will be recorded at a standard paper speed of 25mm/sec and gain of 10mm/mV, with a lead II rhythm strip. There will be electronic capture and storage of the data by a validated method.
- Paper ECG traces are required to be maintained at the site with other source documents.
- Refer to Section 6.5 and Section 6.6 for QTc withdrawal and discontinuation of IP criteria.

8.4.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments (haematology and clinical chemistry) must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule (Table 5, Table 6, Table 7 and Table 8). Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the Laboratory Manual. Standard reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

All blood samples should be taken pre-dose, and will be sent to a central laboratory for analysis or for shipment to a GSK laboratory (details provided in the Laboratory Manual).

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the eCRF. Please note that any non-protocol specified local laboratory result has the potential to break the blind due to the eosinophils result being available. Please see the Study Reference Manual for guidance.

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

Haematology, clinical chemistry and additional parameters to be tested are listed in Table 9.

Table 9 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count	*RBC Indices*:	*WBC count with Differential:*	
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes	
	Hematocrit		Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry [1]	BUN	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Albumin
Other Screening Tests	• Hepatitis B (HBsAg) • Hepatitis C (Hep C antibody)[2] • FSH and estradiol (if clinically indicated, in women of non-child bearing potential only) • Alcohol and drug screen (if clinically indicated, to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Urine hCG Pregnancy test (for women of child bearing potential)[3]			

NOTES :

1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Appendix 2 and Appendix 3
2. If Hepatitis C antibody positive result, a hepatitis C confirmatory test should be automatically performed to confirm the result. Test should be repeated as necessary if clinically indicated.
3. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

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

To maintain the treatment blind, the site and the central study team will not be sent information on haematology differential or IL-5 value from any visits post-randomization.

8.4.6.1. Immunogenicity

Blood samples will be collected for the determination of anti-mepolizumab antibodies, prior to dosing, as detailed in the Time and Events Schedules (Table 5, Table 7 and Table 8).

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

8.5. Biomarker(s)/Pharmacodynamic Markers

The following tests will be performed on the blood sample:

Blood eosinophil counts will be recorded as part of the standard haematological assessments performed at the visits specified in the Time and Events Schedules (Table 5, Table 6, Table 7 and Table 8). The site staff and central study team will be blinded to each subject's eosinophil count (including blood count differential) from any visits post-randomization.

Blood (serum) samples will be collected during this study and may be used for the purposes of measuring biomarkers to identify factors that may influence the development of asthma and/or medically related conditions, as well as the biological and clinical responses to mepolizumab. Blood samples for biomarker testing will be stored for up to 15 years. Those biomarker results, which have the potential to break the blind will be blinded to the site staff until the clinical study report is finalised.

Full details regarding sample collection, processing and shipping are provided in the central Laboratory Manual.

8.6. Genetics

Data and genetic samples have previously been obtained from precursor studies: MEA112997, MEA115588, and MEA115575. These samples may be used as part of a genetic analysis using data collected in this study, if relevant. No additional genetic samples are required.

9. DATA MANAGEMENT

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

- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials, date of birth or other personally identifiable information will not be collected or transmitted to GSK according to GSK policy.

10. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

10.1. Hypotheses

The study is designed to test the superiority of continued mepolizumab 100 mg SC treatment vs. mepolizumab discontinuation (placebo). Significance tests will be performed at the two-sided 5% alpha level (one-sided 2.5%).

10.2. Sample Size Considerations

Sample size is based on the primary efficacy endpoint of time to first clinically significant exacerbation.

10.2.1. Sample Size Assumptions

With a sample size of 300 randomised subjects (150 per arm), it is estimated that statistical significance will be declared if the proportion of subjects with a clinically significant exacerbation following withdrawal of mepolizumab is 52.5% compared to 40% for those continuing to receive mepolizumab (hazard ratio = 0.686).

If the true hazard ratio is 0.55 (corresponding to a proportion with an exacerbation following discontinuation of mepolizumab of 60.5%), then the study has a probability of 90% of observing a hazard ratio of < 0.686 and therefore the study has 90% power for declaring statistical significance on this endpoint.

The estimated event rate for subjects randomized to mepolizumab is based on interim data from study MEA115666 which suggests 40% of subjects will experience an exacerbation within one year of randomization. In study MEA115588, the observed hazard ratio for the combined treatment arms of mepolizumab 100mg SC and 75mg SC vs placebo was 0.5. A lower event rate among those discontinuing mepolizumab is expected in this study than was observed for placebo in MEA115588 because of the continuing effects of previous treatment with mepolizumab.The sample size calculations assume 20% of subjects will withdraw prior to the end of the double-blind treatment phase before experiencing an exacerbation.

10.2.2. Sample Size Sensitivity

If the true hazard ratio or proportion of events seen within the mepolizumab discontinuation (placebo) treatment group observed within this study differs from the

values assumed within Section 10.2.1, the power to detect a difference between the two treatment groups will be affected.

Table 10 illustrates the estimated power which would be obtained with different hazard ratios and proportion of events observed within the mepolizumab discontinuation (placebo) group, assuming a sample size of 150 randomised subjects per arm.

Table 10 Effect on power for varying hazard ratios and proportions of events observed within the mepolizumab discontinuation (placebo) treatment group

Proportion of events within the placebo group	Hazard ratio						
	0.40	0.45	0.50	**0.55**	0.60	0.65	0.70
50%	98.6%	96.0%	90.9%	82.6%	71.3%	58.0%	44.3%
55%	99.2%	97.5%	93.6%	86.4%	75.8%	62.5%	48.1%
60%	99.6%	98.5%	95.5%	**89.5%**	79.8%	66.7%	51.8%
65%	99.8%	99.1%	97.0%	92.1%	83.3%	70.6%	55.5%

10.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation is planned for this study.

10.3. Data Analysis Considerations

10.3.1. Analysis Populations

All Subjects Enrolled (ASE) Population

The ASE population will comprise all subjects enrolled and for whom a record exists on the study database. This population will be used for summarising reasons for screen and run-in failures and to report data collected within the variable open-label run-in (Part A) and fixed run-in (Part B).

Intent-to-Treat (ITT) Population

This population will consist of all randomized subjects who receive at least one dose of double-blind study medication, and will be the primary population for all analyses of efficacy and safety data. In cases where there is a discrepancy between the treatment to which a subject was randomized and the treatment they actually received a profile of the subjects' data will be produced.

Per Protocol (PP) Population

The PP population will consist of all subjects in the ITT population who have not been identified as full protocol deviators with respect to criteria that are considered to impact the primary efficacy analysis. The decision to exclude a subject from the PP Population or exclude part of their data from the PP Population analyses will be made prior to breaking the blind. The PP population will be used for a supplementary analysis of the primary endpoint.

10.3.2. Interim Analysis

No interim analysis of data is planned for this study.

10.4. Key Elements of Analysis Plan

Full details of all analysis methods to be used will be provided in the RAP which will be finalised prior to unblinding.

The study will be unblinded once the final subject has completed the Exit or EW Visit, all queries for data collected up to this time are resolved and the clinical study database is frozen.

10.4.1. Primary Analyses

Time to first clinically significant exacerbation will be compared between treatment groups using a Cox's proportional hazards model allowing for covariates of region, exacerbations in the year prior to randomization and use of baseline maintenance oral corticosteroids (OCS vs no OCS). For geographical region, a grouping system for countries will be defined in the RAP.

Only Part C exacerbation data will be included in the primary analysis from the start of double-blind treatment until no greater than 4 weeks post-last-dose of double-blind treatment. The analysis will be performed on the Intent-to-Treat (ITT) population. A supporting analysis of the PP population will also be performed.

10.4.2. Secondary Analyses

For subjects that complete Part C of the study, data will be included in the analysis of the secondary and other endpoints from the start of double-blind treatment until the Exit visit date. For those subjects that switch to open-label Part D, discontinue IP early or early withdraw from the study altogether, data will be included from the start of double-blind treatment until no greater than approximately 4 weeks post-last-dose of double-blind treatment. Data collected following the switch to open-label treatment within Part D or IP discontinuation will also be omitted from the analysis of the these endpoints.

Ratio to baseline in blood eosinophil count will be analysed using mixed models repeated measures adjusting for the aforementioned covariates within the primary analysis and visit, plus interaction terms for visit by baseline and visit by treatment group.

Time to a decrease in asthma control, defined as an increase from baseline in Asthma Control Questionnaire-5 (ACQ-5) score of ≥ 0.5 units, will be compared using a Cox's proportional hazards model, as described for the primary endpoint.

Time to first exacerbation requiring hospitalization or ED visit will be compared using a Cox's proportional hazards model, as described for the primary endpoint.

10.4.3. Other Analyses

10.4.3.1. Efficacy Analyses

See Section 4 for a list of all other efficacy endpoints. Full details of any analyses to be performed on these endpoints will be provided in the RAP.

10.4.3.2. Safety Analyses

Summaries of data will report data according to the nominal visit for which it was recorded. Further details will be provided in the RAP.

10.4.3.2.1. Extent of Exposure

The number of subjects administered investigational product, the number of treatments administered and the number of days over which treatment was administered will be summarised.

10.4.3.2.2. Adverse Events

Adverse Events (AEs) will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) and will be grouped by system organ class. AEs will be summarised by frequency and percentage of subjects, by system organ class and preferred term within each treatment group. Separate summaries will be presented for all AEs, drug-related AEs, serious AEs (SAEs), AE's leading to permanent discontinuation of study treatment or withdrawal from study and for any AEs of special interest.

10.4.3.2.3. Clinical Laboratory Evaluations

Haematology (including blood eosinophils) and clinical chemistry data will be summarized at each scheduled assessment. The proportion of values outside of the normal reference range and those meeting the criteria for potential clinical significance will also be summarised. Further details will be provided in the RAP.

10.4.3.2.4. Other Safety Measures

Actual values and change from baseline for other scheduled safety assessments will be summarized at each visit per the Time and Events schedule (Table 5, Table 6, Table 7, Table 8). Further details will be provided in the RAP.

10.4.3.2.5. Immunogenicity

Immunogenicity data will be summarised using appropriate descriptive statistics.

10.4.3.3. Pharmacogenetic Analyses

Data and genetic samples have previously been obtained from precursor studies: MEA112997, MEA115588, and MEA115575. These samples may be used as part of a genetic analysis using data collected in this study, if relevant. No additional genetic samples are required.

11. STUDY GOVERNANCE CONSIDERATIONS

11.1. 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.

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

Prior to initiation of a site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonization (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
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.

- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

11.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

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

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

11.4. 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.

11.5. 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.

11.6. 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.

11.7. 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.

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

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

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

12. REFERENCES

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13. APPENDICES

13.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ACQ	Asthma Control Questionnaire
ADA	Anti-Drug Antibody
AE	Adverse Event
ALT	Alanine Transaminase
ASE	All Subjects Enrolled
AST	Aspartate Transaminase
ATS	American Thoracic Society
BP	Blood Pressure
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CPK	Serum Creatine Phosphokinase
CRP	C-Reactive Protein
CS	Corticosteroid
CV	Cardiovascular
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Emergency Department
eDiary	Electronic Diary
ERS	European Respiratory Society
EW	Early Withdrawal
FAAN	Food Allergy and Anaphylaxis Network
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FRP	Females of Reproductive Potential
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good clinical practice
GCSP	Global Clinical Safety and Pharmacovigilance
GINA	Global Initiative for Asthma
GSK	GlaxoSmithKline
HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin
HPLC	High Performance Liquid Chromatography
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
Ig	Immunoglobulin

IL	Interleukin
IM	Intramuscular
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent to Treat
IV	Intravenous
IRT	Interactive Response Technology
kg	Kilogram
L/min	Liters per minute
LABA	Long-Acting Beta-2-Agonists
LFT	Liver Function Test
mAb	Monoclonal Antibody
MedDRA	Medicinal dictionary for regulatory activities
mcg (μg)	Microgram
mcL (μL)	Microliter
MDI	Metered Dose Inhaler
mg	Milligram
mL	Milliliter
N/A	Not Applicable
NaB	Neutralizing Antibodies
NIAID	National Institute of Allergy and Infectious Diseases
OCS	Oral Corticosteroids
PD	Pharmacodynamic
PEF	Peak Expiratory Flow
PK	Pharmacokinetic
PP	Per Protocol
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SC	Subcutaneous
SGRQ	St. George's Respiratory Questionnaire
SOC	System Organ Class
SPD	Surfactant Protein D
SRM	Study Reference Manual
ULN	Upper Limit of Normal
URTI	Upper Respiratory Tract Infection

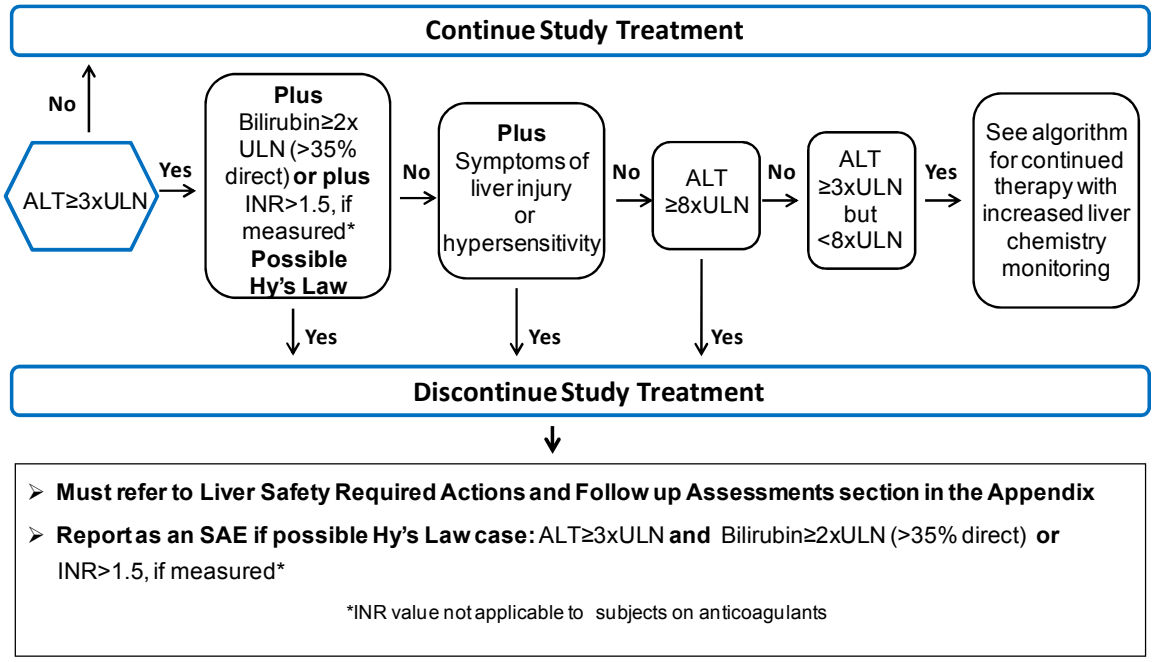
Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
None

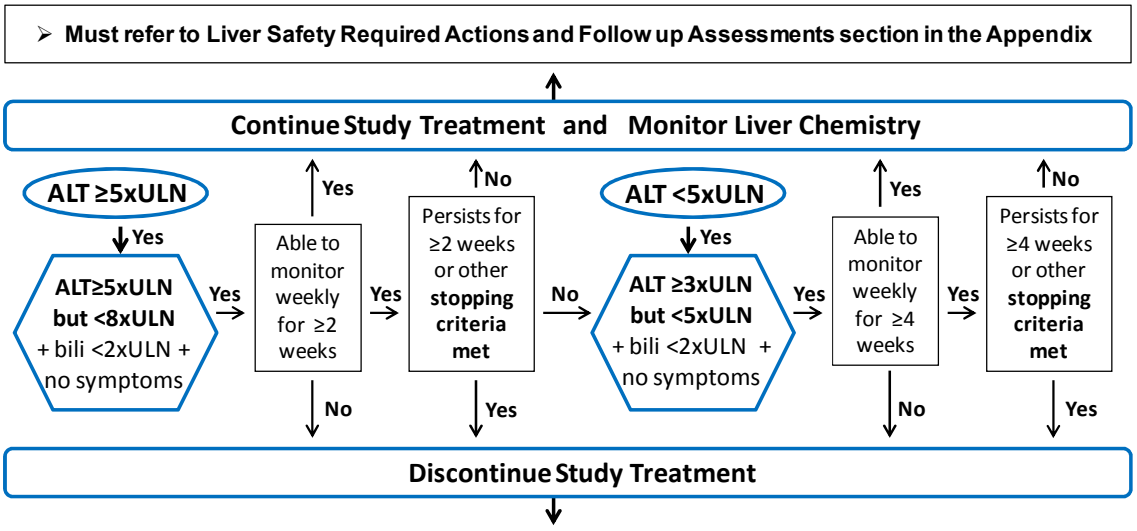
13.2. Appendix 2: Liver Chemistry Stopping and Increased Monitoring Algorithm

Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 3.

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



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 3.

13.3. Appendix 3: Liver Safety Required Actions and Follow up Assessments

Phase III-IV 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 III-IV liver chemistry stopping criteria and required follow up assessments

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

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• Immediately discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment. • Restart/rechallenge is **not allowed**, permanently discontinue study treatment and subject may continue in the study for any protocol specified follow up assessments	• Viral hepatitis serology[4] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5]. • Blood sample for pharmacokinetic (PK) analysis, obtained within 4 weeks after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form

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

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** international normalized ratio (INR) >1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase III-IV liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

13.4. Appendix 4: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

13.4.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology or clinical chemistry), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "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. • 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.

13.4.2. Definition of Serious Adverse Events

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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

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

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

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

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

• This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.
• See Appendix 2 for the required liver chemistry follow-up instructions

13.4.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy

- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

13.4.4. 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.
- Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

13.4.5. 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 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.

13.4.6. Reporting of SAEs to GSK

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

13.5. Appendix 5: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) and Collection of Pregnancy Information

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

Subjects who are FRP must agree to acceptable contraceptive methods approved in their local country, when used consistently and correctly (i.e., in accordance with the approved product label and the instructions of the physician) for the duration of the study and for 4 months after the last study drug administration.

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
- Injectable progestogen [Hatcher, 2011]
- Contraceptive vaginal ring [Hatcher, 2011]
- Percutaneous contraceptive patches [Hatcher, 2011]
- Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011].

This is an all inclusive list of those methods that meet the GSK definition of highly effective: having a failure rate of less than 1% per year when used consistently and, correctly and, when applicable, in accordance with the product label. For non-product methods (e.g. male sterility), the investigator determines what is consistent and correct use. The GSK definition is based on the definition provided by the ICH (ICH, M3 [R2],2009)

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

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.

13.5.1. 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 4. 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 discontinue study medication or be withdrawn from the study (Section 6.5, Section 6.6 and Section 6.7).

13.6. Appendix 6: Cardiovascular Screening Questions

At screening each subject should be asked the following:

Unrelated to the symptoms you experience with your asthma:

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

If the subject responds "yes" to any of the above questions a study physician should further assess for the presence of undiagnosed or unrecognized angina when evaluating Exclusion Criterion 4 (see Section 6.2)

13.7. Appendix 7: Daily Asthma Symptom Score

Each morning subjects will record an asthma symptom score using the following scale:

- Daily Symptom Score:
  - 0 = No symptoms during the previous 24-hours.
  - 1 = Symptoms for one short period during the previous 24-hours.
  - 2 = Symptoms for two or more short periods during the previous 24-hours.
  - 3 = Symptoms for most of the previous 24-hours which did not affect my normal daily activities.
  - 4 = Symptoms for most of the previous 24-hours which did affect my normal daily activities.
  - 5 = Symptoms so severe that I could not go to work/school or perform normal daily activities.

13.8. Appendix 8: Anaphylaxis Criteria

Joint NIAID/FAAN Second Symposium on Anaphylaxis [Sampson, 2006]. The criteria do not make a distinction based on underlying mechanism. These criteria are summarized as follows:

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
    a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a) Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    b) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    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

13.9. Appendix 9: Country Specific Requirements

No country-specific requirements exist.

13.10. Appendix 10: Protocol Amendment Changes

13.10.1. Amendment 01 (06-Nov-2015) from the Original Protocol (23-Jun-2015)

Scope: this applies to all sites

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

Change 1: Updated Medical Monitor/SAE Contact Information:

Original Text:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD PP PPD MD, MFPM	PPD	Not Applicable	PPD PPD	Stockley Park West 1-3 Ironbridge Road Uxbridge, Middlesex, UB11 1BT United Kingdom
Secondary Medical Monitor	PPD PPD		PPD PPD	Not Applicable	5 Moore Drive RTP, NC 27709
SAE contact information	Medical monitor as above				

Revised Text:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD PPD MD, MFPM	PPD	Not Applicable	PPD PPD PPD PPD	Stockley Park West 1-3 Ironbridge Road Uxbridge, Middlesex UB11 1BT United Kingdom
Secondary Medical Monitor	PPD PPD MD, PMP		Not Applicable	PPD PPD PPD PPD	Stockley Park West 1-3 Ironbridge Road Uxbridge, Middlesex UB11 1BT United Kingdom
SAE contact information	Medical monitor as above				

Change 2: Protocol Summary, Overall Design paragraph 1. Simplification of continuous treatment.

Original Text:

This is a 52-week, 2-arm, randomized, double-blind, parallel-group, multi-center study evaluating mepolizumab 100 mg and placebo administered subcutaneously (SC) every 4 weeks in subjects with severe eosinophilic asthma who have been treated with mepolizumab continuously in addition to standard of care therapy for at least 3 years. Subjects who participated in the open-label studies MEA115666 or 201312 with at least 6 months of treatment with mepolizumab prior to Visit 1 and who have no more than 2 consecutive missed doses of mepolizumab treatment [no treatment gaps of more than 12

weeks (84 days) between any two doses while treated with mepolizumab in MEA115666 or 201312] will be eligible to participate in this study. It is intended that the Follow up/Exit Visit or Early Withdrawal (EW) Visit for studies MEA115666 and 201312 will serve as the Pre-Screening/Screening Visit (Visit 0/Visit 1) for this study.

Revised Text:

This is a 52-week, 2-arm, randomized, double-blind, parallel-group, multi-center study evaluating mepolizumab 100 mg and placebo administered subcutaneously (SC) every 4 weeks in subjects with severe eosinophilic asthma who have been treated with mepolizumab continuously in addition to standard of care therapy for at least 3 years. Subjects who participated in the open-label studies MEA115666 or 201312 and who have no treatment gaps of more than 12 weeks (84 days) between any two doses of mepolizumab in MEA115666 or 201312, will be eligible to participate in this study.

It is intended that the Follow up/Exit Visit or Early Withdrawal (EW) Visit for studies MEA115666 and 201312 will serve as the Pre-Screening/Screening Visit (Visit 0/Visit 1) for this study.

Change 3: Study Design, Part D: Optional Switch to Open-Label Mepolizumab, last paragraph: clarification to process of subject moving from Part C to Part D.

Original Text:
Subjects who permanently discontinue study treatment in Part C or D of the study are NOT required to withdraw from the study.

Revised Text:

Subjects who permanently discontinue study treatment in Part C or D of the study are NOT required to withdraw from the study. If a subject discontinues double blind study treatment during Part C and does not switch to Part D at their next visit (IP Discontinuation Visit) after experiencing a clinically significant asthma exacerbation, the subject cannot enter Part D at a later visit.

Change 4: Simplification to definition of "continuous mepolizumab treatment". Section 5.1 Overall Design.

Original Text:

This is a 52-week, 2-arm, randomized, double-blind, parallel-group, multi-center study evaluating mepolizumab 100 mg and placebo administered SC every 4 weeks in subjects with severe eosinophilic asthma who have been treated with mepolizumab continuously in addition to standard of care therapy for at least 3 years. Subjects who participated in the open-label studies MEA115666 and 201312 with at least 6 months of continuous treatment with mepolizumab prior to Visit 1 will be eligible to participate in this study.

Continuous mepolizumab treatment: Continuous treatment with mepolizumab is defined as no more than 2 consecutive missed doses [no treatment gaps of more than 12 weeks (84 days) between any two doses]. To calculate the duration of continuous mepolizumab

treatment, the start date should be at least the start of treatment in studies MEA115666 and 201312, and may include continuous mepolizumab treatment from the following prior studies: MEA115661, MEA115588, MEA115575.

Revised Text:

This is a 52-week, 2-arm, randomized, double-blind, parallel-group, multi-center study evaluating mepolizumab 100 mg and placebo administered SC every 4 weeks in subjects with severe eosinophilic asthma who have been treated with mepolizumab continuously in addition to standard of care therapy for at least 3 years.

Definition of Continuous Mepolizumab Treatment

Continuous treatment with mepolizumab is defined as no more than 2 consecutive missed doses, i.e. no treatment gaps of more than 12 weeks (84 days) between any two doses.

When deriving the period of continuous mepolizumab exposure, treatment from the following studies may be considered: MEA115666, MEA115588, MEA115575, MEA115661 and 201312. The earliest date of initiating mepolizumab treatment may be considered when deriving this total exposure, however if a gap of > 84 days between any two doses of mepolizumab is experienced, this exposure period can no longer be considered ‘continuous’. If such an instance occurs the subject's period of continuous mepolizumab treatment will be derived from the first dose of mepolizumab following this gap in mepolizumab treatment.

However, if a subject has experienced a gap of >12 weeks (84 days) between any two doses of mepolizumab within studies MEA115666 or 201312 this will exclude the subject from entry into 201810.

Change 5: To clarify that the controller medication from Part B and Part C should not be altered. Section 5.1 Overall Design

Original Text:

Any increase in controller therapy in Part B and Part C (except for OCS use for the treatment of exacerbations) should be discussed with the medical monitor.

Revised Text:

Any change in controller regimen or dose in Part B and Part C (except for OCS use for the treatment of exacerbations) should be discussed with the medical monitor.

Change 6: To clarify the process of a subject switching from Part C to Part D. Section 5.1 Overall Design: Part D: Optional Switch to Open-Label Mepolizumab.

Original Text:

Subjects who permanently discontinue study treatment in Part C or D of the study are NOT required to withdraw from the study.

Revised Text:

Subjects who permanently discontinue study treatment in Part C or D of the study are NOT required to withdraw from the study. If a subject discontinues double blind study treatment during Part C and does not switch to Part D at their next visit (IP Discontinuation Visit) after experiencing a clinically significant asthma exacerbation, the subject cannot enter Part D at a later visit.

Change 7: Entry Criterion No. 2, Section 6.1 Inclusion Criteria updated to reflect simplification of continuous mepolizumab treatment.

Original Text:

2. **MEA115666 or 201312 Study Participation:** Participation (through the Follow Up/Exit Visit or Early Withdrawal) in either study with documented evidence of at least 6 months of continous mepolizumab treatment prior to Visit 1. See Section 5.1 for the definition of continuous mepolizumab treatment.

Revised Text:

2. **Continuous Mepolizumab Treatment during MEA115666 or 201312:** Participation through the Follow Up/Exit Visit or Early Withdrawal Visit and documented evidence of treatment with mepolizumab with no treatment gaps of more than 12 weeks (84 days) between any two doses within MEA115666 or 201312. (A treatment gap of more than 12 weeks [84 days] cannot occur between the end of MEA115666 or 201312 and Visit 1).

Change 8: Added a reference to Section 5.1 in Section 6.3.1 Randomization Inclusion Criteria.

Original Text:

1. **Continuous Mepolizumab Treatment:** Documented evidence of at least **3 years (156 weeks) of treatment with mepolizumab** with no treatment gaps of more than 12 weeks (84 days) between any two doses while treated with mepolizumab.

Revised Text:

1. **Continuous Mepolizumab Treatment:** Documented evidence of at least **3 years (156 weeks) of treatment with mepolizumab** with no treatment gaps of more than 12 weeks (84 days) between any two doses while treated with mepolizumab. See Section 5.1 for the definition of continuous mepolizumab treatment.

Change 9: Removal of the Urinalysis test as it is not required within the mepolizumab programme in Section 6.5. Study Withdrawal Prior to Randomization: Withdrawal during Part A or Part B

Original Text:

3. **Laboratory abnormality:** Evidence of clinically significant abnormality in the haematological, biochemical or urinalysis screen, which in the opinion of the investigator would make the subject unsuitable for participation in this study.

Revised Text:

3. **Laboratory abnormality:** Evidence of clinically significant abnormality in the haematological or biochemical screen, which in the opinion of the investigator would make the subject unsuitable for participation in this study.

Change 10: Removal of a withdrawal criterion number 4 in Section 6.6 Discontinuation of Investigational Product (IP) during Part C or Part D

Removed Text:

4. **Study treatment unblinded**: Unblinding of the study treatment assigned to a subject in Part C.

Unblinded subjects may switch to open label Part D, per Investigators discrection.

Change 11: Updated section 7.3 Blinding.

Original Text:

- Subjects will be discontinued from study treatment if the treatment code is unblinded by the investigator or treating physician. Unblinded subjects may switch to open label Part D, per Investigators discrection (Section 6.6).

Revised Text:

- If the treatment code assigned to a subject in Part C is unblinded to the subject, Investigator and/or the treating physician/blinded member of site staff, please consult the Study Reference Manual and GSK for guidance. Remediation will be assessed on a case by case basis to minimise the impact of any possible bias.

Change 12: Section 7.9.1 Permitted Medications and Non-Drug Therapies updated to reflect Change 5.

Original Text:

During the fixed open-label period (Part B) and the double-blind treatment period (Part C), subjects should maintain the stable dose and regimen of controller therapy established in Part A or in studies MEA115666 and 201312. Any increase in controller therapy in Part B and Part C (except for OCS use for the treatment of exacerbations) should be discussed with the medical monitor.

Revised Text:

During the fixed open-label period (Part B) and the double-blind treatment period (Part C), subjects should maintain the stable dose and regimen of controller therapy established in Part A or in studies MEA115666 and 201312. Any change in controller regimen or dose in Part B and Part C (except for OCS use for the treatment of exacerbations) should be discussed with the medical monitor.

Change 13: The Time and Event table, Table 5, Table 6, Table 7 and Table 8 in Section 8.1 Time and Event Tables, corrected.

Original Section:

Section 8.1 Time and Events Tables

Table 5 Time and Events Table: Screening/Variable Open-Label Run-In Weeks 0 - 52 - Part A

PART A Procedures	Pre-Screen[1]	Exit/EW Visit MEA115666 or 201312/ Screen[1]	Variable Open-Label Treatment Part A[2] (window is ± 1 week)													EW[9] 4 weeks post last injection
Visit	**0**	**1**	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**	**A10**	**A11**	**A12**	**A13**	
Week of Variable Run-In		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Written Informed Consent	X															
Demography		X														
Medical History		X														
Assess cardiac risk factors		X														
Smoking status		X														
Inclusion/Exclusion Criteria		X														
Safety Assessments																
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination		X[3]												X		X
Vital Signs		X[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG		X[4]						X						X		X
Adverse Events	X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[6]																
Haematology		X[3]						X						X		X
Chemistry (incl. LFT)		X[3]						X						X		X
Urinalysis		X[3]						X						X		X
Pregnancy Test[7]		U[3]	U	U	U	U	U	U	U	U	U	U	U	U	U	X
Immunogenicity		X[3]												X		X

PART A **Procedures**	**Pre-Screen[1]**	**Exit/EW Visit MEA115666 or 201312/ Screen[1]**	**Variable Open-Label Treatment Part A[2] (window is ± 1 week)**													EW[9] 4 weeks post last injection
Visit	**0**	**1**	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**	**A10**	**A11**	**A12**	**A13**	
Week of Variable Run-In		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
HbsAg and hepatitis C antibody[8]		X														
Efficacy Assessments																
Exacerbation review	X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Asthma Control Questionnaire-5		X[3]			X			X			X			X		X
Spirometry		X[3]						X						X		X
Worksheets/Diary/IP/ eCRF																
Administer open-label mepolizumab[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense albuterol/salbutamol		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect albuterol/salbutamol			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense paper diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect/review paper diary			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	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. The Pre-Screen Visit and Screening Visit may occur on the same day.
2. Visits should be conducted every 4 weeks until the subject has reached 3 years of mepolizumab exposure.
3. As assessed from the Follow Up/Exit Visit or EW from studies MEA115666 or 201312, if Screening for 201810 is conducted on the SAME day. If the MEA115666 or 201312 Exit Visit/EW and 201810 Screening Visit are conducted on different days (no more than 84 days apart), the Physical Exam, Immunogenicity assessment, and Spirometry do not need to be repeated at Screening. Other assessments should be conducted at the Screening Visit.
4. Screening ECG must be conducted with ECG equipment for study 201810.
5. Any SAEs and exacerbations related to study participation should be recorded from the time of consent.
6. All laboratory assessments to be completed prior to dosing
7. Urine pregnancy tests (U) should be conducted every 4 weeks for women of child bearing potential during the variable open-label run-in period. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.
8. Hepatitis B Surface Antigen and Hepatitis C antibody (if Hepatitis C antibody positive, a hepatitis C confirmatory test should be automatically performed to confirm the result. Test should be repeated as necessary if clinically indicated)
9. EW = Early Withdrawal. Should be conducted 4 ± 1 weeks from the subjects last dose

Table 6 Time and Events Table: Screening/Variable Open-Label Run-In Weeks 56 - 132- Part A

PART A **Procedures**	**Variable Open-Label Treatment Part A[1] (window is ± 1 week)**													EW[4] 4 weeks post last injection
Visit	**A14/A27**	**A15/A28**	**A16/A29**	**A17/A30**	**A18/A31**	**A19/A32**	**A20/A33**	**A21**	**A22**	**A23**	**A24**	**A25**	**A26**	
Week of Variable Run-In	**56/108**	**60/112**	**64/116**	**68/120**	**72/124**	**76/128**	**80/132**	**84**	**88**	**92**	**96**	**100**	**104**	
Safety Assessments														
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination												X		X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG					X							X		X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[2]														
Haematology					X							X		X
Chemistry (incl. LFT)					X							X		X
Urinalysis					X							X		X
Pregnancy Test[3]	U	U	U	U	U	U	U	U	U	U	U	U	U	X
Immunogenicity												X		X
Efficacy Assessments														
Exacerbation review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Asthma Control Questionnaire-5		X			X			X				X		X
Spirometry					X							X		X
Worksheets/Diary/IP/eCRF														
Administer open-label mepolizumab[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense albuterol/salbutamol	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect albuterol/salbutamol	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense paper diary	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect/review paper diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	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

1. Visits should be conducted every 4 weeks until the subject has reached 3 years of mepolizumab exposure.
2. All laboratory assessments to be completed prior to dosing
3. Urine pregnancy tests (U) should be conducted every 4 weeks for women of child bearing potential during the variable open-label run-in period. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.
4. EW=Early Withdrawal. Should be conducted 4 ± 1 weeks from the subjects last dose.

Table 7 Time and Events Table: Fixed Run-In & Double-Blind Treatment Period – Parts B and C

PARTS B&C Procedures	Fixed Run-in Part B		Randomization	Double-Blind Treatment Part C (window is ± 1 week)												IPDISC/EW[2] 4 weeks post last injection
Visit	**B1**	**B2[1]**	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**	**C13**	**Exit Visit**	
Week of Study	**-4 ± 1**	**-4 ± 1[1]**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Smoking status			X														
Randomization Criteria			X														
Safety Assessments																	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X															X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X								X							X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[3]																	
Haematology	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry (incl. LFT)	X		X						X							X	X
Biomarkers			X	X	X	X	X	X	X							X	X
Urinalysis	X		X						X							X	X
Pregnancy Test [4]	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Immunogenicity																X	X
Efficacy Assessments																	
Subject/Clinician Global Impression Rating			X			X			X			X				X	X
Subject/Clinician Rating of Response to Therapy						X			X			X				X	X
SGRQ			X			X			X			X				X	X
Exacerbation review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

PARTS B&C Procedures	Fixed Run-in Part B		Randomization	Double-Blind Treatment Part C (window is ± 1 week)												IPDISC/EW[2] 4 weeks post last injection
Visit	**B1**	**B2[1]**	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**	**C13**	**Exit Visit**	
Week of Study	**-4 ± 1**	**-4 ± 1[1]**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Spirometry (pre- and post-albuterol/salbutamol)			X			X			X			X				X	X
Healthcare resource utilization				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review eDiary[5] (symptoms, rescue use, nocturnal awakenings, PEF, ACQ-5, missed days of work/school)		←															→
Worksheets/Diary/IP/ eCRF																	
Administer open-label mepolizumab[4]	X	X															
Administer double blind study treatment[3]			X[6]	X	X	X	X	X	X	X	X	X	X	X	X		
Dispense albuterol/salbutamol	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Collect albuterol/salbutamol	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense paper diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Dispense eDiary	X																
Collect eDiary																X	X[7]
Collect/review paper diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	X	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	X

1. Visit B2 is only intended for subjects who experience an exacerbation in the run-in Part B which is not resolved within 7 days of Visit C1 or subjects who fail eDiary Compliance Criteria (Section 6.3). These subjects may extend their run-in Part B by 4 weeks and complete Visit B2. All other eligible subjects should proceed directly to Visit C1 following Visit B1. B2 will be scheduled 4 ± 1 week after B1, and 4 ± 1 week prior to C1.

2. IPDISC = Discontinuation of IP Visit (only applies to subjects in Part C). EW = Early Withdrawal. Either visit should be conducted 4 ± 1 weeks from the subjects last dose.
3. All laboratory assessments to be completed prior to dosing.
4. Urine pregnancy tests (U) should be conducted every 4 weeks for women of child bearing potential during the variable open-label run-in period. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.
5. Subjects eDiary entries should be reviewed by the site weekly
6. An unblinding card will be dispensed after Randomization at Visit C1.
7. The eDiary is only collected at an Early Withdrawal visit.

Table 8 Time and Events Table: Optional Open-Label Switch to Mepolizumab – Part D

PART D Procedures	OPTIONAL Open-Label Switch to mepolizumab Part D[1] (window is ± 1 week)														IPDISC/EW 4 weeks post last injection[3]
Visit	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D13**	**Exit Visit**	
Week of Study[2]	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Safety Assessments															
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination														X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG							X							X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[4]															
Haematology[5]				X			X			X				X	X
Chemistry (incl. LFT)							X							X	X
Urinalysis							X							X	X
Pregnancy Test [6]	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Immunogenicity														X	X
Efficacy Assessments															
Exacerbation review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry				X			X			X				X	X
Worksheets/Diary/IP/ eCRF															
Administer open-label mepolizumab[4]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Dispense albuterol/salbutamol	X	X	X	X	X	X	X	X	X	X	X	X	X		
Collect albuterol/salbutamol	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense paper diary	X	X	X	X	X	X	X	X	X	X	X	X	X		
Review eDiary (symptoms, rescue use, nocturnal awakenings, PEF, ACQ-5, missed days of work/school)[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

PART D Procedures	**OPTIONAL Open-Label Switch to mepolizumab Part D[1] (window is ± 1 week)**														**IPDISC/EW 4 weeks post last injection[3]**
Visit	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D13**	**Exit Visit**	
Week of Study[2]	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Collect eDiary														X	X[8]
Collect/review paper diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. The combined treatment period (Part C) and any switch to open-label mepolizumab (Part D) should not exceed a total duration of 52 weeks.
2. Subjects may enter the Open-label Switch Part D at any point during Part C provided they meet switch criteria, starting with the week of study that the switch is made and continuing until week 52, discontinuation of IP or early withdrawal.
3. IPDISC = Discontinuation of IP Visit. EW = Early Withdrawal. Either visit should be conducted 4 ± 1 weeks from the subjects last dose.
4. All laboratory assessments to be completed prior to dosing
5. Haematology samples will be collected for each of the subject's first 3 visits of Part D, and then according to designated Visits in Table 8
6. Urine pregnancy tests (U) should be conducted every 4 weeks for women of child bearing potential during the variable open-label run-in period. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.
7. The eDiary should be reviewed at each visit. Weekly review is not required in Part D.
8. The eDiary is only collected at an Early Withdrawal visit.

Revised Section:
Section 8.1 Time and Events Tables

Table 5 Time and Events Table: Screening/Variable Open-Label Run-In Weeks 0 - 52 - Part A

PART A **Procedures**	**Pre-Screen[1]**	**Exit/EW Visit MEA115666 or 201312/ Screen[1]**	**Variable Open-Label Treatment Part A[2] (window is ± 1 week)**													EW Visit[5]
Visit	**0**	**1**	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**	**A10**	**A11**	**A12**	**A13**	
Week of Variable Run-In		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Written Informed Consent	X															
Demography		X														
Medical History		X														
Assess cardiac risk factors		X														
Smoking status		X														
Inclusion/Exclusion Criteria		X														
Safety Assessments[3]																
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination		X												X		X
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG		X						X						X		X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[3]																
Haematology		X						X						X		X
Chemistry (incl. LFT)		X						X						X		X
Pregnancy Test[4]		U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Immunogenicity		X												X		X
HbsAg and hepatitis C antibody		X														
Efficacy Assessments[3]																
Exacerbation review	X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

PART A **Procedures**	**Pre-Screen[1]**	**Exit/EW Visit MEA115666 or 201312/ Screen[1]**	**Variable Open-Label Treatment Part A[2] (window is ± 1 week)**													EW Visit[5]
Visit	**0**	**1**	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**	**A10**	**A11**	**A12**	**A13**	
Week of Variable Run-In		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Asthma Control Questionnaire-5		X			X			X			X			X		X
Spirometry		X						X						X		X
Worksheets/Diary/IP/ eCRF																
Administer open-label mepolizumab		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense albuterol/salbutamol		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect albuterol/salbutamol			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense paper diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect/review paper diary			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	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. The Pre-Screen Visit and Screening Visit may occur on the same day.
2. Visits should be conducted every 4 weeks until the subject has reached 3 years of mepolizumab exposure.
3. Please see the SRM for details on which screening procedures to perform for subjects entering from 201312 and MEA115666. ALL procedures should be completed prior to dosing with open-label mepolizumab.
4. Urine pregnancy tests (U) should be conducted for women of child bearing potential.
5. EW = Early Withdrawal. Should be conducted 4 ± 1 weeks from the subject's last dose

Table 6 Time and Events Table: Screening/Variable Open-Label Run-In Weeks 56 - 132- Part A

PART A Procedures	Variable Open-Label Treatment Part A[1] (window is ± 1 week)													EW Visit[3]
Visit	**A14/A27**	**A15/A28**	**A16/A29**	**A17/A30**	**A18/A31**	**A19/A32**	**A20/A33**	**A21**	**A22**	**A23**	**A24**	**A25**	**A26**	
Week of Variable Run-In	**56/108**	**60/112**	**64/116**	**68/120**	**72/124**	**76/128**	**80/132**	**84**	**88**	**92**	**96**	**100**	**104**	
Safety Assessments														
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination												X		X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG					X							X		X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments														
Haematology					X							X		X
Chemistry (incl. LFT)					X							X		X
Pregnancy Test[2]	U	U	U	U	U	U	U	U	U	U	U	U	U	X
Immunogenicity												X		X
Efficacy Assessments														
Exacerbation review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Asthma Control Questionnaire-5		X			X			X				X		X
Spirometry					X							X		X
Worksheets/Diary/IP/eCRF														
Administer open-label mepolizumab	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense albuterol/salbutamol	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect albuterol/salbutamol	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense paper diary	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect/review paper diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	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

1. Visits should be conducted every 4 weeks until the subject has reached 3 years of mepolizumab exposure.
2. Urine pregnancy tests (U) should be conducted for women of child bearing potential.
3. EW = Early Withdrawal. Should be conducted 4 ± 1 weeks from the subject's last dose

Table 7 Time and Events Table: Fixed Run-In & Double-Blind Treatment Period – Parts B and C

PARTS B&C Procedures	Fixed Run-in Part B		EW from Part B[7]	Randomization	Double-Blind Treatment Part C (window is ± 1 week)												IPDISC/EW Visit [7]
Visit	**B1**	**B2[1]**	**Part B EW**	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**	**C13**	**Exit Visit**	
Week of Study	**-4 ± 1**	**-4 ± 1[1]**		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Smoking status				X														
Randomization Criteria				X														
Safety Assessments[2]																		
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X		X														X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X		X							X							X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[2]																		
Haematology	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry (incl. LFT)	X		X	X						X							X	X
Biomarkers				X	X	X	X	X	X	X							X	X
Pregnancy Test [3]	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Immunogenicity			X														X	X
Efficacy Assessments[2]																		
Subject/Clinician Global Impression Rating				X			X			X			X				X	X
Subject/Clinician Rating of Response to Therapy							X			X			X				X	X

PARTS B&C Procedures	Fixed Run-in Part B		EW from Part B[7]	Randomization	Double-Blind Treatment Part C (window is ± 1 week)												IPDISC/EW Visit [7]
Visit	**B1**	**B2[1]**	**Part B EW**	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**	**C13**	**Exit Visit**	
Week of Study	**-4 ± 1**	**-4 ± 1[1]**		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
SGRQ				X			X			X			X				X	X
Exacerbation review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry (pre- and post-albuterol/salbutamol)			X[8]	X			X			X			X				X	X
Healthcare resource utilization					X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review eDiary[4] (symptoms, rescue use, nocturnal awakenings, PEF, ACQ-5, missed days of work/school)	←																	→
Worksheets/Diary/IP/ eCRF[2]																		
Administer open-label mepolizumab[4]	X	X																
Administer double blind study treatment				X[5]	X	X	X	X	X	X	X	X	X	X	X	X		
Dispense albuterol/salbutamol	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Collect albuterol/salbutamol	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense paper diary	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Dispense eDiary	X																	
Collect eDiary			X														X	X[6]

PARTS B&C Procedures	Fixed Run-in Part B		EW from Part B[7]	Randomization	Double-Blind Treatment Part C (window is ± 1 week)													IPDISC/EW Visit [7]
Visit	**B1**	**B2[1]**	**Part B EW**	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**	**C13**	**Exit Visit**	
Week of Study	**-4 ± 1**	**-4 ± 1[1]**		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Collect/review paper diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	X	X	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	X	X

1. Visit B2 is only intended for subjects who experience an exacerbation in the run-in Part B which is not resolved within 7 days of Visit C1 or subjects who fail eDiary Compliance Criteria (Section 6.3).
2. All assessments to be completed prior to dosing.
3. Urine pregnancy tests (U) should be conducted every 4 weeks for women of child bearing potential.
4. Subjects eDiary entries should be reviewed by the site weekly during Part C
5. An unblinding card will be dispensed after Randomization at Visit C1.
6. The eDiary is only collected at an Early Withdrawal visit and not at IPDISC in Part C.
7. IPDISC/EW visit should be conducted 4 ± 1 weeks from the subject's last dose
8. Only *pre*-bronchodilator spirometry required at this visit.

Table 8 Time and Events Table: Optional Open-Label Switch to Mepolizumab – Part D

PART D Procedures	OPTIONAL Open-Label Switch to mepolizumab Part D[1] (window is ± 1 week)														IPDISC/EW Visit [8]
Visit	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D13**	**Exit Visit**	
Week of Study[2]	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Safety Assessments[3]															
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination														X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG							X							X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[3]															
Haematology[4]				X			X			X				X	X
Chemistry (incl. LFT)							X							X	X
Pregnancy Test [5]	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Immunogenicity														X	X
Efficacy Assessments[3]															
Exacerbation review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry				X			X			X				X	X
Worksheets/Diary/IP/ eCRF[3]															
Administer open-label mepolizumab	X	X	X	X	X	X	X	X	X	X	X	X	X		
Dispense albuterol/salbutamol	X	X	X	X	X	X	X	X	X	X	X	X	X		
Collect albuterol/salbutamol	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense paper diary	X	X	X	X	X	X	X	X	X	X	X	X	X		
Review eDiary[6] (symptoms, rescue use, nocturnal awakenings, PEF, ACQ-5, missed days of work/school)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect eDiary														X	X[7]

PART D **Procedures**	**OPTIONAL Open-Label Switch to mepolizumab Part D[1] (window is ± 1 week)**														**IPDISC/EW Visit [8]**
Visit	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D13**	**Exit Visit**	
Week of Study[2]	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Collect/review paper diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. The combined treatment period (Part C) and any switch to open-label mepolizumab (Part D) should not exceed a total duration of 52 weeks.
2. Subjects may enter the Open-label Switch Part D at any point during Part C provided they meet switch criteria, starting with the week of study that the switch is made and continuing until week 52, discontinuation of IP or early withdrawal.
3. All assessments to be completed prior to dosing
4. Haematology samples will be collected for each of the subject's first 3 visits of Part D, and then according to designated Visits in Table 8
5. Urine pregnancy tests (U) should be conducted every 4 weeks for women of child bearing potential.
6. The eDiary should be reviewed at each visit. Weekly review is not required in Part D.
7. The eDiary is only collected at an Early Withdrawal or Exit visit.
8. IPDISC/EW visit should be conducted 4 ± 1 weeks from the subject's last dose

Change 14: Section 8.2 Screening and Critical Baseline Assessments updated to reflect changes made throughout protocol and specifically in the Tine and Event Tables.

Original Text:

8.2. Screening and Critical Baseline Assessments

Informed consent/assent will be obtained at the Pre-screen Visit or Screening Visit (if Pre-screen and Screening Visits are performed on the same day).

8.2.1. Critical procedures performed at Screening (Visit 1)

If the MEA115666 or 201312 Exit Visit/EW and 201810 Screening Visit are conducted on different days (no more than 84 days apart), the Physical Exam, Immunogenicity assessment, and Spirometry do not need to be repeated at Screening. Other assessments should be conducted at the Screening Visit.

- Review Inclusion/Exclusion criteria (see Section 6)
- Demographic information including gender, ethnic origin, race, year of birth
- Medical history including smoking status, history of sinusitis, nasal polyposis, aspirin allergy, duration of asthma, courses of rescue corticosteroids, history of previous intubations, asthma exacerbation history in previous year, asthma triggers
- Vital signs
- Physical exam (conducted at the Exit/EW Visit from study MEA115666 or 201312)
- Resting 12 lead ECG (using 201810 equipment)
- Therapy history (review concomitant medications from the previous 12 weeks prior to the first dose of study medication)
- Cardiovascular medical history/risk factors (as detailed in the eCRF) will be assessed at screening. This assessment must include a review of the subject responses to the cardiovascular assessment questions (see Appendix 6)
- Exacerbation review
- Smoking status
- Asthma Control Questionnaire (ACQ-5)
- Spirometry (conducted at the Exit/EW Visit from study MEA115666 or 201312)
- Laboratory tests:
    - Chemistry (including liver function test [LFT])
    - Haematology with differential
    - Urinalysis

- Immunogenicity (conducted at the Exit/EW Visit from study MEA115666 or 201312)
- Hepatitis B Surface Antigen and hepatitis C antibody
- Urine pregnancy test- for all females of child bearing potential (Follicle Stimulating Hormone [FSH] will be assessed to confirm child-bearing status, if clinically indicated)

- AE/SAE assessment

8.2.2. Critical procedures performed at entry to Part B (Visit B1)

- Vital signs
- Resting 12- lead ECG
- Physical examination
- Concomitant medication review
- Exacerbation review
- Laboratory tests:
  - Chemistry (including LFT)
  - Haematology with differential
  - Urinalysis
  - Urine pregnancy test- for all females of child bearing potential
- AE/SAE assessment

8.2.3. Critical procedures performed at Randomization (Visit C1)

- Review of randomization criteria (see Section 6.3)
- Subject/Clinician global impression of asthma severity rating
- Subject/Clinician rating of response to therapy
- St. George's Respiratory Questionnaire (SGRQ)
- Vital signs
- Spirometry (pre- and post-albuterol/salbutamol)
- Review/Collect eDiary data
- Exacerbation review
- Smoking status
- Concomitant medication assessment
- Laboratory tests:
- Clinical Chemistry (including LFT)
- Haematology with differential

- Biomarker sample
- Urinalysis
- Urine pregnancy test for all females of childbearing potential
- AE/SAE assessment

Revised Text:

8.2. Screening and Critical Baseline Assessments

Informed consent/assent will be obtained at the Pre-screen Visit or Screening Visit (if Pre-screen and Screening Visits are performed on the same day).

8.2.1. Critical procedures performed at Screening (Visit 1)

If the MEA115666 or 201312 Exit Visit/EW and 201810 Screening Visit are conducted on different days (no more than 84 days apart), the Physical Exam, Immunogenicity assessment, and Spirometry do not need to be repeated at Screening. Other assessments should be conducted at the Screening Visit. Please see the Study Reference Manual (SRM) for full details.

- Review Inclusion/Exclusion criteria (see Section 6)
- Demographic information including gender, ethnic origin, race, year of birth
- Medical history including smoking status, history of sinusitis, nasal polyposis, aspirin allergy, courses of rescue corticosteroids,
- Vital signs
- Physical exam
- Resting 12 lead ECG
- Therapy history (review concomitant medications from the previous 12 weeks prior to the first dose of study medication)
- Cardiovascular medical history/risk factors (as detailed in the eCRF) will be assessed at screening. This assessment must include a review of the subject responses to the cardiovascular assessment questions (see Appendix 6)
- Exacerbation review
- Smoking status
- Asthma Control Questionnaire (ACQ-5)
- Spirometry
- Laboratory tests:
  - Chemistry (including liver function test [LFT])
  - Haematology with differential
  - Immunogenicity
  - Hepatitis B Surface Antigen and hepatitis C antibody

- Urine pregnancy test- for all females of child bearing potential (Follicle Stimulating Hormone [FSH] will be assessed to confirm child-bearing status, if clinically indicated)

- AE/SAE assessment

8.2.2. Critical procedures performed at entry to Part B (Visit B1)

- Vital signs
- Resting 12- lead ECG
- Physical examination
- Concomitant medication review
- Exacerbation review
- Laboratory tests:
  - Chemistry (including LFT)
  - Haematology with differential
  - Urine pregnancy test- for all females of child bearing potential
- AE/SAE assessment

8.2.3. Critical procedures performed at Randomization (Visit C1)

- History of previous intubations, asthma exacerbation history in previous year, asthma triggers
- Review of randomization criteria (see Section 6.3)
- Subject/Clinician global impression of asthma severity rating
- St. George's Respiratory Questionnaire (SGRQ)
- Vital signs
- Spirometry (pre- and post-albuterol/salbutamol)
- Review/Collect eDiary data
- Exacerbation review
- Smoking status
- Concomitant medication assessment
- Laboratory tests:
  - Clinical Chemistry (including LFT)
  - Haematology with differential
  - Biomarker sample
  - Urine pregnancy test for all females of childbearing potential
- AE/SAE assessment

Change 14: Removal of text in Section 8.4.5 Electrocardiogram (ECG)

Original Text:

8.4.5. Electrocardiogram (ECG)

- Twelve-lead ECGs will be obtained at each time point specified in the Time and Events Schedules (Table 5, Table 6, Table 7 and Table 8), using the equipment provided for Study 201810.

Revised Text:

8.4.5. Electrocardiogram (ECG)

- Twelve-lead ECGs will be obtained at each time point specified in the Time and Events Schedules (Table 5, Table 6, Table 7 and Table 8).

Change 15: Removal of Urinalysis from Section 8.4.6 Clinical Safety Laboratory Assessments and updating Table 9 to reflect updated footnotes in Time and Event tables.

Original Text:

All protocol required laboratory assessments (haematology, clinical chemistry and urinalysis) must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule (Table 5, Table 6, Table 7 and Table 8)..

Revised Text:

All protocol required laboratory assessments (haematology and clinical chemistry) must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule (Table 5, Table 6, Table 7 and Table 8).

Original Text:

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 9.

Table 9 Protocol Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th>Parameters</th></tr>
<tr><td>Haematology</td><td>
<table>
<tr><td>Platelet Count</td><td><u>RBC Indices</u>:</td><td><u>WBC count with Differential</u>:</td></tr>
<tr><td>RBC Count</td><td>MCV</td><td>Neutrophils</td></tr>
<tr><td>Hemoglobin</td><td>MCH</td><td>Lymphocytes</td></tr>
<tr><td>Hematocrit</td><td></td><td>Monocytes</td></tr>
<tr><td></td><td></td><td>Eosinophils</td></tr>
<tr><td></td><td></td><td>Basophils</td></tr>
</table>
</td></tr>
<tr><td>Clinical Chemistry [1]</td><td>
<table>
<tr><td>BUN</td><td>Potassium</td><td>AST (SGOT)</td><td>Total and direct bilirubin</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>ALT (SGPT)</td><td>Total Protein</td></tr>
<tr><td>Glucose</td><td>Calcium</td><td>Alkaline phosphatase</td><td>Albumin</td></tr>
</table>
</td></tr>
<tr><td>Routine Urinalysis</td><td>• Specific gravity
• pH, glucose, protein, blood and ketones by dipstick
• Microscopic examination (if blood or protein is abnormal)</td></tr>
</table>

Laboratory Assessments	**Parameters**
Other Screening Tests	• Hepatitis B (HBsAg) • Hepatitis C (Hep C antibody) • FSH and estradiol (if clinically indicated, in women of non-child bearing potential only) • Alcohol and drug screen (if clinically indicated, to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Urine hCG Pregnancy test (for women of child bearing potential) [2]
NOTES : 1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Appendix 2 and Appendix 3 2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.	

Revised Text:

Haematology, clinical chemistry and additional parameters to be tested are listed in Table 9.

Table 9 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count	*RBC Indices*:	*WBC count with Differential:*	
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes	
	Hematocrit		Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry [1]	BUN	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Albumin
Other Screening Tests	• Hepatitis B (HBsAg) • Hepatitis C (Hep C antibody)[2] • FSH and estradiol (if clinically indicated, in women of non-child bearing potential only) • Alcohol and drug screen (if clinically indicated, to include at minimum: amphetamines, barbiturates, cocaine, opiates,			

Laboratory Assessments	Parameters
	cannabinoids and benzodiazepines) • Urine hCG Pregnancy test (for women of child bearing potential) [3]

NOTES :

1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Appendix 2 and Appendix 3
2. If Hepatitis C antibody positive result, a hepatitis C confirmatory test should be automatically performed to confirm the result. Test should be repeated as necessary if clinically indicated.
3. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

Change 15: Removal of urinalysis from Section 13.4.1 Definition of an AE.

Original Text:

- 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.

Revised Text:

- Any abnormal laboratory test results (hematology or clinical chemistry) 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.

Change 16: Updated Appendix 13.5 Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) and Collection of Pregnancy Information

Original Text:

Section 13.5: Appendix 5: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) and Collection of Pregnancy Information

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

Subjects who are FRP must agree to acceptable contraceptive methods approved in their local country, when used consistently and correctly (i.e., in accordance with the approved

product label and the instructions of the physician) for the duration of the study and for 4 months after the last study drug administration.

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a]
- Injectable progestogen [Hatcher, 2007a]
- Contraceptive vaginal ring [Hatcher, 2007a]
- Percutaneous contraceptive patches [Hatcher, 2007a]
- Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2007a].
- Male condom plus partner use of one of the contraceptive options below:
    - Contraceptive subdermal implant
    - Intrauterine device or intrauterine system
    - Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007a] Injectable progestogen [Hatcher, 2007a]
    - Contraceptive vaginal ring [Hatcher, 2007a]
    - Percutaneous contraceptive patches [Hatcher, 2007a]

This is an all inclusive list of those methods that meet the GSK definition of highly effective: having a failure rate of less than 1% per year when used consistently and, correctly and, when applicable, in accordance with the product label. For non-product methods (e.g. male sterility), the investigator determines what is consistent and correct use. The GSK definition is based on the definition provided by the ICH (ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals, 2009; EMA/CPMP/ICH/286/1995).

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

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.

Revised Text:

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

Subjects who are FRP must agree to acceptable contraceptive methods approved in their local country, when used consistently and correctly (i.e., in accordance with the approved product label and the instructions of the physician) for the duration of the study and for 4 months after the last study drug administration.

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
- Injectable progestogen [Hatcher, 2011]
- Contraceptive vaginal ring [Hatcher, 2011]
- Percutaneous contraceptive patches [Hatcher, 2011]
- Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011].

This is an all inclusive list of those methods that meet the GSK definition of highly effective: having a failure rate of less than 1% per year when used consistently and, correctly and, when applicable, in accordance with the product label. For non-product methods (e.g. male sterility), the investigator determines what is consistent and correct use. The GSK definition is based on the definition provided by the ICH (ICH, M3 [R2]

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

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.

Change 17: Changed Reference related to change 16 in Section 12 References

Original Text:

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

Revised Text:

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, Policar MS, editors. *Contraceptive Technology*. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011:50. Table 3-2.

Change 18: Changed entry criterion No. 5 in Section 6.3.2 Randomisation Exclusion Criteria to allow the result to be communicated to Site Staff if positive.

Original Text:

5. **Immunogenicity:** Positive neutralizing antibody status based on the last sample obtained.

Revised Text:

5. **Immunogenicity:** Positive neutralizing antibody status based on the last result obtained.

13.10.2. Amendment 2 (07-JUL-2016) from the Amendment 1 (06-NOV-2015)

Scope: this applies to all sites

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

Change 1: To amend Section 5.6.1 Risk Assessment.

Original text:

- The majority of reports of systemic non-allergic and allergic (i.e., hypersensitivity) reactions have been non-serious and resolved without sequelae following minimal supportive care. There have been rare reports of serious reactions. To date, there have been no reports of severe life-threatening anaphylaxis.

Revised text:

- The majority of reports of systemic non-allergic and allergic (i.e., hypersensitivity) reactions have been non-serious and resolved without sequelae following minimal supportive care. There have been rare reports of serious reactions.

Change 2: To correct the numbering of Section 6.2: Exclusion Criteria, which started at No. 2. All consequent exclusion criteria also change.

Original Text:

2. **MEA115666 or 201312 IP Discontinuation:** Subjects withdrawn from IP or withdrawn from study participation from either MEA115666 or 201312 for safety reasons

Revised text:

1. **MEA115666 or 201312 IP Discontinuation:** Subjects withdrawn from IP or withdrawn from study participation from either MEA115666 or 201312 for safety reasons

Change 3: To amend Exclusion criterion No. 7 in Section 6.2: Exclusion Criteria.

Original text:

8. **Other Monoclonal Antibodies**: Subjects who have received any monoclonal antibody (other than Xolair) to treat inflammatory disease within 5 half-lives of Visit 1.

Revised text:

7. **Other Monoclonal Antibodies**: Subjects who have received any monoclonal antibody within 5 half-lives of Visit 1.

Change 4: To amend Randomization Exclusion criterion No. 7 in Section 6.3.2: Randomization Exclusion Criteria.

Original text:

7. **Current Asthma Exacerbation:** Subjects with an asthma exacerbation that has not resolved completely within 7 days of Visit C1. Subjects who experience an exacerbation in the fixed run-in Part B which is not resolved within 7 days of Visit C1 may extend their run-in Part B by 4 weeks.

Revised text:

7. **Current Asthma Exacerbation:** Subjects with an asthma exacerbation (or asthma worsening) that has not resolved completely within 7 days of Visit C1. Subjects who experience an exacerbation (or asthma worsening) in the fixed run-in Part B which is not resolved within 7 days of Visit C1 may extend their run-in Part B by 4 weeks.

Change 5: Added text to Section 7.1 Investigational Product and Other Study Treatments.

Original Text:

- Safety monitoring of subjects is required during SC administration in accordance with standard of care at the site.

Revised text:

- Safety monitoring of subjects is required during SC administration in accordance with standard of care at the site. Such monitoring will include general safety monitoring including monitoring for systemic (i.e., allergic/IgE-mediated and non-allergic) and local injection site reactions. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study treatment, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the subject including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the patient to another facility for additional care if appropriate.

Change 6: To amend Section 7.9.1 Permitted Medications and Non-Drug Therapies.

Original text:

Additional asthma medications such as theophyllines, anti-leukotrienes or Xolair (omalizumab) will be permitted provided that they have been taken regularly (per label) in the 12 weeks prior to randomization (Visit C1).

Revised text:

Additional asthma medications such as theophyllines or anti-leukotrienes will be permitted provided that they have been taken regularly (per label) in the 12 weeks prior to randomization (Visit C1). If uncertain whether a medication is permitted please confirm with the medical monitor.

Change 7: Multiple changes to Section 7.9.2 Prohibited Medications and Non-Drug Therapies.

Original text:

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

Table 11 Medications not allowed prior to the Screening Visit 1 and throughout the study

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

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

Recreational drug use is not allowed during the study.

Revised text:

The following medications are not permitted during the 201810 study:

Table 12 Medications not permitted during the study

Medications
Investigational drugs (other than mepolizumab)
Other monoclonal antibodies
Experimental anti-inflammatory drugs
Any medication with a significant immunosupressive effect. (some examples listed below)
• Methotrexate, troleandomycin, cyclosporin, azathioprine
• Oral gold
• Chemotherapy
• Regular systemic (oral or parenteral) corticosteroids for the treatment of conditions other than asthma
• Long acting depot, intramuscular injections of corticosteroids if used to treat a condition other than asthma

Additionally, Bronchial Thermoplasty and Radiotherapy are excluded for 12 months prior to Visit 1 and throughout the study.

Neither CPAP nor oxygen therapy may be initiated on or after Visit 1.

Recreational drug use is not allowed during the study.

If uncertain whether a medication is permitted please contact the medical monitor prior to administration to confirm if the medication is prohibited.

Change 8: Within Table5, 6, 7 and 8, in Section 8.1, removal of the per visit task of registering each visit via the IRT system. In the interest of reducing replication, only Table 5 is shown below.

Original table:

Table 5 Time and Events Table: Screening/Variable Open-Label Run-In Weeks 0 - 52 - Part A

PART A **Procedures**	**Pre-Screen[1]**	**Exit/EW Visit MEA115666 or 201312/ Screen[1]**	**Variable Open-Label Treatment Part A[2] (window is ± 1 week)**													EW Visit[5]
Visit	**0**	**1**	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**	**A10**	**A11**	**A12**	**A13**	
Week of Variable Run-In		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Written Informed Consent	X															
Demography		X														
Medical History		X														
Assess cardiac risk factors		X														
Smoking status		X														
Inclusion/Exclusion Criteria		X														
Safety Assessments[3]																
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination		X												X		X
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG		X						X						X		X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[3]																
Haematology		X						X						X		X
Chemistry (incl. LFT)		X						X						X		X
Pregnancy Test[4]		U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Immunogenicity		X												X		X
HbsAg and hepatitis C antibody		X														
Efficacy Assessments[3]																
Exacerbation review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Asthma Control Questionnaire-5		X			X			X			X			X		X
Spirometry		X						X						X		X
Worksheets/Diary/IP/ eCRF																

PART A **Procedures**	**Pre-Screen[1]**	**Exit/EW Visit MEA115666 or 201312/ Screen[1]**	**Variable Open-Label Treatment Part A[2] (window is ± 1 week)**													EW Visit[5]
Visit	**0**	**1**	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**	**A10**	**A11**	**A12**	**A13**	
Week of Variable Run-In		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Administer open-label mepolizumab		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense albuterol/salbutamol		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect albuterol/salbutamol			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense paper diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect/review paper diary			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	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

Revised Table:

Table 13 Time and Events Table: Screening/Variable Open-Label Run-In Weeks 0 - 52 - Part A

PART A **Procedures**	**Pre-Screen[1]**	**Exit/EW Visit MEA115666 or 201312/ Screen[1]**	**Variable Open-Label Treatment Part A[2] (window is ± 1 week)**													EW Visit[5]
Visit	**0**	**1**	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**	**A10**	**A11**	**A12**	**A13**	
Week of Variable Run-In		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Written Informed Consent	X															
Demography		X														
Medical History		X														
Assess cardiac risk factors		X														
Smoking status		X														
Inclusion/Exclusion Criteria		X														
Safety Assessments[3]																

PART A **Procedures**	**Pre-Screen[1]**	**Exit/EW Visit MEA115666 or 201312/ Screen[1]**	**Variable Open-Label Treatment Part A[2] (window is ± 1 week)**													EW Visit[5]
Visit	**0**	**1**	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**	**A10**	**A11**	**A12**	**A13**	
Week of Variable Run-In		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination		X												X		X
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG		X						X						X		X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[3]																
Haematology		X						X						X		X
Chemistry (incl. LFT)		X						X						X		X
Pregnancy Test[4]		U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Immunogenicity		X												X		X
HbsAg and hepatitis C antibody		X														
Efficacy Assessments[3]																
Exacerbation review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Asthma Control Questionnaire-5		X			X			X			X			X		X
Spirometry		X						X						X		X
Worksheets/Diary/IP/ eCRF																
Administer open-label mepolizumab		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense albuterol/salbutamol		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect albuterol/salbutamol			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense paper diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect/review paper diary			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	X															X
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Change 9: Adding Physical Examination to Table 7.

Original Table:

Table 7 Time and Events Table: Fixed Run-In & Double-Blind Treatment Period – Parts B and C

PARTS B&C Procedures	Fixed Run-in Part B		EW from Part B[7]	Randomization	Double-Blind Treatment Part C (window is ± 1 week)													IPDISC/EW Visit [7]
Visit	**B1**	**B2[1]**	**Part B EW**	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**	**C13**	**Exit Visit**	
Week of Study	**-4 ± 1**	**-4 ± 1[1]**		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Smoking status				X														
Randomization Criteria				X														
Safety Assessments[2]																		
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X		X														X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X		X							X							X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Revised Table:

Table 7 Time and Events Table: Fixed Run-In & Double-Blind Treatment Period – Parts B and C

PARTS B&C Procedures	Fixed Run-in Part B		EW from Part B[7]	Randomization	Double-Blind Treatment Part C (window is ± 1 week)												IPDISC/EW Visit [7]
Visit	**B1**	**B2[1]**	**Part B EW**	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**	**C13**	**Exit Visit**	
Week of Study	**-4 ± 1**	**-4 ± 1[1]**		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Smoking status				X														
Randomization Criteria				X														
Safety Assessments[2]																		
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X		X	X													X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X		X							X							X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Change 10: Adding Physical Examination to Section 8.2.3

Original text:

8.2.3 Critical procedures performed at Randomization (Visit C1)

- History of previous intubations, asthma exacerbation history in previous year, asthma triggers
- Review of randomization criteria (see Section 6.3)
- Subject/Clinician global impression of asthma severity rating
- St. George's Respiratory Questionnaire (SGRQ)
- Vital signs
- Spirometry (pre- and post-albuterol/salbutamol)
- Review/Collect eDiary data
- Exacerbation review
- Smoking status
- Concomitant medication assessment Laboratory tests:
  - Clinical Chemistry (including LFT)
  - Haematology with differential
  - Biomarker sample
  - Urine pregnancy test for all females of childbearing potential
- AE/SAE assessment

Revised text:

8.2.3 Critical procedures performed at Randomization (Visit C1)

- History of previous intubations, asthma exacerbation history in previous year, asthma triggers
- Review of randomization criteria (see Section 6.3)
- Subject/Clinician global impression of asthma severity rating
- St. George's Respiratory Questionnaire (SGRQ)
- Vital signs
- Physical examination
- Spirometry (pre- and post-albuterol/salbutamol)
- Review/Collect eDiary data
- Exacerbation review

- Smoking status
- Concomitant medication assessment
- Laboratory tests:
  - Clinical Chemistry (including LFT)
  - Haematology with differential
  - Biomarker sample
  - Urine pregnancy test for all females of childbearing potential
- AE/SAE assessment

Change 11: To clarify how to administer and who should administer the Subject/Clinician Rating of Global Impression of Disease Severity and Response to Therapy

Original text:

8.3.2.7 Subject/Clinician Rating of Global Impression of Disease Severity and Response to Therapy

The Global Impressions of Disease Severity and Response to Therapy should be the first procedure completed by the subject at the specified study visit. To avoid biasing responses, the subjects should not be told the results of diagnostic tests prior to completing the questionnaire and should be completed before any procedures are performed on the subject to avoid influencing the subject's response.

Revised Text:

8.3.2.7 Subject/Clinician Rating of Global Impression of Disease Severity and Response to Therapy

The Global Impressions of Disease Severity and Response to Therapy should be the first procedure completed by the subject and clinician (Primary or Sub Investigators) at the specified study visit. To avoid biasing responses, the subjects should not be told the results of diagnostic tests prior to completing the questionnaires and these questionnaires should be completed before any procedures are performed on the subject to avoid influencing the subject's and Investigator's response.

Change 12: Clarifying the risks to blind break when performing local laboratory testing in Section 8.4.6 Clinical Safety Laboratory Assessments

Original text:

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

Revised text:

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the eCRF. Please note that any non-protocol specified local laboratory result has the potential to break the blind due to the eosinophils result being available. Please see the Study Reference Manual for guidance.

Change 13: To amend Section 8.5 Biomarker(s)/Pharmacodynamic Markers to align it with recent standard text.

Original text:

Additionally, a broad spectrum of inflammatory biomarkers of interest in the blood will also be considered for examination (e.g., interleukin (IL)-4, IL-5 (total and free), IL13, and periostin, IL9, IL25, IL33, YKL-40, osteopontin, C-reactive protein [CRP], surfactant protein D [SPD], etc.). All blood will be analyzed by a central laboratory or by GSK. The site staff and central study team will be blinded to each subject's IL-5 values from any visits post-randomization. Full details regarding sample collection, processing and shipping are provided in the central Laboratory Manual.

Revised text:

Blood (serum) samples will be collected during this study and may be used for the purposes of measuring biomarkers to identify factors that may influence the development of asthma and/or medically related conditions, as well as the biological and clinical responses to mepolizumab. Blood samples for biomarker testing will be stored for up to 15 years. Those biomarker results, which have the potential to break the blind will be blinded to the site staff until the clinical study report is finalised.

Full details regarding sample collection, processing and shipping are provided in the central Laboratory Manual.

Change 14: Xolair removed from the Trademark Information section.

Original text:

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Xolair

Revised text:

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
None