TITLE PAGE

Division: Worldwide Development

Information Type: Protocol Amendment

Title:	Mepolizumab Long-term Access Programme for Subjects who Participated in Study MEA115921 (Placebo-controlled Study of Mepolizumab in the Treatment of Eosinophilic Granulomatosis with Polyangiitis in Subjects Receiving Standard-of-care Therapy)

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Development Phase III

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2014N201870_01	2015-FEB-26	Amendment No. 1
Country-specific amendment for the UK: clarification regarding the estimated study end date for the UK and clarification regarding definition of abstinence as acceptable method of birth control.		
2014N201870_02	2015-MAR-12	Amendment No. 2
Country-specific amendment for the UK: Further clarification regarding the estimated study end date for the UK.		
2014N201870_03	2015-AUG-20	Amendment No. 3
Amendment to indicate that use of other biological agents will be permitted on agreement with the GSK Medical Monitor. Administrative updates.		
2014N201870_04	2019-May22	Amendment No. 4
Non-substantial amendment for the addition of an interim analyses and an update of medical monitor information. Country-specific amendment for the UK: Further clarification regarding the estimated study end date for the UK.		
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Non-substantial amendment for the addition of a Country-specific amendment for the UK: Further clarification regarding the estimated study end date for the UK.		

SPONSOR SIGNATORY:

Namhee Kwon MD Physician, Medicine Delivery Unit	**Date**

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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

Regulatory Agency Identifying Number(s):

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- 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 MEA116841

Rationale

Eosinophilia is central to the pathophysiology of Eosinophilic Granulomatosis with Polyangiitis (EGPA) and interleukin-5 (IL-5) is a key cytokine regulating the life-cycle of the eosinophil. Neutralisation of IL-5 with mepolizumab, an anti-IL5 monoclonal antibody, therefore offers a potential therapeutic option for EGPA. This was shown by data from two investigator-sponsored studies which attest to the clinical utility/proof-of-concept of mepolizumab in the treatment of EGPA by demonstrating the potential for mepolizumab to allow safe reduction in corticosteroid dose while maintaining clinical stability (study CRT109797) and for induction of remission (study MHE109435) in subjects with EGPA. These studies supported the subsequent initiation of a randomised, double-blind, phase 3 study (MEA115921) investigating the efficacy and safety of mepolizumab (300 mg subcutaneously [SC] every 4 weeks) compared with placebo over a 52-week study treatment period (with 8-week follow-up) in subjects with relapsing or refractory EGPA receiving standard-of-care therapy including background corticosteroid therapy with or without immunosuppressive therapy.

The purpose of this protocol is to support provision of open-label mepolizumab from GlaxoSmithKline (GSK), on an individual basis, to eligible subjects who participated in study MEA115921 and satisfy specific requirements, including requiring a dose of prednisolone (or equivalent) of ≥5 mg/day for adequate control of their EGPA. This will be referred to as a 'Long-term access programme (LAP)' and this protocol outlines the procedures to support treatment with mepolizumab in appropriate subjects.

Objective

The objective of this protocol is to provide a mechanism to supply mepolizumab on an individual subject basis to eligible subjects who previously participated in GSK-sponsored study MEA115921.

Overall Design

This is a Long-term Access Programme (LAP) to support provision of open-label mepolizumab on an individual basis to eligible subjects who participated in clinical study MEA115921 and who require a dose of prednisolone (or equivalent) of ≥5 mg/day for adequate control of their EGPA. Eligible subjects can initiate mepolizumab under this LAP within a 6-month period starting from completion of study MEA115921 (i.e., at Week 60) or, if the subject discontinued study MEA115921 prematurely, from the time-point that would have been Week 60 if the subject had completed the study. Initiation of mepolizumab treatment under this LAP more than 6 months after the MEA115921 Week 60 time-point will be considered on an individual subject basis by the GSK Medical Monitor.

After IRB/Ethics Committee approval is received for this protocol, the treating physician will be required to complete a 'Long-term Access Programme' Subject Application Form' if he/she identifies a subject who may be eligible for treatment. The completed application form must be sent to GSK for review and approval by the GSK Medical

Monitor to confirm the subject is eligible for treatment with mepolizumab under this LAP. Approval will be communicated to the treating physician and mepolizumab supplies provided for initiation of treatment.

Individual investigators will be responsible for identifying subjects from MEA115921 who may be eligible for treatment with mepolizumab under this LAP and for ensuring the necessary approval is obtained from GSK. In the event a subject is deemed appropriate for treatment with mepolizumab the investigator will then be responsible for ongoing benefit:risk evaluation to support continued treatment with mepolizumab irrespective of oral corticosteroid dose. It is expected that the treating physician will monitor subjects as per standard-of-care therapy (including any requirements for blood and urine tests).

Eligible subjects will receive subcutaneously administered mepolizumab at a dose of 300 mg SC every 4 weeks.

Information including demography, cardiovascular risk, date of randomization and last visit in study MEA115921 will be collected from participating subjects. Study visits will include assessment of adverse events and serious adverse events and recording of corticosteroid use. Based on regular standard-of-care management, at each visit the investigator will be required to make an overall assessment of benefit:risk for treatment with mepolizumab prior to administration. To support continued supply of mepolizumab, the investigator is required to record the overall assessment of benefit risk every 12 weeks. Urine pregnancy tests will be conducted on females of child-bearing potential. In the event a subject discontinues treatment, for any reason, a follow-up assessment will be required 12 weeks after the last dose of mepolizumab.

Eligible subjects can continue to receive mepolizumab under this LAP until mepolizumab is commercially licensed for the treatment of EGPA in the relevant country or until the Sponsor discontinues development in EGPA or until the subject meets any of the withdrawal/stopping criteria. United Kingdom (UK) only clarification: Eligible subjects can continue to receive mepolizumab under this LAP until July 2022 or until the Sponsor discontinues development in EGPA or until the subject meets any of the withdrawal/stopping criteria.

2. INTRODUCTION

2.1. Study Rationale

GlaxoSmith Kline (GSK) is sponsoring a randomised, double-blind, phase 3 study (MEA115921) investigating the efficacy and safety of mepolizumab (300 mg subcutaneously [SC] every 4 weeks) compared with placebo over a 52-week study treatment period in subjects with relapsing or refractory EGPA receiving standard-of-care therapy including background corticosteroid therapy with or without immunosuppressive therapy [GlaxoSmithKline Document Number 2012N142276_02].

The purpose of this protocol is to support provision of mepolizumab from GSK, on an individual compassionate basis, to eligible subjects who have participated in study MEA115921 and who satisfy specific requirements, including requiring a dose of prednisolone (or equivalent) of ≥5 mg/day for adequate control of their EGPA. This mechanism will be referred to as a 'Long-term Access Programme' (LAP) in this protocol and outlines procedures to support treatment with mepolizumab in appropriate subjects.

2.2. Brief Background

Eosinophilic Granulomatosis with Polyangiitis (EGPA), also referred to as Churg-Strauss syndrome (CSS), is a rare hypereosinophilic syndrome characterised by small vessel vasculitis in association with asthma, sinusitis, and pulmonary infiltrates. Multiple organs can be affected including the heart, lungs, skin, gastrointestinal tract, kidneys, and nervous system [Keogh, 2006; Vaglio, 2012; Holle, 2009].

Eosinophilia is central to the pathophysiology of Eosinophilic Granulomatosis with Polyangiitis (EGPA) and interleukin-5 (IL-5) is a key cytokine regulating the life-cycle of the eosinophil [Keogh, 2006; Vaglio, 2012; Holle, 2009; Clutterbuck, 1989; Lopez, 1988; Rothenberg, 2006]. Neutralisation of IL-5 with mepolizumab, an anti-IL5 monoclonal antibody, therefore offers a potential therapeutic option for EGPA.

Mepolizumab is a fully humanized monoclonal antibody (IgG1, kappa, mAb) which is specific for human IL-5 and which blocks binding of human IL-5 (hIL-5) to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface. In patients with conditions where eosinophilia is considered to play an important part in the pathology, a consistent reduction in eosinophil number is observed in association with mepolizumab administration, with concomitant clinical improvement [Haldar, 2009; Pavord, 2012; Stein, 2006; Rothenberg, 2008; Nair, 2009].

Data from two investigator-sponsored studies attested to the clinical utility/proof-of-concept of mepolizumab in the treatment of EGPA having demonstrated the potential for mepolizumab to allow safe reduction in corticosteroid dose while maintaining clinical stability (study CRT109797; [Kim, 2010; IB; GlaxoSmithKline Document Number: CM2003/00010/08]) and for induction of remission (study MHE109435; [Moosig, 2011; IB; GlaxoSmithKline Document Number: CM2003/00010/08]) in subjects with EGPA.

This has supported initiation of a phase 3, double-blind, randomised, placebo-controlled study, MEA115921 [GlaxoSmithKline Document Number 2012N142276_02].

The objective of study MEA115921 is focussed on investigating the efficacy and safety of mepolizumab plus standard-of-care compared with placebo plus standard-of-care. In this study, 130 subjects are randomised in a 1:1 ratio to receive either: 300 mg mepolizumab SC every 4 weeks (n=65) or Placebo SC every 4 weeks (n=65) in addition to their background standard-of-care therapy including corticosteroid therapy with or without immunosuppressive therapy. Subjects are treated for a period of 52 weeks and then followed up for a further 8 weeks to study completion at Week 60.

3. OBJECTIVE

The objective of this protocol is to provide a mechanism to supply mepolizumab on an individual subject basis to eligible subjects who previously participated in GSK-sponsored study MEA115921.

4. STUDY DESIGN

4.1. Overall Design

This is a LAP to support provision of open-label mepolizumab on an individual basis to eligible subjects who participated in clinical study MEA115921 who satisfy specific requirements, including requiring a dose of prednisolone (or equivalent) of ≥5 mg/day for adequate control of their EGPA. Eligible subjects can initiate mepolizumab under this LAP within a 6-month period starting from completion of study MEA115921 (i.e., at Week 60) or, if the subject discontinued study MEA115921 prematurely, from the time-point that would have been Week 60 if the subject had completed the study. Initiation of mepolizumab treatment under this LAP more than 6 months after the MEA115921 Week 60 time-point will be considered on an individual subject basis by the GSK Medical Monitor.

After IRB/Ethics Committee approval is received for this protocol, the treating physician will be required to complete a 'Long-term Access Programme Subject Application Form' if he/she identifies a subject who may be eligible for treatment (a copy will be provided in the Study Reference Manual). The completed application form must be sent to GSK for review and approval by the GSK Medical Monitor to confirm the subject is eligible for treatment with mepolizumab under this LAP. Approval will be communicated to the treating physician and mepolizumab supplies provided for initiation of treatment.

Individual investigators will be responsible for identifying subjects from MEA115921 who may be eligible for treatment with mepolizumab under this LAP and for ensuring the necessary approval is obtained from GSK. In the event a subject is deemed appropriate for treatment with mepolizumab the investigator will then be responsible for ongoing benefit:risk evaluation to support continued treatment with mepolizumab irrespective of oral corticosteroid dose. It is expected that the treating physician will monitor subjects as per standard-of-care therapy (including any requirements for blood and urine tests).

Eligible subjects will receive subcutaneously administered mepolizumab at a dose of 300 mg SC every 4 weeks.

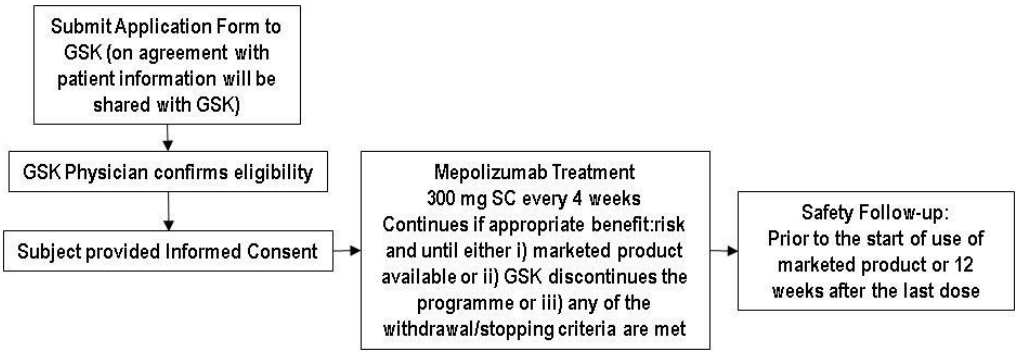
Information including demography, cardiovascular risk, date of randomization and last visit in study MEA115921 will be collected from participating subjects. Study visits will include assessment of adverse events and serious adverse events and recording of corticosteroid use. Based on regular standard-of-care management, at each visit the investigator will be required to make an overall assessment of benefit:risk for treatment with mepolizumab prior to administration. To support continued supply of mepolizumab, the investigator is required to record the overall assessment of benefit risk every 12 weeks. Urine pregnancy tests will be conducted on females of child-bearing potential (FCBP). In the event a subject discontinues treatment, for any reason, a follow-up assessment will be required 12 weeks after the last dose of mepolizumab.

Eligible subjects can continue to receive mepolizumab under this LAP until mepolizumab is commercially licensed for the treatment of EGPA in the relevant country or until the Sponsor discontinues development in EGPA or until the subject meets any of the withdrawal/stopping criteria.

UK only clarification: Eligible subjects can continue to receive mepolizumab under this LAP until July 2022 or until the Sponsor discontinues development in EGPA or until the subject meets any of the withdrawal/stopping criteria.

A summary of the study design is provided in Figure 1.

Figure 1 Study Design



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

Data Monitoring Committee (IDMC) will be utilized until completion of the lead study MEA115921; their primary focus will be the monitoring of cardiovascular safety and all cause mortality.

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

4.2. Type and Number of Subjects

Any subject who participated in study MEA115921 who requires a dose of prednisolone (or equivalent) of ≥5 mg/day for adequate control of their EGPA will be eligible to be considered for treatment with mepolizumab under the LAP outlined in this protocol.

4.3. Dose Justification

The dose of mepolizumab for this LAP is the same as that investigated in the lead clinical study, MEA115921, i.e., 300 mg mepolizumab SC every 4 weeks.

4.4. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with SB-240563, mepolizumab, can be found in the Investigator's Brochure IB and Supplement [GlaxoSmithKline Document Number: CM2003/00010/08 and GlaxoSmithKline Document Number 2014N200212_00].

4.4.1. Risk Assessment

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigative Medicinal Product (IMP): Mepolizumab		
Pre-Clinical and Clinical Findings		
Risk of Systemic Allergic and Non-allergic Reactions, including Anaphylaxis	• Biopharmaceutical products may elicit ADA and NAB, which have the potential to modulate PK, PD or produce adverse reactions. However, humanized and fully human antibodies are less immunogenic than mouse or chimeric monoclonal antibodies. • Reactions reported to date across the mepolizumab program are summarized in the IB and Supplement; see 'Special Warnings and Special Precautions for Use' section located in Section 6 titled 'Summary of Data and Guidance for the Investigator'. [GlaxoSmithKline Document Number: CM2003/00010/08 and GlaxoSmithKline Document Number: 2014N200212_00].	• Daily monitoring of SAEs by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team. • Independent Data Monitoring Committee (IDMC) will be utilized during study until completion of the lead study MEA115921. • Specific Case Report Form (CRF) pages utilized for targeted collection of reactions data. • Utilization of Joint NIAID/FAAN 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (see **Error! Reference source not found.**). • Subjects are monitored in clinic for 1 hour following dosing (first 3 administrations only)
Risk of Immunogenicity	• See previous risk for background information in literature. • Immunogenicity data reported to date across the mepolizumab development program are summarized in the IB; see Section 5.4 'Clinical Immunogenicity' and a summary of immunogenicity findings in the 'Other Potentially Clinically Relevant Information for the Investigator' section located in Section 6 titled 'Summary	• See previous risk for mitigation strategy related to clinical safety risks.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigative Medicinal Product (IMP): Mepolizumab		
Pre-Clinical and Clinical Findings		
	of Data and Guidance for the Investigator'.	

Potential risk for adverse cardiovascular (CV) effects	• Mepolizumab binding restricted to human lymphoid tissues in an immunohistochemistry tissue binding study suggesting a low likelihood of non-pharmacologic effects on CV function.
	• No adverse effects on 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 a similar frequency of SAEs reported overall from the cardiac and vascular system organ class (SOC). Additionally, similar findings were observed in other SOCs with thrombotic events (e.g., stroke in the Nervous System SOC). Data from 2 subsequently completed placebo-controlled severe asthma trials did not show an increased risk of serious
		• Daily monitoring of SAE by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team.
		• CV monitoring for study includes:
		  • Enhanced baseline collection of CV risk factors & functional status;
		  • Baseline evaluation of clinical symptoms of ischemic heart disease, if clinically indicated;
		  • 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);
		  • Use of an IDMC and external adjudication panel for CV events (until completion of the lead study MEA115921)

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigative Medicinal Product (IMP): Mepolizumab		
Pre-Clinical and Clinical Findings		
	ischemic cardiac events; there were no new reports in any treatment groups including placebo	
Potential risk for increase in infections – 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 SAEs reported in the infection and infestation SOC were 5/345 (1%) in placebo subjects and 18/754 (2%) in mepolizumab subjects. • Infections reported to date across the mepolizumab development program are summarized in the IB and Supplement; see 'Special Precautions and Warnings' (for exclusion of subjects with underlying parasitic infections) and 'Undesirable Effects' (for very common infections of nasopharyngitis, URTI, rhinitis and bronchitis reported in other patient populations) sections located in Section 6 titled 'Summary of Data and Guidance for the Investigator'.	• Daily monitoring of SAE by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team • IDMC will be utilized during study (until completion of the lead study MEA115921).

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigative Medicinal Product (IMP): Mepolizumab		
Pre-Clinical and Clinical Findings		
	[GlaxoSmithKline Document Number: CM2003/00010/08 and GlaxoSmithKline Document Number 2014N200212_00].	
Potential risk for increase in malignancies – theoretical concern with biologics; however, blockade of IL-5 is not associated with generalized nform-suppression or impaired host resistance.	• Role of IL-5 and eosinophils in tumour surveillance is not fully characterised in the literature. • No evidence of defective tumour 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. • Malignancies reported to date across the mepolizumab development program are summarized in the IB.	• Daily monitoring of SAE by medical monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team • IDMC will be utilized during study (until completion of the lead study MEA115921).

4.4.2. Benefit Assessment

Data from two investigator-sponsored studies attested to the clinical utility/proof-of-concept of mepolizumab in the treatment of EGPA having demonstrated the potential for mepolizumab to allow safe reduction in corticosteroid dose while maintaining clinical stability (study CRT109797; [Kim, 2010; IB; GlaxoSmithKline Document Number: CM2003/00010/08]) and for induction of remission (study MHE109435; [Moosig, 2011; IB; GlaxoSmithKline Document Number: CM2003/00010/08]) in subjects with EGPA. Furthermore, mepolizumab has also demonstrated clinical benefit in other conditions where eosinophilia is considered to play an important part in the pathology, e.g., severe asthma [Haldar, 2009; Nair, 2009; Pavord, 2012], hypereosinophilic syndrome [Rothenberg, 2008] and eosinophilic esophagitis [Stein, 2006].

Study MEA115921 is a phase 3, double-blind, randomised, placebo-controlled study investigating the efficacy and safety of mepolizumab in the treatment of EGPA in subjects receiving standard-of-care therapy.

The Sponsor considers that the available data support provision of mepolizumab to subjects who participated in study MEA115921 and who require a dose of prednisolone (or equivalent) of ≥5 mg/day for adequate control of their EGPA, as outlined in the eligibility criteria for supply of mepolizumab as outlined in this protocol/'LAP'.

4.4.3. Overall Benefit:Risk Conclusion

Current data from mepolizumab preclinical and clinical development indicate the ability of mepolizumab to inhibit IL-5, with demonstration of the potential for clinical utility in the treatment of conditions associated with hypereosinophilia such as EGPA. To date, the safety profile of mepolizumab has been favourable and Aes reported commonly are non-serious and manageable with minimal supportive care. Furthermore, there have been no safety concerns identified or signals observed with mepolizumab that would preclude investigation in EGPA. The Sponsor therefore considers that the available data and overall benefit/risk profile support treatment of subjects who participated in study MEA115921.

5. SELECTION OF POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Investigator's Brochure and Supplement [GlaxoSmithKline Document Number: CM2003/00010/08 and GlaxoSmithKline Document Number: 2014N200212_00].

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

All requests for continued treatment will be submitted to GSK using the LAP Application Form. The Lead Mepolizumab Medical Advisor for the mepolizumab EGPA programme, reserves the right to review the necessary information to confirm whether each subject, in the opinion of GSK, meets the required eligibility criteria and may be approved for treatment with mepolizumab under this LAP. Approval will be based on review of the eligibility criteria outlined below, in addition to any other information (if required), with careful consideration of each individual case.

5.1. Inclusion Criteria

Subjects will be required to satisfy the specified inclusion and exclusion criteria requirements listed below to be eligible to receive mepolizumab under the LAP. In addition, GSK may request additional information, not specified here, to support approval of mepolizumab supply.

A subject will be eligible for the LAP only if all of the following criteria apply:

[1] MEA115921 PARTICIPATION
1. Subject participated in study MEA115921

[2] MEA115921 COMPLETION
2. Subject has <u>either</u>: i. completed study MEA115921 to Week 60, i.e., completion of follow up period, <u>or</u> ii. if the subject was withdrawn prematurely from study MEA115921, the subject has reached the date of what would have been the Week 60 if the subject had completed the study, i.e., 60 weeks from Baseline (Visit 2).

[3] SUBJECT REQUIRES PREDNISOLONE (OR EQUIVALENT) ≥5 MG/DAY
3. At or up to 6 months after the MEA115921 Week 60 time- point the subject requires a dose of prednisolone (or equivalent) of ≥5 mg/day for adequate control of their EGPA.

Note: Inclusion of subjects >6 months after the MEA115921 Week 60 time-point will be considered on an individual subject basis by the GSK Medical Monitor.

[4] PHYSICIAN ASSESSMENT SUPPORTS MEPOLIZUMAB TREATMENT

4. The treating physician requesting mepolizumab under this Long-term Access Programme considers the benefits of treatment with mepolizumab outweigh the risks for the individual subject.

[5] FEMALE SUBJECTS

5. To be eligible for mepolizumab treatment under this Long-term Access Programme, females of childbearing potential (FCBP) must commit to consistent and correct use of an acceptable method of birth control, as summarised in Appendix 2 – Anaphylaxis Criteria

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

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

6. Appendix 3, beginning with consent, for the duration of the treatment with mepolizumab and for 4 months after the last mepolizumab administration.

[6] INFORMED CONSENT
7. The subject consents to receiving treatment with mepolizumab under this Long-term Access Programme.

5.2. Exclusion Criteria

A subject will not be eligible for the LAP if any of the following criteria apply:

[1] MALIGNANCY
1. A current malignancy or history of cancer in remission for less than 12 months (Subjects who had localized carcinoma (i.e., basal or squamous cell) of the skin which was resected for cure will not be excluded).

[2] OTHER CLINICALLY SIGNIFICANT MEDICAL CONDITIONS
2. Subject has other clinically significant medical conditions uncontrolled with standard-of-care therapy not associated with EGPA, e.g., unstable liver disease, uncontrolled cardiovascular disease, ongoing active infectious disease requiring systemic treatment.

[3] PREGNANCY
3. Subject is pregnant or breastfeeding. Subjects should not be considered for continued treatment if they plan to become pregnant during the course of treatment with mepolizumab.

[4] HYPERSENSITIVITY
4. Subject has a known allergy or intolerance to a monoclonal antibody or biologic therapy including mepolizumab.

[5] PREMATURE WITHDRAWAL OF STUDY TREATMENT IN MEA115921
5. Subject had an adverse event (serious or non-serious) considered related to study treatment whilst participating in study MEA115921 which resulted in permanent withdrawal of study treatment.

[6] OTHER BIOLOGICAL THERAPY
6. Subject is receiving treatment with another biological therapy such as a monoclonal antibody therapy or IV immunoglobulin therapy without prior agreement from the GSK Medical Monitor.

[7] OTHER INVESTIGATIONAL PRODUCTS
7. Subjects who have received treatment with an investigational drug within the past

30 days or 5 terminal phase half-lives of the drug whichever is longer, prior to initiation of mepolizumab treatment under this Long-term Access Programme (this also includes investigational formulations of marketed products).

[8] OTHER CLINICAL STUDY
8. Subject is currently participating in any other interventional clinical study.

5.3. Withdrawal/Stopping Criteria

GSK must be advised of any permanent discontinuations of mepolizumab under the LAP. Any subject discontinuing mepolizumab should be assessed 12 weeks after receiving their last dose at a follow-up/end of study visit. If the subject is lost to follow-up an Early Withdrawal form should be completed.

Subjects may continue to receive mepolizumab until any of the following apply:

- The physician determines that the subject is no longer deriving clinical benefit from treatment with mepolizumab or the benefit:risk evaluation does not support continued treatment.
- Subject experiences a treatment-limiting adverse event(s), i.e., an event that results in permanent discontinuation of mepolizumab treatment.
- Subject becomes pregnant or is planning to become pregnant.
- GSK discontinues clinical development of mepolizumab in EGPA. Note, under these circumstances, provision of mepolizumab will be discontinued for all subjects regardless of individual patient benefit received during MEA115921 or 116841.
- Mepolizumab becomes commercially licensed for the treatment of EGPA in the relevant country. UK only clarification: Eligible subjects can continue to receive mepolizumab under this LAP until July 2022.

5.4. Subject and Study Completion

Supply of mepolizumab under the LAP will continue until mepolizumab is commercially available in the relevant country. UK only clarification: Eligible subjects can continue to receive mepolizumab under this LAP until July 2022.

Treating physicians are responsible for the individual benefit:risk assessments and safety monitoring in support of continued mepolizumab treatment.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term ‘study treatment’ is used throughout the protocol to describe open-label mepolizumab supply.

Study Treatment	
Product name:	SB-240563 (mepolizumab)
Formulation description:	Mepolizumab 100mg vial for injection contains target quantities of 10.3mg Sodium Phosphate Dibasic Heptahydrate, 0.96 mg Polysorbate 80 and 230.4mg Sucrose per vial.
Dosage form:	Lyophilized powder for injection reconstituted with Sterile Water for Injection, just prior to use.
Unit dose strength(s)/Dosage level(s):	100 mg/300 mg
Route of Administration:	Subcutaneous injection
Dosing instructions:	Subjects will be dosed with 300 mg SC injection administered as three separate 100 mg SC injections every 4 weeks. Injections should be administered into any of the upper arm, thigh or anterior abdominal wall. It is recommended that individual injection sites are separated by at least 5 cm.
Physical description:	Mepolizumab will be provided as a lyopholised cake in sterile vials for individual use.

Safety monitoring of subjects is required during SC administration and for 1 hour after the end of the injections for the first three administrations, i.e., at baseline, and Weeks 4 and 8. Such monitoring will include general safety monitoring including monitoring for both systemic hypersensitivity (i.e., allergic/IgE-mediated and non-allergic) and local site reactions. From Week 12 onwards, subjects can be monitored following mepolizumab administration in accordance with standard of care at the site.

Trained rescue personnel and rescue medications/equipment must be available for use at all times, see **Error! Reference source not found.** for further information.

6.2. Packaging and Labelling

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

6.3. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for reconstitution of mepolizumab will be detailed in the Study Reference Manual (SRM) which will be accompanied by a Quality Agreement.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment.
- Mepolizumab must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Study treatment/mepolizumab must be stored in a secure area under the appropriate physical conditions for the product. Access to study treatment will be limited to the investigator's authorized site staff. Mepolizumab must be stored under the appropriate physical conditions which includes storage in a refrigerator or at a temperature of 2-8°C and protected from light. Maintenance of a temperature log (manual or automated) is required. Study treatment must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. 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.

6.4. Treatment of Mepolizumab Overdose

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

6.5. Concomitant Medications and Non-Drug Therapies

6.5.1. Permitted Medications and Non-Drug Therapies

Other concomitant therapy for the treatment of EGPA is permitted.

Use of corticosteroids (excluding inhaled and topical steroids) will be captured.

Concomitant therapy with another biological therapy (e.g., monoclonal antibodies or IV immunoglobulin therapy) should be discussed with the GSK Medical Monitor prior to beginning therapy. If allowed, therapy should not be administered at the same time as the mepolizumab injection(s) and physicians should take measures to separate administration of another biological therapy as long as possible from administration of mepolizumab.

7. ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the assessment 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 assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1.

7.1. Time and Events Table

Visits and Assessments	Screening (up to 4 weeks)	Baseline	Week 4 (±7 days)	Week 8 (±7 days)	Week 12 (±7 days)	Week 16 (±7 days)	Week 20 (±7 days)	Week 24 (±7 days)	Every 4 week treatment cycle/assessments repeated until End of Treatment	Early withdrawal[3]	End of Treatment[3]/ Follow-up (12 weeks post-last dose)
Application Form sent to GSK for approval	X										
Written Informed Consent	X										
Demography and CV risk assessment	X										
Eligibility assessment: inclusion & exclusion criteria review	X										
Baseline information		X									
Dosing with mepolizumab[1,2]		X	X	X	X	X	X	X			
Corticosteroid use	X	X	X	X	X	X	X	X		X	X
AE/SAE review	X	X	X	X	X	X	X	X		X	X
Urine pregnancy test (FCBP)	X	X	X	X	X	X	X	X		X	X
Documentation of Benefit:risk evaluation to support continued supply of mepolizumab[1]	X	X			X			X			

1. The treating physician should make a benefit:risk evaluation to confirm continued treatment with mepolizumab is appropriate prior to each administration. This will be documented every 12 weeks to support continued supply. Note: it is expected that the treating physician will monitor subjects as per standard-of-care therapy (including any requirements for blood and urine tests).
2. Safety monitoring of subjects is required during SC administration and for 1 hour after the end of the injections for the first three administrations, i.e., at baseline, and Weeks 4 and 8. From Week 12 onwards, subjects can be monitored following mepolizumab administration in accordance with standard of care at the site.
3. See Section 5.3

7.2. Screening and Critical Baseline Assessments

The subject's informed consent will be obtained at the Screening visit.

Review of inclusion/exclusion criteria will be conducted at the Screening visit.

The investigator will make a benefit:risk evaluation to confirm treatment with mepolizumab is appropriate for the subject.

The subject's identification number from study MEA115921 will be recorded in addition to their current oral corticosteroid dose.

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

7.3. Safety

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

The treating physician should make a benefit:risk evaluation to confirm treatment with mepolizumab is appropriate prior to each administration. This will be documented every 12 weeks to support continued supply. It is expected that the treating physician will monitor subjects as per standard-of-care therapy (including any requirements for blood and urine tests).

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

The definitions of an AE or SAE can be found in Appendix 4. Additionally, because mepolizumab is a monoclonal antibody administered subcutaneously, systemic (i.e., allergic/hypersensitivity and non-allergic) reactions and local injection site reactions will be reported and recorded throughout the treatment and follow-up period. 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] (**Error! Reference source not found.**).

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

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

- Aes and SAEs will be collected from administration of the first dose of mepolizumab and will continue indefinitely, see minimum schedule of assessments, Time and Events Table (Section 7.1)
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product

will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 4. The treating physician is 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 discontinued mepolizumab treatment under the LAP, 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

7.3.1.2. Method of Detecting Aes and SAEs

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

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

7.3.1.3. Follow-up of Aes and SAEs

After the initial AE/SAE report, the treating physician is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious Aes of special interest (as defined in Section 4.4.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.3). Further information on follow-up procedures is given in Appendix 4.

7.3.1.4. Cardiovascular and Death Events

Investigators will be required to fill out the specific CV event page of the CRF for the cardiovascular Aes and SAEs, as listed in Appendix 4: Section 12.4.3.

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

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

7.3.1.5. Regulatory Reporting Requirements for SAEs

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

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

Treating physician 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.

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

7.3.2. Pregnancy

Urine pregnancy tests in FCBP will be conducted as indicated in the Time and Events Table (Section 7.1).

Details of all pregnancies in female subjects will be collected after the start of dosing and until 12 weeks post last dose. If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined below.

- Treatment with mepolizumab should be discontinued in the event of pregnancy. .
- Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.
- Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

8. DATA MANAGEMENT

- For this study (1-eDM) subject data will be entered into GSK defined CRFs, transmitted electronically to GSK.
- 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.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

No statistical analysis will be conducted for this study. Reported data will be summarized.

9.1. Interim Analysis

When required, an interim analysis will be performed in order to provide open-label safety data to inform the risk-benefit assessment of mepolizumab in EGPA.

10. STUDY GOVERNANCE CONSIDERATIONS

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

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

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with 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 favourable opinion/approval of the study protocol and amendments as applicable
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)
- Investigator reporting requirements (e.g. reporting of Aes/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.

- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.2. Quality Control (Study Monitoring)

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

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

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

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

10.3. Quality Assurance

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

10.4. 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 nformation studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.5. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any

institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

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

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

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

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

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

10.7. Review Committees

An IDMC will be utilized until completion of the lead study MEA115921; their primary focus will be the monitoring of cardiovascular safety and all cause mortality.

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12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

ADA	Anti-drug antibody
AE	Adverse Event
ALT	Alanine transaminase
CRF	Case Report Form
CV	Cardiovascular
DCSI	Developmental Core Safety Information
ECG	Electrocardiogram
EGPA	Eosinophilic Granulomatosis with Polyangiitis
FCBP	Female of childbearing potential
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IL	Interleukin
IRB	Institutional review Board
IUD	Intrauterine device
IV	Intravenous(ly)
kg	kilogram
LAP	Long-term Access Programme
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
MSDS	Material Safety Data Sheet
NAB	Neutralizing antibodies
SAE	Serious Adverse Event
SC	Subcutaneous(ly)
SOC	System organ class
SRM	Study reference manual
SRT	Safety review team
ULN	Upper limit of normal
UK	United Kingdom

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.2. Appendix 2 – Anaphylaxis Criteria

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

4) 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:
    c) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    d) Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

5) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    e) Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    f) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    g) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    h) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

6) Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    c) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
    d) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

12.3. Appendix 3 – Acceptable Birth Control

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

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

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

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

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

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

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

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

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

12.4.1. 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 unfavourable 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 (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • 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.

12.4.2. 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 fulfils 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, diarrhoea, influenza,

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

12.4.3. 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

12.4.4. 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.

12.4.5. 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 or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.4.6. 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 or the SAE coordinator. • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • 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 or the SAE coordinator by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5 – Country Specific Requirements

Amendments 01, 02 and 04 include a country-specific local amendment generated for the United Kingdom (UK).

The UK regulatory authority has requested the following clarifications highlighted in ***bold italics.***

Overall study design (Section 1: Protocol Synopsis for Study MEA115921, Overall Design, paragraph 6 and Section 4.1: Overall Design, paragraph 6):

UK only clarification: Eligible subjects can continue to receive mepolizumab under this LAP until ***June 2018*** or until the Sponsor discontinues development in EGPA or until the subject meets any of the withdrawal/stopping criteria.

Section 5.3: Withdrawal/Stopping Criteria, paragraph 2, bullet 5 and Section 5.4: Subject and Study Completion

UK only clarification: Eligible subjects can continue to receive mepolizumab under this LAP until June 2018.

12.6. Appendix 2 – Anaphylaxis Criteria

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

7) 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:
    e) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    f) Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

8) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    i) Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    j) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    k) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    l) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

9) Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    e) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
    f) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Appendix 3 – Acceptable Birth Control:

UK only clarification*: *True abstinence from penile-vaginal intercourse ***when this is in line with the preferred and usual lifestyle of the subject.***

Overall study design (Section 1: Protocol Synopsis for Study MEA115921, Overall Design, paragraph 6 and Section 4.1: Overall Design, paragraph 6):

UK only Clarification*:** Eligible subjects can continue to receive mepolizumab under this LAP until June ***2021 or until the Sponsor discontinues development in EGPA or until the subject meets any of the withdrawal/stopping criteria.

Section 5.3: Withdrawal/Stopping Criteria, paragraph 2, bullet 5 and Section 5.4: Subject and Study Completion

<u>UK only clarification</u>: Eligible subjects can continue to receive mepolizumab under this LAP until June 2021.

<u>UK only clarification</u>: Eligible subjects can continue to receive mepolizumab under this LAP until July 2022.

12.7. Appendix 6 – Protocol Changes

12.6.1 Protocol Amendment 01

This amendment applies to sites in the UK only.

List of protocol changes:

Text which has been added to the protocol is highlighted in ***bold, italic*** typeface. Text which has been deleted from the protocol is indicated by ~~strike-through~~ format.

Change	Section, Text affected, and Rationale
1.	Section 1: Protocol Synopsis for Study MEA115921, Overall Design, paragraph 6. Section 4.1: Overall Design, paragraph 6. ***Added:*** ***United Kingdom (UK) only clarification: Eligible subjects can continue to receive mepolizumab under this LAP until June 2018 unless mepolizumab is commercially licensed for the treatment of EGPA in the relevant country prior to this date or until the Sponsor discontinues development in EGPA or until the subject meets any of the withdrawal/stopping criteria.*** **Rationale:** Clarification requested by the UK regulatory authority.
2.	Appendix 1 – Abbreviations and Trademarks ***Added:*** ***UK: United Kingdom***
3.	Appendix 3– Acceptable Birth Control; bullet 3 ***Modified:*** ***UK only: True*** abstinence from penile-vaginal intercourse ***when this is in line with the preferred and usual lifestyle of the subject.*** **Rationale:** Clarification requested by the UK regulatory authority.
4.	Appendix 5 – Country Specific Requirements: ***Changed from:*** ~~No country-specific requirements exist.~~

Change	Section, Text affected, and Rationale
	Changed to: Amendment 01 includes a country-specific local amendment generated for the United Kingdom (UK). The UK regulatory authority has requested the following clarifications highlighted in ***bold italics.*** Overall study design (Section 1: Protocol Synopsis for Study MEA115921, Overall Design, paragraph 6 and Section 4.1: Overall Design, paragraph 6): ***UK only clarification***: Eligible subjects can continue to receive mepolizumab under this LAP until ***June 2018 unless*** mepolizumab is commercially licensed for the treatment of EGPA in the relevant country ***prior to this date*** or until the Sponsor discontinues development in EGPA or until the subject meets any of the withdrawal/stopping criteria. Appendix 3 – Acceptable Birth Control: ***UK only clarification: True*** abstinence from penile-vaginal intercourse ***when this is in line with the preferred and usual lifestyle of the subject.***

12.6.2 Protocol Amendment 02

This amendment applies to sites in the UK only.

List of protocol changes:

Text which has been added to the protocol is highlighted in ***bold, italic*** typeface. Text which has been deleted from the protocol is indicated by ~~strike-through~~ format.

Change	Section, Text affected, and Rationale
1.	Section 1: Protocol Synopsis for Study MEA115921, Overall Design, paragraph 6. Section 4.1: Overall Design, paragraph 6: ***Deleted:*** United Kingdom (UK) only clarification: Eligible subjects can continue to receive mepolizumab under this LAP until June 2018 ~~unless mepolizumab is commercially licensed for the treatment of EGPA in the relevant country prior to this date~~ or until the Sponsor discontinues development in EGPA or until the subject meets any of the withdrawal/stopping criteria. **Rationale:** Clarification requested by the UK regulatory authority.
2.	Section 5.3: Withdrawal/Stopping Criteria, paragraph 2, bullet 5. Section 5.4: Subject and Study Completion, paragraph 1 ***Added:*** ***UK only clarification: Eligible subjects can continue to receive mepolizumab under this LAP until June 2018.*** **Rationale:** Clarification requested by the UK regulatory authority.
3.	Appendix 5 – Country Specific Requirements: ***Added and deleted:*** ***Amendments*** 01 ***and 02*** include~~s~~ a country-specific local amendment generated for the United Kingdom (UK). ***UK only clarification:*** Eligible subjects can continue to receive mepolizumab under this LAP until ***June 2018*** ~~unless mepolizumab is commercially licensed for the treatment of EGPA in the relevant country prior to this date~~ or until the Sponsor discontinues development in EGPA or until the subject meets any of the withdrawal/stopping criteria.

Change	Section, Text affected, and Rationale
	Section 5.3: Withdrawal/Stopping Criteria, paragraph 2, bullet 5 and Section 5.4: Subject and Study Completion ***Added:*** ***<u>UK only clarification</u>: Eligible subjects can continue to receive mepolizumab under this LAP until June 2018.*** **Rationale:** Clarification requested by the UK regulatory authority.

12.6.3 Protocol Amendment 03

This amendment applies to all countries.

List of protocol changes:

Text which has been added to the protocol is highlighted in ***bold, italic*** typeface. Text which has been deleted from the protocol is indicated by ~~strike-through~~ format.

Change	Section, Text affected, and Rationale
1.	**TITLE PAGE:** Authors ***Deleted/Added:*** PPD **Rationale**: Change in team personnel.
2.	**MEDICAL MONITOR/SPONSOR INFORMATION PAGE** ***Deleted:*** ~~Secondary Medical Monitor:~~ PPD ~~BSc MBChB FRCA PhD~~ **Rationale**: Dr PPD has left GSK.
3.	Section 5.2: Exclusion Criteria, Exclusion #6: Other Biological Therapy, Section 6.5.1 Permitted Medications and Non-Drug Therapies and Section 6.5.2: Prohibited Medications and Non-Drug Therapies ***Added:*** Section 5.2: Exclusion Criteria, Exclusion #6 5. Subject is receiving treatment with another biological therapy such as a monoclonal antibody therapy or IV immunoglobulin therapy ***without prior agreement from the GSK Medical Monitor.*** Section 6.5.1 Permitted Medications and Non-Drug Therapies ***Concomitant therapy with another biological therapy (e.g., monoclonal antibodies or IV immunoglobulin therapy) should be discussed with the GSK Medical Monitor prior to beginning therapy. If allowed, therapy***

Change	Section, Text affected, and Rationale
	should not be administered at the same time as the mepolizumab injection(s) and physicians should take measures to separate administration of another biological therapy as long as possible from administration of mepolizumab. ***Deleted:*** Section 6.5.2: Prohibited Medications and Non-Drug Therapies ~~Section 6.5.2 Prohibited Medications and Non-Drug Therapies~~ ~~• Concomitant administration of other biological therapies such as monoclonal antibodies or IV immunoglobulin therapy.~~ **Rationale:** It is recognised that there may be occasions when physicians may want to administer another biological therapy for a condition other than EGPA while a patient is being treated with mepolizumab. The GSK Medical Monitor will need to assess each drug's safety profile and any potential safety concern with the combination and thus as a precaution, use of another biologic therapy in addition to mepolizumab will require approval from the GSK Medical Monitor. In addition, the treating physician will be asked to take measures to separate administration of another biological therapy as long as possible from administration of mepolizumab.

12.6.4 Protocol Amendment 04

Amendment changes 1 and 2 apply to all countries. Amendment change 3 and 4 apply to sites in the UK only.

List of protocol changes:

Text which has been added to the protocol is highlighted in ***bold, italic*** typeface.

<table>
<tr><th>Change</th><th>Section, Text affected, and Rationale</th></tr>
<tr><td>1.</td><td>Section 9 Statistical Considerations and Data Analyses

Added:

9.1 Interim Analysis

When required, an interim analysis will be performed in order to provide open-label safety data to inform the risk-benefit assessment of mepolizumab in EGPA.</td></tr>
<tr><td>2.</td><td>MEDICAL MONITOR/SPONSOR INFORMATION PAGE

<table>
<tr><th>Role</th><th>Name</th><th>Day Time Phone Number and email address</th><th>After-hours Phone/Cell/ Pager Number</th><th>Fax Number</th><th>Site Address</th></tr>
<tr><td>Primary Medical Monitor</td><td>PPD</td><td></td><td></td><td>n/a</td><td>GSK Upper Providence, PA, USA</td></tr>
<tr><td>Secondary Medical Monitor</td><td></td><td></td><td></td><td>n/a</td><td>GSK Research Triangle Park, NC, USA</td></tr>
<tr><td>SAE contact information</td><td>Medical monitor as above</td><td></td><td></td><td></td><td></td></tr>
</table>
</td></tr>
<tr><td>3.</td><td>Section 1: Protocol Synopsis for Study MEA115921, Overall Design,</td></tr>
</table>

Change	Section, Text affected, and Rationale
	paragraph 6. Section 4.1: Overall Design, paragraph 6. ***Added:*** ***<u>UK only Clarification</u>:*** Eligible subjects can continue to receive mepolizumab under this LAP until June ***2021*** or until the Sponsor discontinues development in EGPA or until the subject meets any of the withdrawal/stopping criteria. **Rationale:** Clarification requested by the UK regulatory authority.
4.	Section 5.3: Withdrawal/Stopping Criteria, paragraph 2, bullet 5. Section 5.4: Subject and Study Completion, paragraph 1 ***Added:*** ***<u>UK only clarification</u>:*** Eligible subjects can continue to receive mepolizumab under this LAP until June ***2021***. **Rationale:** Clarification requested by the UK regulatory authority.

12.7.5. Protocol Amendment 05

Amendment changes 1 and 2 apply to all countries. Amendment change 3, 4 and 5 apply to sites in the UK only.

List of protocol changes:

TEXT WHICH HAS BEEN ADDED TO THE PROTOCOL IS HIGHLIGHTED IN *BOLD, ITALIC* TYPEFACE

<table>
<tr><th>Change</th><th>Section, Text affected, and Rationale</th></tr>
<tr><td>1.</td><td>MEDICAL MONITOR/SPONSOR INFORMATION PAGE
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<tr><th>Role</th><th>Name</th><th>Day Time Phone Number and email address</th><th>After-hours Phone/Cell/ Pager Number</th><th>Fax Number</th><th>Site Address</th></tr>
<tr><td>Primary Medical Monitor</td><td>PPD</td><td></td><td></td><td>n/a</td><td>GSK 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom</td></tr>
<tr><td>Secondaty Medical Monitor</td><td></td><td></td><td></td><td>n/a</td><td>GSK Upper Providence, PA, USA</td></tr>
<tr><td>SAE contact information</td><td>Medical monitor as above</td><td></td><td></td><td></td><td></td></tr>
</table></td></tr>
</table>

Change	Section, Text affected, and Rationale			
	Clinical Investigation Lead - CIL	PPD	***n/a***	***GSK 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom***
	Operations & Science Lead-OSL		***n/a***	***GSK Homebased Spain***
	Data Manager Lead		***n/a***	***TCS Maharashtra, India***
2.	Section 1: Protocol Synopsis for Study MEA115921, Overall Design, paragraph 6. Section 4.1: Overall Design, paragraph 6. ***Added:*** ***<u>UK only Clarification</u>:*** Eligible subjects can continue to receive mepolizumab under this LAP until ***July 2022*** or until the Sponsor discontinues development in EGPA or until the subject meets any of the withdrawal/stopping criteria. **Rationale:** Clarification requested by the UK regulatory authority.			
3.	Section 5.3: Withdrawal/Stopping Criteria, paragraph 2, bullet 5. Section 5.4: Subject and Study Completion, paragraph 1 ***Added:*** ***<u>UK only clarification</u>:*** Eligible subjects can continue to receive mepolizumab under this LAP until ***July 2022***. **Rationale:** Clarification requested by the UK regulatory authority.			
4.	**Appendix 5 – Country Specific Requirements**			

Change	Section, Text affected, and Rationale
	Added: ***<u>UK only clarification</u>: Eligible subjects can continue to receive mepolizumab under this LAP until July 2022.***