TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A multi-centre, open-label, single arm, 32-week treatment study in subjects with severe eosinophilic asthma not optimally controlled with current omalizumab treatment who are switched from omalizumab to mepolizumab 100mg subcutaneous (study number 204471-the OSMO study)

Compound Number: SB-240563

Development Phase: IIIB/IV

Effective Date: 23-MAR-2016

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Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2015N243304_00	2015-OCT-19	Original
2015N243304_01	2016-MAR-23	Amendment No. 1

This protocol amendment was created to make the following changes:

Secondary Medical Monitor details updated to reflect changes in personnel.

IND Number added.

Section 1 and Section 3 Objective(s)/Endpoints: The wording of the primary objective was revised to reflect the pragmatic approach of the study. "To determine whether there is an improvement in asthma control when directly switched to mepolizumab, in subjects with a severe eosinophilic asthma phenotype not optimally controlled on omalizumab" changed to: "To describe in a pragmatic setting whether there is an improvement in asthma control ,from the beginning to the end of the study, when directly switched from omalizumab to mepolizumab, in subjects with a severe eosinophilic asthma phenotype not optimally controlled on omalizumab.

Section 4.6.1 Table 3: Risk assessment. "Subjects are to be monitored post-injection for one hour" was changed to "Subjects are to be monitored post-injection for one hour for the first 3 injections, then per institutional guidelines".

Section 5.1, Inclusion criterion 6, was updated to include long-acting anticholinergic (tiotropium bromide).

Section 5.3, Required Criteria to Start Treatment. No. 2, "run-in" was added for consistency.

Section 5.5.3, Liver Chemistry Stopping Criteria "Appendix 2" was corrected to "Appendix 5" as this was a typographical error.

Section 5.5.4, QTc Stopping Criteria "change from baseline (Visit 2)", was replaced with "change from screening (Visit 1)". In addition, "Baseline (Visit 2)" was changed to "Screening (Visit 1)" as this was a typographical error.

Section 6.1, Investigational Product and Other Study Treatment. Ventolin Diskus for Sweden was added to reflect its use as a rescue medication in Sweden. "MDI", was replaced by "rescue inhaler"

Section 7, Time and Event Table was updated. The "x", in Dispense paper diary/worksheet row for The Exit Visit/Early withdrawal Visit column, was removed to correct a typographical error. In addition, in the table footnote the assay for Hepatitis C was updated.

Section 7.3.2.3.1, Pre and post bronchodilator FEV1, "long-acting anticholinergic (LAMA)" was added.

Section 7.4.7, Clinical Safety Laboratory Assessments Table 5 footnote, "Appendix 2", was changed to "Appendix 5" as this was typographical error.

Section 7.5, Biomarker(s)/Pharmacodynamic Markers, a sentence referring to the blinding of eosinophil counts was removed.

Section 12.7 Appendix 7 Sub-section 12.7.2 last bullet point, Appendix 2 was replaced by Appendix 5 to correct a typographical error.

Typographical errors have been corrected throughout the document.

SPONSOR SIGNATORY:

PPD

23rd March 2016

Steve Pascoe, MD
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Date

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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): EudraCT no.2015-003697-32, IND no.006971

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 204471

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

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY 204471

Rationale

Severe asthma is associated with substantial morbidity and mortality and a large fraction of the health care cost among patients with asthma. Eosinophilic airways are associated with high risk of asthma exacerbations. Mepolizumab is an anti-interleukin-5 (IL-5) monoclonal antibody that neutralizes IL-5 and reduces eosinophil counts in both sputum and blood. Clinical trials have shown that mepolizumab reduces asthma symptoms, exacerbations, improves quality of life and is a promising intervention to manage patients with severe eosinophilic asthma.

Omalizumab an anti-immunoglobulin E (IgE) monoclonal antibody (mAb) is effective in the treatment of moderate to severe allergic asthma. However there are some patients who continue to have asthma that is not optimally controlled with omalizumab treatment.

Allergic and eosinophilic severe asthma are recognized as two distinctive phenotypes with a degree of overlap (~30%), but with differences in their associations with inflammatory biomarkers. Mepolizumab has been shown to be effective in subjects with both atopic and non-atopic asthma.

The aim of this study is to investigate whether subjects not optimally controlled on their current omalizumab treatment, who are eligible for therapy with mepolizumab can be effectively and safely switched to treatment with mepolizumab to improve asthma control. As this is a single arm study, comparisons will be made back to baseline.

The study will provide data on the efficacy, safety, immunogenicity, and tolerability of mepolizumab when switched directly from omalizumab without any wash-out. In clinical practice, mepolizumab would likely be started 2-4 weeks after the last dose of omalizumab. The learnings from this study may help guide physicians when substituting one biologic with another for the treatment of patients with severe eosinophilic asthma.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
To describe in a pragmatic setting whether there is an improvement in asthma control, from the beginning to the end of the study, when directly switched from omalizumab to mepolizumab in subjects with a severe eosinophilic asthma phenotype not optimally controlled on omalizumab	• Mean change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at Week 32
Secondary	
To determine whether there is an	• Mean change from baseline in St.

Objectives	Endpoints
improvement in Health related Quality of Life (HR-QoL) when directly switched to mepolizumab, in subjects with a severe eosinophilic asthma phenotype not optimally controlled on omalizumab	George's Respiratory Questionnaire (SGRQ) score at Week 32
To determine the frequency of asthma exacerbations, when directly switched to mepolizumab, in subjects with a severe eosinophilic asthma phenotype not optimally controlled on omalizumab.	• Frequency of clinically significant asthma exacerbations over 32 week treatment
To evaluate the pharmacodynamic effects when directly switched to mepolizumab, in subjects with a severe eosinophilic asthma phenotype not optimally controlled on omalizumab.	• Ratio to baseline in blood eosinophils at Week 32

Overall Design

The study will be a multi-centre, open-label single arm trial. Patients with severe eosinophilic asthma who are receiving omalizumab, but are not optimally controlled will be eligible to participate and will be identified through the ACQ-5 with a screening (Visit 1) and baseline (Visit 2) score of ≥1.5 and a history of ≥2 exacerbations in the past 12 months. For those subjects receiving omalizumab for ≥ 8 months, at least 1 exacerbation must be while on omalizumab treatment.

Subjects meeting all the inclusion/exclusion criteria at screening Visit 1, will enter a run-in period for a minimum of one week and a up to 4 weeks.

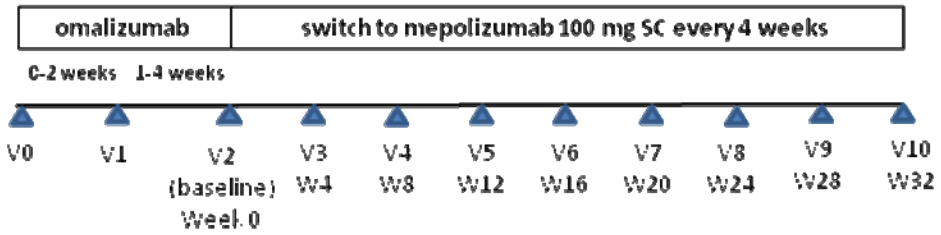
Subjects will remain on their current maintenance therapy including omalizumab throughout the run-in period. At Visit 2 subjects will discontinue their omalizumab treatment and be switched to mepolizumab 100 mg subcutaneous (SC) every 4 weeks. The treatment period is 32 weeks, including an Exit Visit/Early Withdrawal Visit, 4 weeks following the subject's last dose of mepolizumab. Except for omalizumab, subjects will remain on their current maintenance therapy throughout the treatment period.

Efficacy and safety assessments include blood tests, physical exam, ECGs, vital signs, pulmonary function tests (PFTs) and questionnaires (including ACQ-5, SGRQ, Treatment satisfaction questionnaire and patient and physician rated response to therapy).

An optional Exit interview will be conducted during the Exit Visit/Early Withdrawal Visit in a subset of participating sites and in a subset of patients who consent to participate.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition. At the end of the study, subjects may be prescribed appropriate alternative asthma therapy if needed and as determined by the study Investigator.

The study design is shown in the figure below



Treatment Arms and Duration

Eligible patients will receive mepolizumab 100 mg SC every 4 weeks for 28 weeks and will be requested to participate in the study for a maximum of 38 weeks inclusive of the Exit Visit.

Approximately 155 subjects will be screened to achieve 120 treated with mepolizumab. Assuming a 15% withdrawal rate, this will result in approximately 100 evaluable subjects completing 32 weeks of mepolizumab treatment.

Sample Size and Analysis

With a sample size of 120 treated subjects, it is estimated that this study has over 90% power to detect a statistically significant improvement from baseline. Further it is estimated that a significant improvement over the 'placebo effect' of -0.55 from baseline in ACQ score will be observed at the two-sided 5% level of significance if the observed change from baseline is at least -0.74 units.

If the true change from baseline is -0.86 units, then the study has a probability of 90% of observing a change from baseline of at least -0.74 units and therefore the study has 90% power for declaring statistical significance over the 'placebo effect'

Analysis of change from baseline in ACQ score will be performed using mixed models repeated measures (MMRM) analysis, allowing for covariates of baseline ACQ score, region, baseline maintenance oral corticosteroid (OCS) therapy, exacerbations in the year prior to the study (as an ordinal variable), visit and an interaction term for visit by baseline ACQ score.

2. INTRODUCTION

Eosinophilic inflammation of the airways specifically plays a central role in the pathogenesis of asthma [Kim, 2004]. Eosinophils are not 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 patients have shown that more than half of these patients have persistent eosinophilic (>3% sputum 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) immunoglobulin G (IgG Kappa) monoclonal antibody (mAb) that binds to and inactivates IL-5. Mepolizumab has completed a phase III program and is under regulatory review for market authorization in a number of countries.

Recently completed studies in severe eosinophilic asthma have demonstrated mepolizumab to be effective in reducing asthma symptoms and exacerbations and in improving respiratory quality of life [Pavord, 2012; Ortega, 2014b; Bel, 2014].

2.1. Study Rationale

Severe asthma is associated with substantial morbidity and mortality and a large fraction of the health care cost among patients of asthma [Wenzel, 2012] . Eosinophilic airways, and high eosinohil count blood is associated with frequent asthma exacerbations (Tran, 2014). Completed clinical trials have shown that mepolizumab, neutralizes IL-5 and reduces eosinophil counts in both sputum and blood (Pavord, 2012) and is a promising intervention to manage patients with severe eosinophilic asthma.

Omalizumab an anti-immunoglobulin E (IgE) monoclonal antibody (mAb) is effective in the treatment of moderate to severe allergic asthma. [European medicines Agency EMEA, 2015] summary of product characteristics (SmPC); Xolair US prescribing information, 2014]. However there are some patients who continue to have asthma that is not optimally controlled with omalizumab treatment.

The key principal of treatment management is to achieve asthma control with a goal of improving symptoms and reducing future risk [Chung, 2014]. Due to the heterogeneous nature of asthma, no single clinical parameter completely reflects asthma control. Multiple measures are important as each may assess different domains of disease, including health related quality of life.

Allergic and eosinophilic severe asthma are recognized as two distinctive phenotypes with a degree of overlap (~30 %) but with also differences in their associations with inflammatory biomarkers [Chung, 2014]. Mepolizumab has been shown to be effective in subjects with both atopic and non-atopic asthma [Ortega, 2014a]. With the availability of mAbs with different mechanisms of action, the opportunity for personalized and specifically targeted treatment becomes possible.

The aim of the present study is to investigate whether subjects not optimally controlled on their current omalizumab treatment, who are eligible for therapy with mepolizumab can be effectively and safely switched to treatment with mepolizumab to improve asthma control. As this is a single arm study, comparisons will be made back to baseline.

The study will provide data on the efficacy, safety, immunogenicity, and tolerability of mepolizumab when switched directly from omalizumab without a wash-out period of approximately 4.5 months. In clinical practice, mepolizumab would likely be started 2-4 weeks after the last dose of omalizumab. The learnings from this study may help physicians when substituting one biologic with another for the treatment of patients with severe eosinophilic asthma.

2.2. Brief Background

Severe asthma represents approximately 5-10% of the asthma population and is associated with a greater frequency of asthma exacerbations, and a greater symptom burden [Chung, 2014; Moore, 2007]. Asthma is a heterogeneous condition characterized by airflow obstruction, bronchial hyper responsiveness and underlying inflammation. Eosinophils are major effector cells involved in the initiation and propagation of diverse inflammatory responses and are considered a central mediator of asthma pathology [Catley, 2011]. An increase in eosinophils is associated with cough, airway remodelling, worse lung function and asthma exacerbations which are, in-turn, associated with a more rapid decline in forced expiratory volume in 1 second (FEV_1)[Desai, 2012; O'Byrne, 2011].

Mepolizumab is a humanised monoclonal antibody that binds to and inactivate interleukin-5, a cytokine that recruits eosinophils from the bone marrow and promotes the persistence and activation of these cells [Sumitas, 2011; Pavord, 2012].

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

- Reduce the rate of clinically significant exacerbations by approximately 50%. [Pavord, 2012, Ortega, 2014b].
- Reduce the rate of exacerbations requiring hospitalisations and/or Emergency Department (ED) visits, with reductions ranging from 32% to 61% [Pavord, 2012, Ortega, 2014b].

- Produce statistically significant and/or clinically relevant improvements in lung function based on FEV_1, improvement in Asthma Control Questionnaire (ACQ-5), St. George's Respiratory Questionnaire (SGRQ) and clinician and subject-rated overall response to therapy [Ortega, 2014b, Bel, 2014]
- Consistently reduce blood eosinophil levels detected at Week 4 and sustained for the duration of treatment [Pavord, 2012, Ortega, 2014b, Bel, 2014].

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

3. OBJECTIVE(S) AND ENDPOINT(S)

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To describe in a pragmatic setting whether there is an improvement in asthma control, from the beginning to the end of the study, when directly switched from omalizumab to mepolizumab in subjects with a severe eosinophilic asthma phenotype not optimally controlled on omalizumab	• Mean change from baseline in ACQ-5 score at Week 32
Secondary	
To determine whether there is an improvement in Health related Quality of Life (HR-QoL) when directly switched to mepolizumab, in subjects with a severe eosinophilic asthma phenotype not optimally controlled on omalizumab	• Mean change from baseline in SGRQ score at Week 32
To determine the frequency of asthma exacerbations, when directly switched to mepolizumab, in subjects with a severe eosinophilic asthma phenotype not optimally controlled on omalizumab.	• Frequency of clinically significant asthma exacerbations over 32 week treatment
To evaluate the pharmacodynamic effects when directly switched to mepolizumab, in subjects with a severe eosinophilic asthma phenotype not optimally controlled on omalizumab.	• Ratio to baseline in blood eosinophils at Week 32
Others	
To determine the response to asthma clinical parameters when directly switched to mepolizumab in subjects	• Percentage of subjects achieving a 0.5-point or greater reduction from

Objectives	Endpoints
with a severe eosinophilic asthma phenotype not optimally controlled on omalizumab.	baseline in ACQ-5 score at Week 32 • Percentage of subjects achieving a 4-point or greater reduction from baseline in SGRQ score at Week 32 • Mean change from baseline in pre- and post bronchodilator FEV_1 at Week 32 • Frequency of exacerbations requiring ED visit/hospitalization during the treatment period • Subject/Clinician rated response to therapy • Mean change from baseline in treatment satisfaction questionnaire
Exploratory	
To determine the effect on inflammatory biomarkers, when directly switched to mepolizumab, in subjects with a severe eosinophilic asthma phenotype not optimally controlled on omalizumab To characterize patient treatment benefit of mepolizumab	• Change from baseline in some inflammatory biomarkers expression at week 32. • Subject Exit Interviews
Safety	
To determine the safety, immunogenicity and tolerability of mepolizumab when directly switched to mepolizumab, in subjects with a severe eosinophilic asthma phenotype not optimally controlled on omalizumab.	• Incidence and frequency of Adverse/Serious Adverse Events (including systemic and injection site reactions) • Clinically significant change in electrocardiogram (ECGs) • Clinically significant change in vital signs • Incidence of immunogenicity

4. STUDY DESIGN

4.1. Overall Design

The study will be a multi-centre, open-label single arm trial. Patients with severe eosinophilic asthma who are receiving omalizumab, but are not optimally controlled will be eligible to participate and will be identified through the ACQ-5 with a screening (Visit 1) and baseline (Visit 2) score of ≥1.5 and a history of ≥2 exacerbations in the past 12 months. For those subjects receiving omalizumab for ≥ 8 months, at least 1 exacerbation must be while on omalizumab treatment.

Subjects meeting all the inclusion/exclusion criteria at screening Visit 1, will enter a run-in period for a minimum of one week and a up to 4 weeks to assess subjects' eligibility and compliance with study-related procedures.

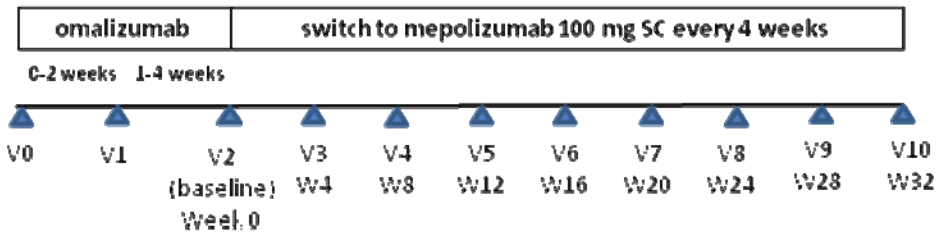
Subjects will remain on their current maintenance therapy throughout the run-in period, including omalizumab. At Visit 2 subjects will discontinue omalizumab treatment and be switched to mepolizumab 100 mg SC every 4 weeks. Except for omalizumab, subjects will remain on their current maintenance therapy throughout the open-label treatment period.

Every subject, including those who withdraw early from the study, will be asked to return for an Exit Visit approximately 4 weeks after their last dose of study treatment.

An Exit interview will be conducted during the Exit Visit or early withdrawal Visit in a subset of participating sites and in a subset of patient who consent to participate.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition. At the end of the study, subjects may be prescribed appropriate alternative asthma therapy if needed and as determined by the study Investigator.

Figure 1 Study Design



4.2. Treatment Arms and Duration

Eligible patients will receive mepolizumab 100 mg SC every 4 weeks for 28 weeks and will be requested to participate in the study for a maximum of 38 weeks (Visit 0 to the Exit Visit (Visit 10), inclusive as described in Table 2.

Table 2 Study phases

Phase	Phase Title	Duration	Description
1	Pre-screening	0 to 2 weeks	At the Pre-screening Visit, details about the study and procedures will be explained through the informed consent process. The Pre-screening Visit (Visit 0) can occur on the same day as the Screening Visit (Visit 1) but must be completed prior to initiating any Visit 1 procedures.
2	Screening / Run-in	1 to 4 weeks	Subjects who meet all the eligibility criteria at Screening, will enter the run-in period for a minimum of 1 week and a maximum of 4 weeks in order to continue to assess the subject's eligibility for the study. Subjects who experience an asthma exacerbation during the run-in period should receive treatment for their exacerbation and remain in the run-in period until the investigator considers that the subject has returned to their baseline asthma status for at least one week. Those subjects that are not eligible to continue in the study at the end of the 4 week run-in period will be deemed run-in failures (see Section 5.4).
3	Treatment	32 weeks	At Visit 2 (Week 0) those subjects who successfully complete the run-in period as well as meet the other pre-defined eligibility and continuation to treatment criteria (see Section 5.3) will receive mepolizumab 100 mg SC every 4 weeks for a total of 8 doses. The treatment period will conclude with subjects completing Exit Visit (Visit 10) assessments approximately 4 weeks after the subject was administered their last dose of study treatment at Visit 9.

4.2.1. Exit Interview

A Single optional Exit Interview to characterize the patient experience of change in asthma will be conducted at the Exit Visit (Visit 10) or Early Withdrawal Visit in a sub-set of sites and in a subset of patients who consent to participate (See Section 7.3.2.2).

4.3. Type and Number of Subjects

Approximately 155 subjects will be screened to achieve 120 treated with mepolizumab. Assuming a 15% withdrawal rate, this will result in approximately 100 evaluable subjects completing 32 weeks of mepolizumab treatment.

4.4. Design Justification

The study is designed to investigate whether subjects not optimally controlled on current omalizumab can be safely and effectively switched to treatment with mepolizumab. Subjects enrolled into the study will already be receiving omalizumab and therefore have previously been identified as suitable for omalizumab treatment according to the product label, and any additional criteria applicable in the participating countries. The dose of omalizumab should previously have been determined by the subject's weight and level of IgE.

Subjects with severe asthma who are not optimally controlled on omalizumab will be identified through the ACQ-5 with a score of ≥1.5, at both Visits 1 and 2 respectively and a history of ≥2 exacerbations in the past 12 months. For those subjects receiving omalizumab for ≥ 8 months, at least 1 exacerbation must be while on omalizumab treatment.

The treatment duration of 32 weeks (inclusive of Exit Visit) will enable an adequate time to assess the impact of mepolizumab on ACQ-5, lung function and SGRQ after wash-out of omalizumab, usually 5 half-lives or 4.5 months. In addition, safety, immunogenicity and tolerability endpoints will be assessed during the study.

An open-label single arm design with a direct switch, i.e. the substitution of one biologic with another biologic with no wash-out period, is expected to reflect clinical practice.

4.5. Dose Justification

The dose selection is based on previous experience from the mepolizumab Phase III program, including two Phase III placebo-controlled studies MEA115588 [Ortega, 2014b] and MEA115575 [Bel, 2014] that demonstrated the safety and efficacy of mepolizumab at a dose of 100 mg SC every 4 weeks.

4.6. Benefit: Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with mepolizumab (SB-240563) can be found in the Investigator's Brochure. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. 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. To date, in the phase II and III program in severe asthma there have been no reports of severe life-threatening anaphylaxis related to mepolizumab.
- 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.
- In previous studies patients on omalizumab and other monoclonal antibodies have been excluded to minimise the risk of confounding factors. Cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of mepolizumab; furthermore mepolizumab target is specific (cytokine IL-5). The potential for drug-drug interactions with mepolizumab is therefore considered low.

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

Table 3 Risk Assessment for mepolizumab

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 National Institute of Allergy and Infectious Diseases (NIAID)/ Food Allergy and Anaphylaxis Network (FAAN) 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (see Appendix 7) Subjects are to be monitored post-injection for one hour for the first 3 injections, then per institutional guidelines.
Risk of Immunogenicity	Biopharmaceutical products may elicit anti-drug antibody (ADA) and neutralizing antibody (NaB), which has 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 Immunogenicity' and a summary of immunogenicity findings in the 'Other Potentially Clinically Relevant Information for the	Blood samples are collected in clinical studies for detection of both ADA and NaB See previous risk for mitigation strategy related to clinical safety risks

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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 immuno-histochemistry tissue binding study suggesting a low likelihood of non-pharmacologic effects on cardiovascular (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 System SOC).	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 case report form (CRFs) to collect relevant data on CV as per GSK standard practice.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential risk for increase in infections- a theoretical concern with biologics	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 (cluster of differentiation)CD4/CD8 subtypes or T helper cell (Th1/Th2) cytokine patterns, B-cells, natural killer (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 titled 'Summary of Data and Guidance for the Investigator'.	Daily monitoring of SAEs by the 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 for increase in malignancies- theoretical concern with biologics.	Blockage of IL-5 is not associated with generalized immune-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	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
	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.	
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 '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.	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.
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)

4.6.2. Benefit Assessment

Data from earlier studies [Haldar 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, 2014b].

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

- Potential benefit of receiving a drug which may have clinical utility in patients with uncontrolled asthma symptoms
- Medical evaluations/assessments associated with study procedures

4.6.3. Overall Benefit: Risk Conclusion

Current data from mepolizumab clinical development have demonstrated its clinical utility in the treatment of eosinophilic asthma. Data from the Phase III asthma programme with mepolizumab demonstrated, 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 has been similar to placebo 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 further investigation in severe asthma.

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with mepolizumab are justified by the anticipated benefits that may be afforded to a subject with severe asthma. Therefore, the Sponsor considers that the efficacy, safety and tolerability of mepolizumab is justified in study 204471 with a positive benefit/risk ratio.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

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

Deviations from inclusion and exclusion criteria (see Inclusion Criteria Section 5.1, Exclusion Criteria Section 5.2 and continuation to treatment Section 5.3) are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

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

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

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Asthma: A physician diagnosis of asthma for ≥2 years that meets the National Heart and Lung Institute guidelines [National heart, lung and blood institute (NIH), 2007] or GINA guidelines (GINA, 2015]
3. FEV1: Persistent airflow obstruction as indicated by: For subjects ≥18 years of age at Visit 1, a pre-bronchodilator FEV_1 <80% predicted [Quanjer, 2012] recorded at Visit 1 For subjects 12-17 years of age at Visit 1, a pre-bronchodilator FEV_1 <90% predicted [Quanjer, 2012] recorded at Visit 1 OR FEV_1/FVC ratio <0.8 recorded at Visit 1
4. **Eosinophilic asthma**: Airway inflammation characterized as eosinophilic in nature as indicated by one of the following: a. A peripheral blood eosinophil count of ≥300 cells/μL that is related to asthma demonstrated in the past 12 months prior to Visit 1
OR b. A peripheral blood eosinophil count of ≥150 cells/μL at Visit 1 that is related to asthma.
5. **Inhaled Corticosteroid**: A well-documented requirement for regular treatment with high-dose inhaled corticosteroid (ICS) in the 12 months prior to Visit 1 with or without maintenance oral corticosteroids (OCS). For 18 years of age and older: ICS dose must be ≥880 mcg/day fluticasone propionate (FP) (ex-actuator) or equivalent daily For ICS/LABA combination preparations, the highest approved maintenance dose in the local country will meet this ICS criterion.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
For subjects 12-17 years of age at Visit 1: ICS dose must be ≥440 mcg/day fluticasone propionate (FP) (ex-actuator) or equivalent daily For ICS/LABA combination preparations, the highest approved maintenance dose in the local country will meet this ICS criterion. 6. **Controller Medication**: Current treatment with an additional controller medication, besides ICS, for at least 3 months or a documented failure in the past 12 months of an additional controller medication for at least 3 successive months. [e.g., long-acting beta-2-agonist (LABA), leukotriene receptor antagonist (LTRA), long-acting anticholinergic (tiotropium bromide), or theophylline.] 7. **Asthma symptoms not optimally controlled**: An ACQ-5 score of ≥1.5 recorded at Visit 1. 8. **Omalizumab Treatment**: Receiving omalizumab, based on weight and IgE levels, for at least the 4 months prior to Visit 1. 9. **Exacerbation history**: Previously confirmed history of two or more exacerbations requiring treatment with systemic corticosteroids (intramuscular, intravenous, or oral) in the 12 months prior to Visit 1 despite the use of high-dose ICS. For subjects receiving omalizumab for ≥8 months, at least one exacerbation must have occurred while on omalizumab treatment. For subjects receiving maintenance oral corticosteroids, the corticosteroid treatment for the exacerbations must have been a two-fold dose increase or greater.

SEX
10. Male or eligible Female **Females**: a. Non-reproductive potential defined as: • Pre-menopausal females with one of the following: • Documented tubal ligation • Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion • Hysterectomy • Documented Bilateral Oophorectomy • Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone

SEX
replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods 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. b. Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 3) from 30 days prior to the first dose of study medication and until at least five terminal half-lives OR until any continuing pharmacologic effect has ended, whichever is longer, after the last dose of study medication and completion of the Exit visit/Early Withdrawal visit. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

INFORMED CONSENT
11. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. **Concurrent Respiratory Disease**: Presence of a known pre-existing, clinically important lung condition other than asthma. This includes current infection, bronchiectasis, pulmonary fibrosis, bronchopulmonary aspergillosis, or diagnoses of emphysema or chronic bronchitis (chronic obstructive pulmonary disease other than asthma) or a history of lung cancer. 2. **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). **3. Liver disease:** Subjects must not be enrolled in the study if : At screening (Visit 1) ALT >2xULN; 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,

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)

or persistent jaundice, or cirrhosis

4. **Hepatitis status:** Diagnosis of chronic hepatitis B, as evidenced by positive Hepatitis B surface antigen (HBsAg) at Visit 1. Chronic stable hepatitis C (e.g.,positive hepatitis C antibody test result at screening (Visit 1) or within 3 months prior to first dose of study treatment) are acceptable if subject otherwise meets entry criteria.

5. **Cardiovascular:** Subjects who have severe or clinically significant cardiovascular disease uncontrolled with standard treatment. Including but not limited to:

a. known ejection fraction of <30% **OR**

b. severe heart failure meeting New York Heart Association Class IV (see Appendix 4) classification **OR**

c. hospitalised in the 12 months prior to Visit 1 for severe heart failure meeting New York Heart Association Class III (see Appendix 4)

OR

d. angina diagnosed less than 3 months prior to Visit 1 or at Visit 1

6. **Subjects w**ith QTc > 450 msec or QTc > 480 msec in subjects with Bundle Branch Block at screening Visit 1

NOTES:

- The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read.
- The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial.
- For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).

7. **Other Concurrent Medical Conditions:** Subjects who have known, pre-existing, clinically significant endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, haematological or any other system abnormalities that are uncontrolled with standard treatment.

8. **Eosinophilic Diseases:** Subjects with other conditions that could lead to elevated eosinophils such as Hypereosinophilic Syndromes, including Churg-Strauss Syndrome (Eosinophilic Granulomatosis with Polyangiitis; EGPA), or Eosinophilic Esophagitis.

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
Subjects with a known, pre-existing parasitic infestation within 6 months prior to Visit 1 are also to be excluded. 9. **Immunodeficiency:** A known immunodeficiency (e.g., human immunodeficiency virus – HIV), other than that explained by the use of corticosteroids taken as therapy for asthma.
CONCOMITANT MEDICATIONS
10. **Other Monoclonal Antibodies**: Subjects who have received any monoclonal antibody (other than omalizumab) to treat inflammatory disease within 5 half-lives of Visit 1.

RELEVANT HABITS
11. **Smoking history**: Current smokers or former smokers with a smoking history of ≥10 pack years (number of pack years = (number of cigarettes per day / 20) x number of years smoked). A former smoker is defined as a subject who quit smoking at least 6 months prior to Screening Visit 1. 12. **Alcohol/Substance Abuse**: A history (or suspected history) of alcohol misuse or substance abuse within 2 years prior to Visit 1. 13. **Adherence:** Subjects who have known evidence of lack of adherence to controller medications and/or ability to follow physician's recommendations.

CONTRAINDICATIONS
14. **Hypersensitivity:** Subjects with allergy/intolerance to a monoclonal antibody or biologic. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
15. Investigator opinion: Omalizumab treatment has provided significant clinical benefit despite experiencing 2 exacerbations in the past 12 months, and potential benefit from a switch to mepolizumab would not outweigh the potential harm after omalizumab withdrawal for the subject. 16. **Previous participation:** Previously participated in any study with mepolizumab and received investigational product (including placebo).

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
17. **Investigational Medications**: Subjects who have received treatment with an investigational drug within the past 30 days or five terminal phase half-lives of the drug whichever is longer, prior to Screening (V1) (this also includes investigational formulations of marketed products). 18. **Pregnancy:** Subjects who are pregnant or breastfeeding. Patients should not be enrolled if they plan to become pregnant during the time of study participation.

5.3. Continuation to Treatment Criteria

At Visit 2, those subjects who fulfil the inclusion/exclusion criteria and who meet the continuation to treatment criteria will commence the study treatment phase until the target of approximately 120 treated subjects is reached.

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

REQUIRED CRITERIA TO START TREATMENT
1. **Not optimally controlled:** An ACQ-5 score of ≥1.5 recorded at Visit 2 2. **No Asthma Exacerbation**: Subjects with an ongoing asthma exacerbation at Baseline (Visit 2) should have their Visit 2 delayed until the investigator considers the subject has returned to their baseline asthma status for at least one week. If the 4-week screening/run-in period has elapsed and subjects have not returned to their baseline asthma status, then they should be considered a run-in failure. An exacerbation is defined as worsening of asthma requiring the use of systemic corticosteroids and/or emergency department visit, or hospitalisation (see Section 7.3.2.4 Clinically Significant Asthma Exacerbation). 3. **Maintenance Asthma Therapy**: No changes in the dose or regimen of ICS and/or additional controller medication (except for treatment of an exacerbation) during the run-in period. 4. **Last dose of omalizumab**: For subjects receiving omalizumab every 4 weeks, their last dose must be 3 to 5 weeks prior to Visit 2. For subjects receiving omalizumab every 2 weeks, their last dose must be between 1 to 3 weeks prior to Visit 2.

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

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

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

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

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

For the purposes of this study, screening failures and run-in failures will be defined as follows:

- **Screening failures:** those subjects that complete at least one Visit 1 (Screening) procedure but do not enter the run-in period.
- **Run-in failures:** those subjects that enter the run-in period but do not subsequently receive study treatment.

Subjects who are pre-screen, screen and run-in failure will be recorded in the eCRF.

5.5. Withdrawal/Stopping Criteria

5.5.1. Withdrawal from Study Treatment

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

Subjects who have permanently withdrawn mepolizumab study treatment are not required to withdraw from the study. Every effort should be made to complete all remaining protocol specified visits even if they have discontinued mepolizumab treatment provided there are no safety concerns with doing so.

5.5.2. Withdrawal from the Study

A subject may withdraw from study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

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

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

- Laboratory parameters: Clinically important changes in laboratory parameters identified
- ECG: Clinically significant abnormality identified during the study that meet the QTc stopping criteria described in Section 5.5.4.
- Liver Chemistry: Meets any of the Liver chemistry stopping criteria (See Section 5.5.3 and Appendix 5)
- Pregnancy: Positive pregnancy test (see Appendix 3)

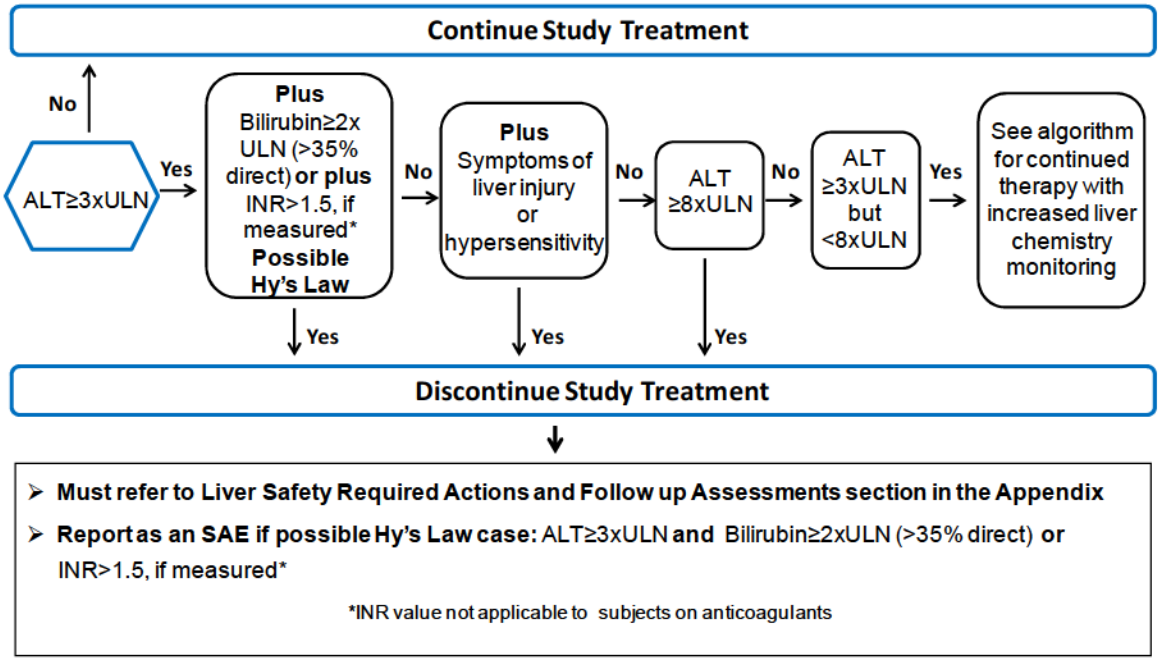
The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

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

5.5.3. Liver Chemistry Stopping Criteria

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

Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver chemistry stopping criteria and required follow up assessments are defined in Appendix 5.

5.5.3.1. Study Treatment Restart or Rechallenge

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

5.5.4. QTc Stopping Criteria

- The *same* QT correction formula *must* be used for *each individual subject* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled.
- For example, if a subject is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual subject as well.
- Once the QT correction formula has been chosen for a subject's eligibility, the *same formula* must continue to be used for that subject *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minutes) recording period. For example if a routine ECG demonstrates a prolonged QT, obtain 2 or more ECGs over a brief period and then use the averaged QTc values of the 3 ECGs to determine whether patient should be withdrawn from the study.

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

- QTc > 500 msec OR Uncorrected QT > 600 msec
- [Change from screening (Visit 1) of QTc > 60 msec]

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

Screening (Visit 1) QTc with Bundle Branch Block	Discontinuation QTc with Bundle Branch Block
< 450 msec	> 500 msec
450 – 480 msec	≥ 530 msec

5.6. Subject and Study Completion

A subject will be considered to have completed study treatment if he/she receives study treatment at Visit 9 (Week 28) and completes the Exit Visit (Week 32). 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 last subject's last visit.

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The study treatment and investigational product is mepolizumab (SB-240563), a fully humanised IgG antibody (IgG1, kappa) with human heavy and light chain frameworks. Mepolizumab will be provided as a lyophilised cake in sterile vials for individual use. The vial will be reconstituted with Sterile Water for Injection, just prior to use. Further information on the preparation and administration of study treatment can be found in Section 6.5.

Trade label albuterol/salbutamol metered dose inhalers (MDIs) will be provided locally by each country (except for US sites where GSK Global Supply Organisation will supply the rescue medication) including Sweden where Ventolin Diskus will be used. Subjects will be dispensed a rescue inhaler at the time of screening to be used to primarily treat asthma symptoms on an as needed basis but also during pre and post bronchodilator spirometry assessments (see Section 7.3.2.3.1). The rescue inhaler should be replaced as needed, and collected at the Exit Visit (or Early Withdrawal Visit, as applicable).

6.2. Treatment Assignment

This is a single arm open label study. At Visit 2 (Week 0) eligible subjects who meet the continuation to treatment criteria will receive mepolizumab 100mg SC into the upper arm or thigh every 4 weeks over a period of 28 weeks.

A web based interactive system RAMOS NG will be used to dispense mepolizumab from Visit 2 to Visit 9.

6.3. Packaging and Labeling

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

6.4. 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 reconstitution of mepolizumab will be detailed in the staff manual which is available in the Study Reference Manual (SRM).
- Study treatment 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).
- The investigator or designated site staff must document the amount of investigational product administered to study subjects.
- 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.

6.5. Compliance with Study Treatment Administration

When subjects are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and reported in the eCRF. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

6.6. Treatment of Study Treatment Overdose

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

6.7. 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 most countries participating in this study.

6.8. Concomitant Medications and Non-Drug Therapies

6.8.1. Permitted Medications and Non-Drug Therapies

Throughout the study, subjects are to be maintained on their baseline standard of care asthma treatment. The only exception to this is the discontinuation of omalizumab from Visit 2 onwards.

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

All concomitant medications taken during the study will be recorded in the eCRF. In addition, all medications taken by the patient for the treatment of asthma including asthma exacerbations in the 12 months prior to Visit 1 must also be recorded in the eCRF. The minimum requirement is that the drug name and the dates of administration are recorded. However, for ICS/LABA, omalizumab and OCS, the dose and regimen (including any change in dose or regimen) must also be recorded. Continuous Positive Airway Pressure (CPAP) for the treatment of obstructive sleep apnea is permitted, if initiated prior to the Screening Visit 1.

6.8.2. Prohibited Medications and Non-Drug Therapies

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

Table 4 Medications not allowed prior to the Screening Visit and throughout the study

Medication	Washout Time Prior to Screening Visit
Investigational drugs	1 month or 5 half-lives whichever is longer
Monoclonal antibodies**	5 half-lives
Experimental anti-inflammatory drugs (non biologicals)	3 months
Immunosuppressive medications such as those listed below (not all inclusive)	
• Regular systemic (oral or parenteral) corticosteroids for the treatment of conditions other than asthma. Long-acting depot **corticoster**oids 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

**= Omalizumab is permitted during screening and run-in but must be discontinued at Visit 2.

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.

7. STUDY ASSESSMENTS AND PROCEDURES

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

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

7.1. Time and Events Table

Procedures	Pre-screen[1]	Screen Run-in	Treatment (visit window is ±7days)								Exit Visit/ Early withdrawal Visit[3]
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Week	**-6 to -4**	**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**4 weeks post last dose ±7 days**
Informed Consent [2]	x										
Subject Demography	x										
Medical History		x									
Asthma History (including triggers)	x	x									
Therapy History[4]		x									
Smoking History		x									
Cardiovascular History/Risk Factors		x									
Inclusion/Exclusion Criteria		x									
Continuation to treatment Criteria			x								
Efficacy Assessments[5]											
ACQ-5		x	x	x	x	x	x	x	x	x	x
Exacerbation review	x	x	x	x	x	x	x	x	x	x	x
Spirometry including pre- and post bronchodilator FEV_1, FVC [6]		x	x			x			x		x
Health Outcome Assessments[5]											
SGRQ			x			x			x		x

Procedures	**Pre-screen[1]**	**Screen Run-in**	**Treatment (visit window is ±7days)**								**Exit Visit/ Early withdrawal Visit[3]**
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Week	**-6 to -4**	**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**4 weeks post last dose ±7 days**
Clinician & Subject rated response to therapy					x		x		x		x
Treatment Satisfaction with Medication Questionnaire (TSQM-9)		x									x
Exit Interview[7]											x
Safety Assessments[5]											
Concomitant Medication	x	x	x	x	x	x	x	x	x	x	x
Physical Examination, including nasal exam		x									x
Vital Signs		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
Serious Adverse Events	x	x	x	x	x	x	x	x	x	x	x
Laboratory Assessments[5]											
Haematology with differential		x	x	x	x	x	x	x	x	x	x
Clinical Chemistry (incl. LFT)		x	x	x	x	x			x		x
Parasitic Screening[8]		x									
Pharmacogenetic sample[9]			←				X			→	
Pregnancy test[10]		U	U	U	U	U	U	U	U	U	U
HBsAg and hepatitis C antibody[11]		x									
Immunogenicity sample			x			x				x	x
Biomarker sample		x	x		x						x

Procedures	**Pre-screen[1]**	**Screen Run-in**	**Treatment (visit window is ±7days)**								**Exit Visit/ Early withdrawal Visit[3]**
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Week	**-6 to -4**	**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**4 weeks post last dose ±7 days**
Investigational product (Mepolizumab) and rescue medication											
Administer mepolizumab. Contact RAMOS NG to register dispensing visit.			x	x	x	x	x	x	x	x	
Albuterol/salbutamol dispensed (as needed)		x	x	x	x	x	x	x	x	x	
Collect dispensed albuterol/salbutamol			x	x	x	x	x	x	x	x	x
eCRF/ paper diary/worksheet											
Complete eCRF	x	x	x	x	x	x	x	x	x	x	x
Dispense paper diary/worksheet	x	x	x	x	x	x	x	x	x	x	
Collect/review paper diary/worksheet		x	x	x	x	x	x	x	x	x	x

1. Pre-screen Visit 0 must be completed prior to Visit 1 (Screening). It can be completed on the same day as Visit 1 or at up to 2 weeks prior to Visit 1.
2. Subjects will be assigned a subject number at the time ICF signed. The ICF must be signed before any study procedures including medication wash out period(s).
3. Exit Visit may be completed 3 to 5 weeks post last dose.
4. Therapy history to include a detailed review of prior biologics received for treatment of asthma, including omalizumab dose and regimen and prior investigational therapies e.g anti-IL5 or anti-IL13 preparations.
5. All study efficacy, safety and all patient reported questionnaires must be completed prior any study procedure.
6. Spirometry to include pre- and post bronchodilator FEV1 from V2.
7. Exit interview will be conducted only in a subset of sites and in a subset of subjects who choose to participate in the Exit interview. Subjects must be consented prior to interview
8. Parasitic screening is only required in countries with high-risk or for subjects who have visited high-risk countries in the past 6 months. Sites should use local laboratories.
9. Pharmacogenetic sample may be drawn at Visit 2 or any visit after.
10. Pregnancy test, U= urine
11. Hepatitis B Surface Antigen and Hepatitis C antibody. (if hepatitis C antibody is positive, hepatitis C will be confirmed by PCR).

7.2. Screening and Critical Baseline Assessments

7.2.1. Pre-screening Visit

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

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

7.2.2. Critical procedures performed at Screening (Visit 1)

- Medical history including smoking status, history of sinusitis, nasal polyposis, aspirin sensitivity, current treatment, duration of asthma, courses of rescue corticosteroids in the past 12 months, history of previous intubations, asthma exacerbation history in the previous 12 months, asthma triggers and smoking history
- Therapy history, including use of omalizumab or previous biologics in the past 12 months (see Section 6.8.1)
- Cardiovascular medical history/risk factors (as detailed in the eCRF and Appendix 6). This assessment must include a review of the subject responses to the cardiovascular assessment questions and height, weight, blood pressure, smoking history, medical conditions, and family history of premature cardiovascular disease.
- Asthma control questionnaire-5 (ACQ-5) (see Section 7.3.2.1.1)
- Treatment Satisfaction Questionnaire with Medication (TSQM-9) (See Section 7.3.2.1.4)
- Vital signs (see Section 7.4.5)
- Resting 12-lead ECG (see Section 7.4.6)
- Physical exam (see Section 7.4.4)
- Nasal exam to check for presence or absence of nasal polyps (if no documented historical assessment in the past 12 months)
- Pulmonary function tests (see Section 7.3.2.3)
- Laboratory tests (see Section 7.4.7). This should include:
    - Chemistry
    - Haematology with differential count
    - Hepatitis B Surface Antigen and hepatitis C antibody

  - Urine pregnancy test- for all women of child bearing potential
  - FSH will be assessed to confirm child-bearing status (if applicable)
  - Parasitic screening (only in countries with a high-risk or in subjects who have visited a high-risk country)
- Review of Inclusion/Exclusion criteria
- Review exacerbations, AEs, SAEs

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

- Asthma Control Questionnaire (ACQ-5) (see Section 7.3.2.1.1)
- St George's Respiratory Questionnaire (SGRQ) (see Section 7.3.2.1.2)
- Vital signs (see Section 7.4.5)
- Laboratory tests (see Section 7.4.7). This should include
  - Clinical Chemistry
  - Haematology with differential
  - Blood for baseline immunogenicity
  - Blood for baseline biomarkers
  - Urine pregnancy test for all females of childbearing potential
- Pulmonary function tests including pre and post-bronchodilator FEV_1 and FVC. (may be repeated at this visit, (see Section 7.3.2.3)
- Review exacerbations, concomitant medications, AEs, SAEs
- Review of continuation to treatment criteria (see Section 5.3).

7.3. Efficacy

7.3.1. Efficacy Endpoints

- Mean change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at Week 32
- Mean change from baseline in St. George's Respiratory Questionnaire (SGRQ) score at Week 32
- Frequency of clinically significant asthma exacerbations
- Ratio to baseline in blood eosinophils at Week 32

- Percentage of subjects achieving a 0.5-point or greater reduction in ACQ-5 score at Week 32
- Percentage of subjects achieving a 4-point or greater reduction in SGRQ score at Week 32
- Mean change from baseline in pre- and post-bronchodilator FEV_1 at Week 32
- Frequency of exacerbations requiring ED visit or hospitalization.
- Subject/Clinician rated response to therapy
- Mean change from baseline in treatment satisfaction questionnaire at Week 32

7.3.2. Efficacy assessments

The timings of all efficacy assessments are documented in the Time and Events Schedule (Section 7.1)

7.3.2.1. Questionnaires

It is requested that questionnaires are administered at the same time of day during each visit (as applicable). They should be presented to the subject in a consistent order at each study visit. To avoid influencing the subject's response, the subjects should not be told the results of diagnostic tests prior to completing the questionnaires and the questionnaires should be completed before any procedures are performed on the subject. All questionnaires will be completed using an electronic device at clinic. Adequate time should be allowed to complete all items on the questionnaires and the questionnaires must be reviewed by the investigator or designated study staff for completeness and, if necessary, the subject must be encouraged to complete any missing items.

Instructions for completing the questionnaires can be found in the SRM.

7.3.2.1.1. Asthma Control Questionnaire (ACQ)

The ACQ-5 is a five-item questionnaire, which has been developed as a measure of subject' asthma control that can be quickly and easily completed [Juniper 1999; Juniper, 2005]. The questions are designed to be self-completed by the subject. The five questions (concerning nocturnal awakening, waking in the morning, activity limitation, shortness of breath and wheeze) enquire about the frequency and/or severity of symptoms over the previous week. The response options for all these questions range from zero (no impairment/limitation) to six (total impairment/ limitation) scale (see Appendix 8)

7.3.2.1.2. 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 [Jones, 1992] with a recall over the past 4 weeks (see Appendix 9).

7.3.2.1.3. Clinician/Subject Rated Response to Therapy

This is an overall evaluation of response to mepolizumab treatment, conducted separately by the investigator and the subject using a rating scale. In this rating scale, a seven-point scale score is used with the following definitions: 1 = significantly improved; 2 = moderately improved; 3 = mildly improved; 4 = no change; 5 = mildly worse; 6 = moderately worse; and 7 = significantly worse. Subjects will enter their response in an electronic device provided to the site as described in the SRM (see Appendix 10 and Appendix 11)

7.3.2.1.4. Treatment Satisfaction Questionnaire for Medication (TSQM-9)

The Treatment Satisfaction Questionnaire for Medication (TSQM-9) measures satisfaction with medication on 3 domains of effectiveness, convenience and global satisfaction [Atkinson, 2004; Bharmal, 2009]. The TSQM-9 has been demonstrated to be a reliable and valid measure of satisfaction with medication. Each of the 9 items is scored by the subject on a 5 or 7 point scale with the ends representing extreme dissatisfaction to extreme satisfaction. The total score is reported as score of 0 to 100 with higher scores representing higher satisfaction. Questions are framed to ask about current satisfaction with medication (see Appendix 12) .

7.3.2.2. Exit Interview

Exit interviews will be conducted as shown in the Schedule of Events table (Section 7.1) to explore subjects' experience with study treatment. Exit interviews are qualitative interviews conducted with study subjects to capture subject experiences in drug development on completion of participation in a clinical study. Interview questions are designed to fully assess a subject's experience with a study medication and are administered in a semi-structured format by a trained interviewer. Subject feedback will be captured in a data collection sheet as well as being audio-taped for subsequent transcription and qualitative analysis. The Exit interview technique and questions will be described in the SRM and training as well as training material references will be provided to site personnel who will administer the Exit interviews (see Appendix 13) .

7.3.2.3. Pulmonary Function test

Spirometry will be performed using the investigator spirometry equipments. The investigator is responsible for ensuring that all spirometry procedures and evaluations follow the recommendations of the American Thoracic Society (ATS)/European Respiratory Society (ERS) Task force: Standardization of Lung Function Testing [Miller, 2005].

7.3.2.3.1. Pre- and post bronchodilator FEV1

Only pre-bronchodilator assessments are required at Visit 1. Both pre- bronchodilator and post-bronchodilator assessments are required from Visit 2 onwards. At each visit, spirometry assessments should be performed at the same time of day (± 1 hour) as the assessment performed at Visit 2 (the baseline assessment). Subjects should withhold short-acting beta-2-agonists (SABAs) for ≥ 6 hours , LABAs for ≥ 12 hours and their dose of long-acting anticholinergic (LAMA) prior to the clinic visit.

7.3.2.4. Clinically Significant Asthma Exacerbation

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

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

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

Exacerbation data will be included in the analysis from Visit 2 until Exit Visit (Week 32) approximately 4 weeks after the last dose of study treatment. For those subjects that stop study treatment early or withdraw early from the study altogether, the time period for collection of exacerbation data will be from Visit 2 until no greater than approximately 4 weeks post-last-dose of mepolizumab. For consistency, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

7.4. Safety

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

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

The definitions of an AE or SAE can be found in Section 12.7, Appendix 7

Adverse Events including systemic (i.e., allergic/IgE-mediated and non-allergic) and local injection site reactions will be reported throughout the 32-week treatment period.

NOTE: Hypersensitivity reactions will be monitored using the diagnostic criteria for anaphylaxis as outlined by the Second Symposium on Anaphylaxis [Sampson, 2006] and (Appendix 7).

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.

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

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until Exit Visit at the time-points specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 7
- 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 Section 12.7, Appendix 7.

7.4.2. 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?"

7.4.2.1. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.5). Further information on follow-up procedures is given in Appendix 7)

7.4.2.2. Cardiovascular and Death Events

7.4.2.2.1. Cardiovascular events

Cardiovascular-related AEs and SAEs that will require the investigator to complete event specific pages in the eCRF are listed in Section 12.7.3, Appendix 4.

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

7.4.2.2.2. 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 Section 12.7, Appendix 7 or timelines for reporting SAEs.

7.4.2.3. Regulatory Reporting Requirements for SAEs

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

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

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

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

7.4.3. Pregnancy

- Details of all pregnancies of female participants in the study will be collected after the start of dosing and until the Exit Visit.

- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 3 .

7.4.4. Physical Exams

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

7.4.5. Vital Signs

- As detailed in the Time and Events Schedule Table (Section 7.1) vital signs will be measured in semi-supine position after 5 minutes rest and will include systolic and diastolic blood pressure and pulse rate.
- Vital signs assessments will be taken before measurement of any clinic lung function tests or ECGs at the specified time point.
- Height and weight will also be measured and recorded at Visit 1.

7.4.6. Electrocardiogram (ECG)

- A single 12-lead ECG will be obtained at each time-point as specified in the Time and event schedule (see Section 7.1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- If a routine single ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine whether the patient should be discontinued from the study. Refer to Section 5.5.4 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- ECG measurements will be made after the subject has rested in the supine position for 5 minutes. The ECG should be obtained after the vital signs assessments but before lung function testing and followed by other study procedures. ECG measurements shortly after a meal or during sleep should be avoided since QT prolongation can occur at these times.

7.4.7. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in (Table 5) must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are

detailed in the laboratory manual. All blood samples must be taken pre-injection of mepolizumab. In case of any Screening assessment (Visit1) occurring on the same day as omalizumab injection, all assessments must be performed pre omalizumab injection. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

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

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

Haematology, clinical chemistry and additional parameters to be tested are listed in Table 5.

Table 5 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 phosphatise	Albumin
Other Screening Tests	• Hepatitis B (HBsAg) • Hepatitis C (Hep C antibody) • FSH and estradiol (as needed in women of non-child bearing potential only) • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Urine hCG Pregnancy test (as needed 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 Section 5.5.3 and Appendix 5
2. 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.

7.4.8. Paper worksheet

Subjects will be issued with a paper worksheet to record adverse events, changes in concomitant medications and any visits to general practioner, hospital and/or emergency department during the study. Subjects will be asked to bring their worksheet to every study site 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.

7.5. Biomarker(s)/Pharmacodynamic Markers

Blood eosinophil counts will be recorded as part of the standard haematological assessments performed at the visits specified in the Time and Events Schedule (Section 7.1). Additional blood samples for exploratory biomarkers of type 2 helper T cells (Th2) response, will be collected at Visits 1, 2, 4 and 10. Details on collecting and handling of biomarker samples can be found in the SRM.

7.6. Immunogenicity

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

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

7.7. Genetics

Information regarding genetic research is included in Appendix 14. IEC/IRB and, where required, the applicable regulatory agency must approve the genetic assessments before these can be conducted at the site. The approval(s) must be in writing and will clearly specify approval of the genetic assessments (i.e., approval of Appendix 3. In some cases, approval of the genetic assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the genetic assessments is being deferred and the study, except for PGx and genetic assessments, can

be initiated. When genetic assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, genetic assessments will not be conducted

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

This study is designed to investigate whether subjects not optimally controlled on omalizumab can be effectively and safely switched to treatment with mepolizumab to improve asthma control. As there is no control arm in this study, comparisons in ACQ score will be made back to baseline.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

The primary analysis will utilise within-subject changes from baseline. As this study is uncontrolled, the potential of a 'placebo effect' within the mepolizumab treated subjects will be considered. A meta-analysis of two previous severe asthma studies with mepolizumab (MEA115588 and MEA112997) estimated a change from baseline at Week 32 of -0.55 and -0.88 in the placebo and mepolizumab groups respectively, with mepolizumab presenting a benefit of -0.34 over placebo.

The following sample size estimates are based on a residual standard deviation of 0.96 units and are based upon the aforementioned meta-analysis. These estimates assume that 15% of subjects will prematurely withdraw from the study and therefore have missing

data at Week 32. This primary analysis will use the "missing at random" assumption for missing data.

With a sample size of 120 treated subjects, it is estimated that this study has over 90% power to detect a statistically significant improvement from baseline. Further it is estimated that a significant improvement over the 'placebo effect' of -0.55 from baseline in ACQ score will be observed at the two-sided 5% level of significance if the observed change from baseline is at least -0.74 units.

If the true change from baseline is -0.86 units, then the study has a probability of 90% of observing a change from baseline of at least -0.74 units and therefore the study has 90% power for declaring statistical significance over the 'placebo effect'.

9.2.2. Sample Size Sensitivity

If either the actual change from baseline or variability are different from the values assumed in Section 9.2.1, the power to detect a change in ACQ score will be affected.

Table 6 illustrates the estimated power which would be obtained with different values of change from baseline and standard deviation, assuming 120 patients are treated.

Table 6 Power for various changes from baseline and standard deviations

Mean change from Baseline	Standard deviation				
	0.85	0.90	0.95	1.00	1.05
-0.75	65%	60%	56%	52%	48%
-0.80	84%	79%	75%	71%	66%
-0.85	94%	92%	88%	85%	82%
-0.90	98%	97%	96%	94%	92%
-0.95	>99%	99%	99%	98%	97%
-1.00	>99%	>99%	>99%	99%	99%

9.3. Data Analysis Considerations

9.3.1. 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.

Intent-to-Treat (ITT) Population

This population will consist of all subjects who receive at least one dose of mepolizumab, and will be the primary population for all analyses of efficacy measures and safety measures.

Per Protocol (PP) Population

The Per Protocol (PP) population will consist of all subjects in the Intent-to-Treat 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 freezing the study database. The PP population will be used for a supplementary analysis of the primary endpoint.

9.3.2. Interim Analysis

No interim analysis is planned for this study.

9.4. Key Elements of Analysis Plan

All pre-specified analyses will be described in a full Reporting and Analysis Plan (RAP) which will be finalised prior to freezing the study database. Any changes to what is detailed in the protocol will also be described in the RAP.

The study database will be frozen once the final subject has completed the Exit visit and all queries for data collected up to this time are resolved.

9.4.1. Primary Analyses

Analysis of change from baseline in ACQ score will be performed using a mixed models repeated measures (MMRM) analysis, allowing for covariates of baseline ACQ score, region, baseline maintenance OCS therapy, exacerbations in the year prior to the study (as an ordinal variable), visit and an interaction term for visit by baseline ACQ score. The primary comparison will be Week 32 vs. Baseline and all data collected up to and including Week 32 from patients, including those who have discontinued study treatment, will be included in the analysis.

The primary population for analysis will be the ITT population. A supporting analysis of the PP population will also be performed.

9.4.2. Secondary Analyses

The secondary efficacy endpoints are listed below and their link to the study objectives is detailed within Section 3:

- Mean change from baseline in SGRQ
- Frequency of clinically significant exacerbations

- Ratio to baseline in blood eosinophils

Mean change from baseline in SGRQ and blood eosinophils will be analyzed using mixed models repeated measures analysis, allowing for the aforementioned covariates within the primary analysis. A log-transformation will be applied to blood eosinophil counts prior to analysis.

The frequency of clinically significant exacerbations will be analyzed using a generalized linear model, assuming the number of exacerbations has a negative binomial probability distribution and that its mean is related to covariate factors with a 'log link' function. The logarithm of time on treatment will be used as an offset variable. The model will include covariates for region, baseline maintenance OCS therapy and number of exacerbations in the year prior to the study (as an ordinal variable).

9.4.3. Other Analyses

9.4.3.1. Other Efficacy Analyses

See Section 3 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.

9.4.3.2. Safety Analyses

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

9.4.3.2.1. 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.

9.4.3.2.2. 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. Separate summaries will be presented for all AEs, drug-related AEs, SAEs, AEs leading to permanent discontinuation of investigational product or withdrawal from the study and for any AEs of special interest.

9.4.3.2.3. 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.

9.4.3.2.4. 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 (Section 7.1). Further details will be provided in the RAP.

9.4.3.2.5. Immunogenicity

Immunogenicity data will be summarised using appropriate descriptive statistics.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

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

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

The study will also be conducted in accordance with 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.

10.2.1. Written Informed Consent/Assent

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

10.3. Quality Control (Study Monitoring)

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

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

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

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

10.4. Quality Assurance

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

conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

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

10.6. Records Retention

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

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

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

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

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

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

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12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

ACQ	Asthma Control Questionnaire
ADA	Anti-Drug Antibody
AE	Adverse Event
ALT	Alanine Transaminase
ASE	All Subjects Enrolled
AST	Aspartate Transaminase
ATS	American Thoracic Society
BMI	Body Mass Index
BP	Blood pressure
CD	Cluster of differentiation
CI	Confidence Interval
CPAP	Continuous Positive Airway Pressure
CS	Corticosteroid
CV	Cardiovascular
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
(e)CRF	(Electronic) Case Report Form
ED	Emergency Department
eDiary	Electronic Diary
EGPA	Eosinophilic Granulomatosis with Polyangiitis
EMEA	European Medicines Agency
ERS	European Respiratory Society
FAAN	Food Allergy and Anaphylaxis Network
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FP	Fluticasone Propionate
FRP	Females of Reproductive Potential
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
g/gm	grams
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
HES	Hypereosinophilic Syndrome
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
HR-QoL	Health-Related Quality of Life

HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
ICU	Intensive Care Unit
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
IVRS	Interactive Voice Response System
kg	Kilogram
L/min	Liters per minute
LABA	Long-Acting Beta-2-Agonists
LTRA	Leukotriene Receptor Antagonist
mAb	Monoclonal Antibody
MedDRA	Medicinal dictionary for regulatory activities
MCID	Minimal Clinically Important Difference
mcg (µg)	Microgram
mcL (µL)	Microliter
MDI	Metered Dose Inhaler
mg	Milligram
ml	Milliliter
MMRM	Mixed Models Repeated Measures
mm Hg	Milliliter of Mercury
MSDS	Material Safety Data Sheet
N/A	Not Applicable
NaB	Neutralizing Antibodies
NHLBI	National Heart Lung and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NK	Natural killer Cell
OCS	Oral Corticosteroids
p.a.	Per annum
PD	Pharmacodynamic
PCR	Polymerase Chain Reaction
PEF	Peak Expiratory Flow
PGx	Pharmacogenetics
PFT	Pulmonary function tests
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
SABA	Short-Acting Beta-2-Agonists
SAE	Serious Adverse Event
SC	Subcutaneous
SGRQ	St. George's Respiratory Questionnaire
SmPC	Summary of Product characteristics
SOC	System Organ Class
Th	T Helper cells
TSQM	Treatment Satisfaction Questionnaire for Medication
Visit	V
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
Omalizumab (Xolair)

12.2. Appendix 2: Anaphylaxis Criteria

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

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
   a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced 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

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

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

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. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Oral Contraceptive. Combined estrogen and progestogen oral contraceptive [Hatcher, 2007]
4. Injectable progestogen [Hatcher, 2007]
5. Contraceptive vaginal ring [Hatcher, 2007]
6. Percutaneous contraceptive patches [Hatcher, 2007]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2007].

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].

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.

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

12.3.2. 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 in the study will immediately discontinue study medication

12.4. Appendix 4: New York Heart Association Functional Classification of Congestive Heart Failure

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

Adapted from American Heart Association, 2011]

12.5. Appendix 5: 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

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)	• 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)

• **Do not restart/rechallenge** subject with study treatment. Permanently **discontinue study treatment and may continue** subject in **the study** for any protocol specified **follow up assessments**	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
MONITORING: **<u>For bilirubin or INR criteria:</u>** • **Repeat liver** chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct 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** 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.

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.

12.6. 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 5 (see Exclusion Criteria Section 5.2).

12.7. Appendix 7: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

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

Events NOT 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.

12.7.2. 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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
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 and 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.
• Refer to Appendix 5 for the required liver chemistry follow-up instructions

12.7.3. 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

12.7.4. 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.

12.7.5. 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.

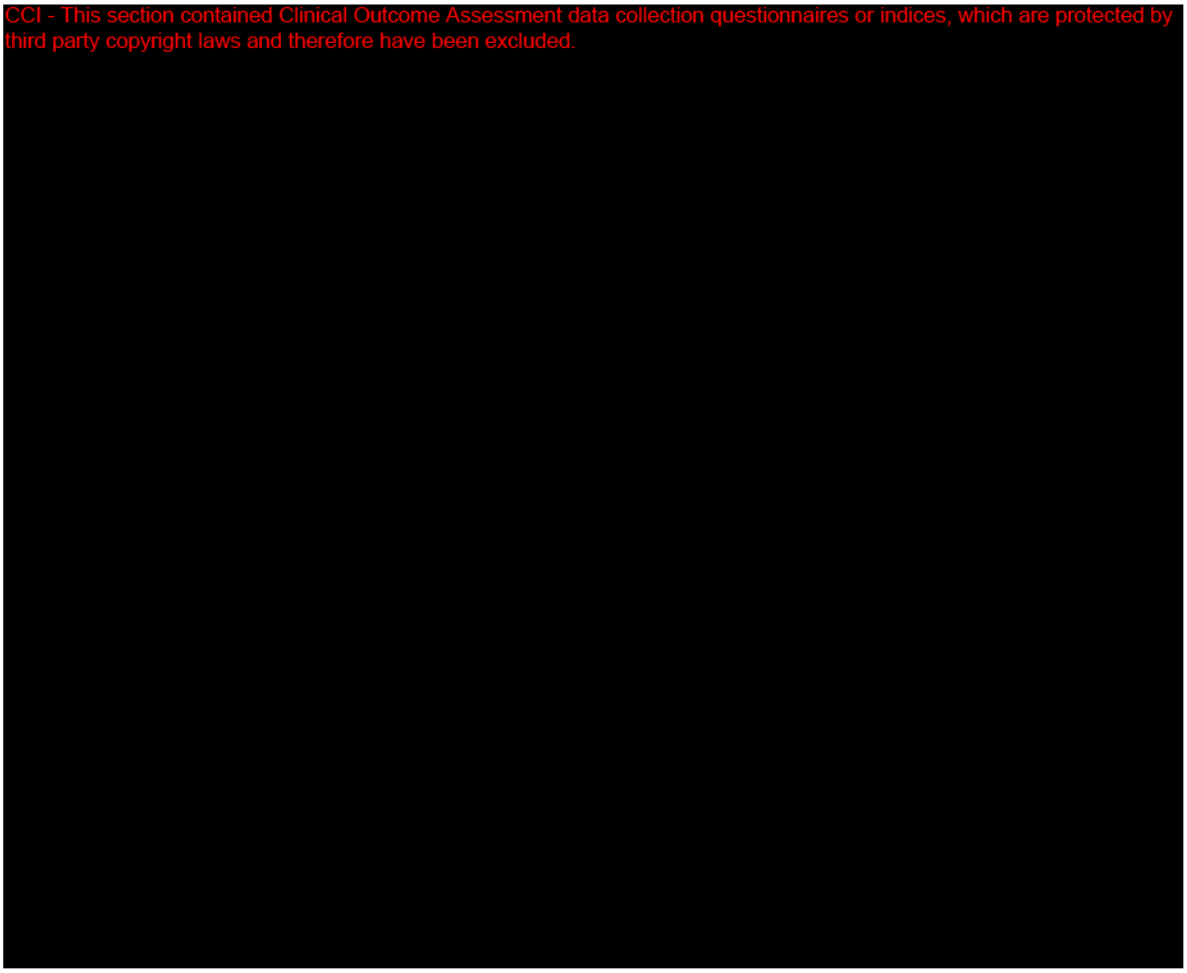
12.7.6. Reporting of SAEs to GSK

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. • 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 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.

12.8. Appendix 8- Asthma control Questionnaire

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

12.9. Appendix 9- St.Geroge's Respiratory Questionnaire



12.10. Appendix 10- Subject Rated Response to Therapy

Evaluate your response to therapy since you started this study.

✓ *only one:*

[1] ☐ Significantly Improved
[2] ☐ Moderately Improved
[3] ☐ Mildly Improved
[4] ☐ No Change
[5] ☐ Mildly Worse
[6] ☐ Moderately Worse
[7] ☐ Significantly Worse

12.11. Appendix 11- Clinician rated response to Therapy

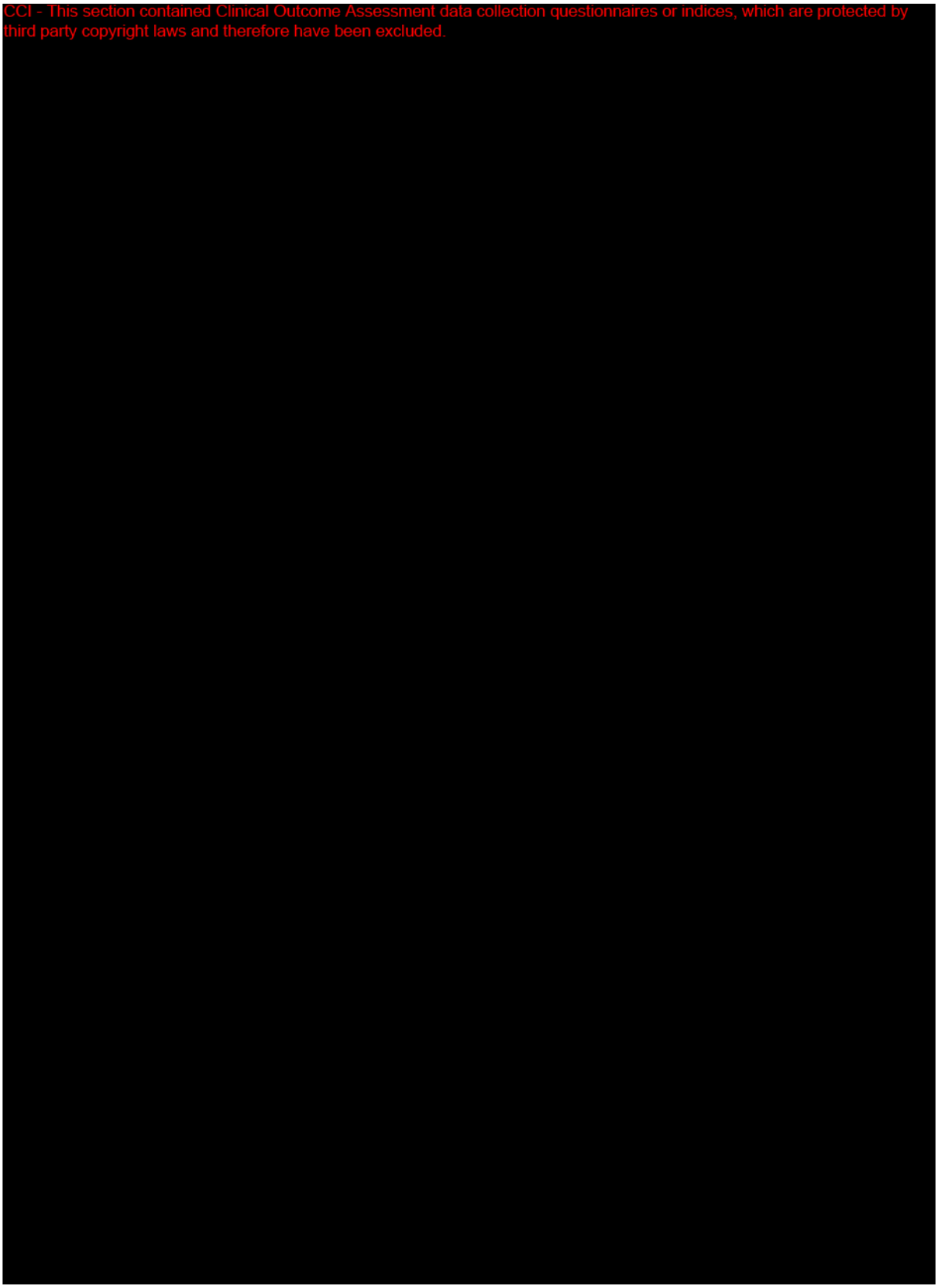
Evaluate the subject's response to therapy since the start of the study by placing a ✓ in the appropriate box below:

✓ only one:

[1] ☐ Significantly Improved
[2] ☐ Moderately Improved
[3] ☐ Mildly Improved
[4] ☐ No Change
[5] ☐ Mildly Worse
[6] ☐ Moderately Worse
[7] ☐ Significantly Worse

12.12. Appendix 12- Treatment Satisfaction Questionnaire for Medication (TSQM-9)

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



12.13. Appendix 13– Exit Interview Guide

1. *Please tell me about your asthma over the past 6 months, during this trial. Has it improved, stayed the same, or gotten worse?*

a. *Please tell me about <u>your symptoms</u> since you've been in the trial compared to before the trial.*

Probes:

- *Describe your symptoms before and during the trial. Symptoms during the day? Symptoms at night?*
- *What symptoms? How often?*

b. *Please tell me about <u>good days and bad days</u> with respect to your asthma since you've been in the trial compared to before the trial.*

Probes:

- *Describe good and bad days before and during the trial.*

c. *Please tell me about <u>activities or things you do day-to-day</u> since you've been in the trial compared to before the trial.*

Probes:

- *Describe your activities or things you do day-to-day before and during the trial.*
- *Is there anything you avoid doing or worry about doing because of your asthma? Has this changed since you've been in the trial?*

d. *Please tell me about how asthma impacted or affected your life since you've been in the trial compared to before the trial.*

Probes:

- *Describe the impact of asthma before and during the trial.*

e. *Please tell me about <u>your asthma triggers, things that make your asthma worse,</u> since you've been in the trial compared to before the trial.*

Probes:

- *Describe your triggers before and during the trial.*

f. *Please tell me about <u>any unplanned visits to your doctor, emergency room or hospital</u> since you've been in the trial compared to before the trial.*

Probes:

- *Describe any unplanned visits before and during the trial.*

2. *Now let's talk (more) about your asthma exacerbations over the past 6 months, during this trial. Exacerbations are also sometimes called asthma attacks and might mean that you needed to take more medication, new medication like steroids, or were admitted to the hospital or emergency room. Would you say your exacerbations have improved, stayed the same, or gotten worse?*

a. *Please tell me about <u>the number of asthma exacerbations</u> since you've been in the trial compared to before the trial.*

   Probes:

   - *Describe your exacerbations.*
   - *How often did you have exacerbations before and during the trial?*

b. *Please tell me about your asthma exacerbations in terms of <u>how long they lasted</u> since you've been in the trial compared to before the trial.*

   Probes:

   - *Describe your exacerbations.*
   - *How long did they last before and during the trial?*

c. *Please tell me about your asthma exacerbations in terms of <u>how severe or bad they were</u> since you've been in the trial compared to before the trial.*

   Probes:

   - *Describe your exacerbations.*
   - *What symptoms were most severe or most affected you?*
   - *What symptoms were least severe or least affected you?*
   - *Did they interfere with your normal activities? If "yes", what activities? Tell me more about those.*
   - *Did you always seek care from a doctor? Or go to an emergency room or hospital? If "yes", tell me more about those.*
   - *Did you have exacerbations you took care of yourself? Without contacting a doctor? If "yes", tell me more about those.*

3. *Do you feel that the study treatment worked for you?*

a. *What makes you say that the treatment [subject's response; worked or didn't work]?*

   Probes:

   - *What is most important to you in terms of your asthma to say that a treatment works?*

12.14. Appendix 14: Genetic Research

Genetics – Background

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

Genetic Research Objectives and Analyses

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

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

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

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

Study Population

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

Study Assessments and Procedures

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

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

A 6 ml blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A blood sample is collected at the baseline (Visit 2) or any other later visit, after the subject has provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

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

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

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

Informed Consent

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

Subject Withdrawal from Study

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

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

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

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

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

Initiation of study treatment not met

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

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

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

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

12.15. Appendix 15- Country Specific Requirements

No country-specific requirements exist.

12.16. Appendix 16: Protocol changes

Scope:

This amendment applies to all sites.

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

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

Protocol Changes

Medical Monitors/Sponsor information Page

Secondary Medical Monitor details

Rationale for change: Contact details update to reflect change in personnel.

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	PPD ~~MD~~ Telephone: PPD PPD	Cell: PPD	Fax PPD	GlaxoSmithKline Five Moore Drive Research Triangle Park, NC 27709-3998, USA
Secondary Medical Monitor	PPD PPD PPD PPD	PPD ~~MD~~ ~~Telephone:~~ PPD PPD PPD Telephone: PPD PPD	~~Cell:~~ PPD PPD PPD PPD Cell: PPD	~~Fax~~ PPD PPD PPD Fax: PPD PPD	GlaxoSmithKline Stockley Park West, 1-3 Ironbridge Road, Heathrow, Uxbridge, Middlesex, UB11 1BT, United Kingdom
SAE contact information	PPD PPD	PPD ~~MD~~ Telephone: PPD PPD	Cell: PPD	PPD	GlaxoSmithKline Five Moore Drive Research Triangle Park, NC 27709-3998, USA

Sponsor Legal Registered Address

Rationale for change: Mepolizumab IND number added

Revised text:

Regulatory Agency Identifying Number(s): EudraCT no.2015-003697-32, IND no.006971

Section 1 and Section 3 Objective(s)/Endpoints

Rationale for change: The wording of the primary objective was revised to reflect the pragmatic approach of the study.

Revised text:

Primary objective: ~~To determine~~ To describe in a pragmatic setting whether there is an improvement in asthma control, from the beginning to the end of the study, when directly switched to mepolizumab in subjects with a severe eosinophilic asthma phenotype not optimally controlled on omalizumab.

Section 4.6.1 Table 3 Risk Assessment for mepolizumab

Rationale for change: To clarify that subjects should be monitored for 1 hr post injection for the first 3 injections and later per institutional guidelines.

Revised text

Subjects are to be monitored post-injection for one hour for the first 3 injections, then per institutional guidelines.

Section 5.1 Inclusion Criteria No.6

Rationale for change: To add long-acting anticholinergic (tiotropium bromide)

Revised text:

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

Section 5.3 Required Criteria to Start Treatment. Criterion No. 2

Rationale for change: "run-in" is added for consistency

Revised text:

No Asthma Exacerbation: Subjects with an ongoing asthma exacerbation at Baseline (Visit 2) should have their Visit 2 delayed until the investigator considers the subject has

returned to their baseline asthma status for at least one week. If the 4-week screening/run-in period has elapsed and subjects have not returned to their baseline asthma status, then they should be considered a run-in failure. An exacerbation is defined as worsening of asthma requiring the use of systemic corticosteroids and/or emergency department visit, or hospitalisation (see Section 7.3.2.4 Clinically Significant Asthma Exacerbation).

Section 5.5.3 Liver Chemistry Stopping Criteria

Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm

Rationale for change: To change **"**Appendix 2" to "Appendix 5" as this was a typographical error.

Revised text

Liver chemistry stopping criteria and required follow up assessments are defined in ~~Appendix 2~~ Appendix5.

Section 5.5.4 QTc Stopping Criteria

Last bullet point

Rationale for change: To correct typographical errors. Change from baseline (Visit 2), was replaced with "change from screening (Visit 1)". In addition, "Baseline (Visit 2)" was changed to "Screening (Visit 1)".

Revised Text

- [Change from ~~baseline~~ screening (Visit ~~2~~ 1) of QTc > 60 msec]

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

~~Baseline~~ Screening (Visit ~~2~~ 1) QTc with Bundle Branch Block	**Discontinuation QTc with Bundle Branch Block**
< 450 msec	> 500 msec
450 – 480 msec	≥ 530 msec

Section 6.1 Investigational Product and Other Study Treatment

Second paragraph

Rationale for change: Ventolin Diskus for Sweden was added to reflect its use as a rescue medication in Sweden. "MDI", was replaced by "rescue inhaler"

Revised text

Trade label albuterol/salbutamol metered dose inhalers (MDIs) will be provided locally by each country (except for US sites where GSK Global Supply Organisation will supply the rescue medication) including Sweden where Ventolin Diskus will be used. Subjects will be dispensed ~~an MDI~~ a rescue inhaler at the time of screening to be used to primarily treat asthma symptoms on an as needed basis but also during pre and post bronchodilator spirometry assessments (see Section 7.3.2.3.1). The ~~MDI~~ rescue inhaler should be replaced as needed, and collected at the Exit Visit (or Early Withdrawal Visit, as applicable).

Section 7.1 Time and Events Table

Rationale for change: To make minor changes, the "x", in Dispense paper diary/worksheet row for The Exit Visit/Early withdrawal Visit column, was removed to correct a typographical error. In addition, in the table footnote the assay for Hepatitis C was updated.

Revised text

Procedures	**Pre-screen[1]**	**Screen Run-in**	**Treatment (visit window is ±7days)**								**Exit Visit/ Early withdrawal Visit[3]**
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Week	**-6 to -4**	**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**4 weeks post last dose ±7 days**
Informed Consent [2]	x										
Subject Demography	x										
Medical History		x									
Asthma History (including triggers)	x	x									
Therapy History[4]		x									
Smoking History		x									
Cardiovascular History/Risk Factors		x									
Inclusion/Exclusion Criteria		x									
Continuation to treatment Criteria			x								
Efficacy Assessments[5]											
ACQ-5		x	x	x	x	x	x	x	x	x	x
Exacerbation review	x	x	x	x	x	x	x	x	x	x	x
Spirometry including pre- and post bronchodilator FEV_1, FVC [6]		x	x			x			x		x
Health Outcome Assessments[5]											
SGRQ			x			x			x		x
Clinician & Subject rated response to therapy					x		x		x		x
Treatment Satisfaction with Medication Questionnaire (TSQM-9)		x									x
Exit Interview[7]											x

Procedures	**Pre-screen[1]**	**Screen Run-in**	**Treatment (visit window is ±7days)**								**Exit Visit/ Early withdrawal Visit[3]**
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Week	**-6 to -4**	**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**4 weeks post last dose ±7 days**
Safety Assessments[5]											
Concomitant Medication	x	x	x	x	x	x	x	x	x	x	x
Physical Examination, including nasal exam		x									x
Vital Signs		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
Serious Adverse Events	x	x	x	x	x	x	x	x	x	x	x
Laboratory Assessments[5]											
Haematology with differential		x	x	x	x	x	x	x	x	x	x
Clinical Chemistry (incl. LFT)		x	x	x	x	x			x		x
Parasitic Screening[8]		x									
Pharmacogenetic sample[9]			←				X			→	
Pregnancy test[10]		U	U	U	U	U	U	U	U	U	U
HBsAg and hepatitis C antibody[11]		x									
Immunogenicity sample			x			x				x	x
Biomarker sample		x	x		x						x

Procedures	**Pre-screen[1]**	**Screen Run-in**	**Treatment (visit window is ±7days)**								**Exit Visit/ Early withdrawal Visit[3]**
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Week	**-6 to -4**	**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**4 weeks post last dose ±7 days**
Investigational product (Mepolizumab) and rescue medication											
Administer mepolizumab. Contact RAMOS NG to register dispensing visit.			x	x	x	x	x	x	x	x	
Albuterol/salbutamol dispensed (as needed)		x	x	x	x	x	x	x	x	x	
Collect dispensed albuterol/salbutamol			x	x	x	x	x	x	x	x	x
eCRF/ paper diary/worksheet											
Complete eCRF	x	x	x	x	x	x	x	x	x	x	x
Dispense paper diary/worksheet	x	x	x	x	x	x	x	x	x	x	~~x~~
Collect/review paper diary/worksheet		x	x	x	x	x	x	x	x	x	x

1. Pre-screen Visit 0 must be completed prior to Visit 1 (Screening). It can be completed on the same day as Visit 1 or at up to 2 weeks prior to Visit 1.
2. Subjects will be assigned a subject number at the time ICF signed. The ICF must be signed before any study procedures including medication wash out period(s).
3. Exit Visit may be completed 3 to 5 weeks post last dose.
4. Therapy history to include a detailed review of prior biologics received for treatment of asthma, including omalizumab dose and regimen and prior investigational therapies e.g anti-IL5 or anti-IL13 preparations.
5. All study efficacy, safety and all patient reported questionnaires must be completed prior any study procedure.
6. Spirometry to include pre- and post bronchodilator FEV1 from V2.
7. Exit interview will be conducted only in a subset of sites and in a subset of subjects who choose to participate in the Exit interview. Subjects must be consented prior to interview
8. Parasitic screening is only required in countries with high-risk or for subjects who have visited high-risk countries in the past 6 months. Sites should use local laboratories.
9. Pharmacogenetic sample may be drawn at Visit 2 or any visit after.
10. Pregnancy test, U= urine
11. Hepatitis B Surface Antigen and Hepatitis C antibody. (if hepatitis C antibody is positive, ~~a RIBA immunoblot assay should be reflexively performed on the serum sample to confirm the results~~ hepatitis C will be confirmed by PCR).

Section 7.3.2.3.1 Pre and post bronchodilator FEV1

Rationale for change: To add "morning long-acting anticholinergic (LAMA)"

Revised text

Only pre-bronchodilator assessments are required at Visit 1. Both pre- bronchodilator and post-bronchodilator assessments are required from Visit 2 onwards. At each visit, spirometry assessments should be performed at the same time of day (± 1 hour) as the assessment performed at Visit 2 (the baseline assessment). Subjects should withhold short-acting beta-2-agonists (SABAs) for ≥ 6 hours and LABAs for ≥ 12 hours and their dose of long-acting anticholinergic (LAMA) prior to the clinic visit. ~~if possible~~.

Section 7.4.7 Clinical Safety Laboratory Assessments

Table 5 Protocol Required Safety Laboratory Assessments

Rationale for change: to correct a typographical error in appendix No.

Revised text

<table>
<tr><td>Laboratory Assessments</td><td>Parameters</td></tr>
<tr><td>Haematology</td><td>
<table>
<tr><td>Platelet Count</td><td>RBC Indices:</td><td>WBC count with Differential:</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 phosphatise</td><td>Albumin</td></tr>
</table>
</td></tr>
<tr><td>Other Screening Tests</td><td>

Hepatitis B (HBsAg)
Hepatitis C (Hep C antibody)
FSH and estradiol (as needed in women of non-child bearing potential only)
Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)
Urine hCG Pregnancy test (as needed for women of child bearing potential) [2]

</td></tr>
</table>

NOTES :

1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.5.3 and ~~Appendix~~ 2 Appendix 5
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.

Section 7.5 Biomarker(s)/Pharmacodynamic Markers

Rationale for change: To clarify that eosinophil count is not blinded

Revised text

Blood eosinophil counts will be recorded as part of the standard haematological assessments performed at the visits specified in the Time and Events Schedule (Section 7.1). ~~From Visit 2 onwards, blood eosinophil counts will not be communicated to investigators, in order not to bias the investigator assessment of patient response to treatment.~~ Additional blood samples for exploratory biomarkers of type 2 helper T cells (Th2) response, will be collected at Visits 1, 2, 4 and 10. Details on collecting and handling of biomarker samples can be found in the SRM.

Section 12.7 Appendix 7 Sub-section 12.7.2 last bullet point

Revised text

Rationale for change: To correct the Appendix No as it was a typographical error

Revised text: Refer to ~~Appendix 2~~ Appendix 5 for the required liver chemistry follow-up instructions