TITLE PAGE

Division: Worldwide Development

Information Type: Clinical Protocol

Title:	Study 200622: A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of mepolizumab in the treatment of adolescent and adult subjects with severe hypereosinophilic syndrome

Compound Number: SB-240563

Development Phase III

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Authors: PPD

SPONSOR SIGNATORY:

PPD

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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): IND#: BB-IND 011295, EudraCT#: 2014-001232-11

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 200622

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

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

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

Investigator Name: _____

Investigator Signature	Date

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY 200622

Rationale

HES is a group of rare hematologic disorders without a known cause in which eosinophils are overproduced in the bone marrow for prolonged periods of time. The sustained overproduction of eosinophils in the bone marrow results in high blood eosinophil levels (eosinophilia). When activated eosinophils from the bloodstream infiltrate various tissues, they cause inflammatory tissue damage and dysfunction. HES is only diagnosed when organ damage and/or dysfunction are present. The current definition and diagnosis of HES in patients uses the following criteria: (1) blood eosinophilia of >1,500 eosinophils/µL on 2 examinations (at an interval ≥1month, except in case of life-threatening organ-damage when diagnosis can be made immediately) and/or tissue eosinophilia; (2) organ damage and/or dysfunction attributable to tissue eosinophilia; and (3) exclusion of other disorders or conditions as the major reason for organ damage [Valent, 2012].

Eosinophilia is central to the pathophysiology of HES and IL-5 is a key cytokine regulating the life-cycle of the eosinophil. Neutralization of IL-5 with an anti-IL5 monoclonal antibody, therefore offers a potential therapeutic option for HES.

Mepolizumab is a humanized monoclonal antibody (IgG1, kappa, mAb) which is specific for human IL-5. Mepolizumab blocks binding of human IL-5 (hIL-5) to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface. In conditions where eosinophilia is considered to play an important part in the pathology, including eosinophilic asthma, HES, and eosinophilic granulomatosis with polyangiitis (EGPA), a consistent reduction in blood eosinophil counts is observed in association with mepolizumab administration, with concomitant clinical improvement [Haldar, 2009; Kim, 2010; Moosig, 2011; Nair, 2009; Ortega, 2014; Pavord, 2012; Rothenberg, 2008; Stein, 2008]. The hypothesis that IL-5 is central to the pathology and clinical manifestations of HES is supported by clinical data from three completed clinical studies (MHE100185 [Rothenberg, 2008], MHE100901 [Roufosse, 2013], CRT112446 [Stein, 2008]) and the ongoing compassionate use program (CUP) providing 'proof-of-concept' evidence of efficacy of IL-5 blockade in the treatment of subjects with HES. In addition, several published case studies have been reported demonstrating activity of mepolizumab in HES patients [Plötz, 2003; Braun-Falco, 2004; Garrett, 2004; Hargreaves, 2007; Mehr, 2009; Schwartz, 2010; Bleeker, 2012].

The purpose of this 32-week, randomized, double-blind, placebo-controlled study is to investigate the efficacy and safety of mepolizumab 300 mg SC every 4 weeks compared with placebo in adolescent and adult subjects with severe HES (demonstrated by a blood eosinophil count of 1000/µL or higher during screening, and a history of two or more HES flares within the past year) receiving standard of care (SoC) therapy. The primary objective of the study is to demonstrate maintenance of control of HES symptoms during the treatment period (i.e., avoidance of HES flare).

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To demonstrate the efficacy of mepolizumab compared with placebo based on maintenance of control of HES symptoms during the treatment period.	• Proportion of subjects who experience an HES flare during the 32-week study treatment period
Secondary	
• To demonstrate supportive evidence of the benefit of mepolizumab compared with placebo based on other measures of efficacy.	• Time to first HES flare • Proportion of subjects who experience an HES flare during Week 20 through Week 32 • Rate of HES flares • Change from baseline in fatigue severity based on Brief Fatigue Inventory (BFI) item 3 (worst level of fatigue during past 24 hours) at Week 32
Exploratory	
• To investigate mepolizumab compared with placebo with respect to additional measures of efficacy.	• Proportion of subjects who receive blinded active OCS due to an elevated blood eosinophil level that meets the pre-defined threshold during the 32-week study treatment period • Lung function tests (FEV_1, FVC, and ratio) • Echocardiogram
• To investigate the efficacy of mepolizumab compared with placebo with respect to patient and clinician reported symptoms, health status, and disease impact.	• Change from baseline in HES symptom severity based on HES Daily Symptoms (HES-DS) at Week 32 • Change from baseline in the BFI total and domain scores at Week 32 • Proportion of subjects with a favorable response as measured by clinician- and subject-rated overall response to therapy score (RTS) at Week 32 • Change from baseline in Subject-rated symptom severity (SSR) at Week 32 • Change from baseline in Modified Memorial Symptom Assessment Scale-Short Form (MSAS-SF) responses at Week 32 • Change from baseline in physical function

Objectives	Endpoints
	(Patient Reported Outcome Measurement Information System [PROMIS] physical function items) at Week 32 • Change from baseline in sleep (PROMIS sleep items) at Week 32
• To characterize the patient burden of HES.	• SF-36 v2 • Healthcare resource utilization (HCRU) • Work Productivity and Activity Impairment Index – General Health (WPAI-GH) v2 • Steroid perception questionnaire
• To investigate the pharmacokinetics (PK) of mepolizumab.	• Plasma concentration of mepolizumab
• To investigate the pharmacodynamics (PD) of mepolizumab.	• IL-5 levels (serum free and total) • Blood eosinophil levels
Safety	
• To evaluate the safety of mepolizumab compared with placebo in subjects with HES receiving standard of care treatment over a 32-week study treatment period	• Adverse events including local injection site reactions and systemic reactions (e.g., hypersensitivity) • Vital signs • 12-lead ECG • Hematological and clinical laboratory tests • Immunogenicity (anti-drug antibody)

Overall Design

- This is a 32-week treatment period, randomized, double-blind, placebo-controlled, parallel group, multicentre study of mepolizumab in adolescent and adult subjects with severe HES receiving SoC therapy (Figure 1 in Section 4.1).

Treatment Arms and Duration

- The study is comprised of a screening period of up to approximately 4 weeks followed by a 32-week study treatment period and up to 8-week additional follow-up period (12 weeks after the last dose of study treatment).

- Approximately 80 subjects who are able to maintain a stable regimen of HES therapy for the 4 weeks prior to Visit 2 will be randomized in a 1:1 ratio to receive either 300 mg mepolizumab *or* placebo subcutaneously (SC) every 4 weeks while

continuing their HES therapy. The sample size may be increased up to a maximum of 120 subjects in total (see details below). The same regimen of HES therapy will be maintained throughout the 32-week study treatment period unless there is worsening of symptom(s) that requires an increase in therapy. A reduction in dose for safety reasons, with return to the original dose if possible, is permitted in consultation with the GlaxoSmithKline (GSK) Medical Monitor.

- The final dose of study treatment will be administered at Visit 10 (Week 28) with completion of the study treatment period achieved at the next 4-weekly visit. At Visit 11 (Week 32), subjects will complete the end-of-treatment assessment (4 weeks after the last dose).

- Subjects who withdraw from study treatment prematurely should continue in the study per protocol (including HES flare-related assessments) until 32 weeks from randomization.

- For subjects whose last dose of study treatment is on Visit 9 (Week 24) or Visit 10 (Week 28) *and* who do not continue with open-label mepolizumab after completing Visit 11 assessment (32 weeks from randomization), there will be up to 8-week additional follow-up period, concluding with the 12 weeks post-last dose follow-up visit (Visit 12).

- Subjects will be eligible to be considered to receive open-label mepolizumab 300 mg SC every 4 weeks after *either*:

  i. Completion of the treatment period in the 200622 study

  or

  ii. If the subject was withdrawn from study treatment prematurely during the 200622 study, but continued in the study per protocol (including HES flare-related assessments) until 32 weeks from randomization.

- Subject management during the study will be according to routine medical care, i.e., subjects will be instructed to contact their investigator for evaluation or seek emergency care as necessary when they experience worsening of symptoms as per their usual practice. The investigator will use the HES Core Assessments (Section 7.3.2) to assess for the presence of a HES flare (unscheduled 'Flare' visit in Section 7.1).

- Investigators, participating subjects, and GSK study personnel will be blinded to absolute blood eosinophil counts, total white blood cell counts, and white blood count differentials (%) from randomization (Visit 2) to the end of the study. Blood eosinophil-unblinded GSK personnel/delegates not involved with other aspects of study conduct will monitor the absolute blood eosinophil count results and trigger blinded OCS treatment to treat an eosinophilia when the blood eosinophil count reaches a pre-defined threshold (Section 6.4).

- An Independent Data Monitoring Committee (IDMC) will be utilized in this study (Section 10.8).

Type and Number of Subjects

- Subjects entering the study must have experienced at least two HES flares within the past 12 months and have a blood eosinophil count of 1000/μL or higher during screening. Historical HES flares for the study entry criteria are defined as documented HES-related worsening of clinical symptoms or blood eosinophil counts requiring an escalation in therapy. In addition, at least one HES flare within the past 12 months must not be related to a decrease in HES therapy during the 4 weeks prior to the flare. For further details on the study entry criteria, see Section 5.

- Approximately 80 subjects will be randomized in the initial recruitment phase. The proportion of subjects that have an HES flare will be monitored and the total number of subjects randomized may be increased if the blinded overall rate is predicted to be <30%. The sample size may be increased up to a maximum of 120 subjects in total.

Analysis

The primary efficacy endpoint is the proportion of subjects who experience an HES flare during the 32-week study treatment period. The study is designed to continue to collect data on HES flares for subjects who prematurely discontinue from their randomized treatment. All data on HES flares collected for these subjects will also be included in the primary analysis. For subjects who withdraw prematurely from the study and for whom collection of data on HES flares is not possible, it will be assumed for the primary endpoint that they are treatment failures, i.e., that they experience a flare following study withdrawal.

This study is designed to test the superiority of mepolizumab versus placebo.

Significance tests will be performed at the two-sided 5% level (one sided 2.5%).

The primary efficacy endpoint will be compared between treatments using a Cochran-Mantel-Haenszel test stratified by baseline OCS dose (0-≤20mg/day and >20mg/day prednisolone/prednisone or equivalent) and region. The analysis will be supplemented with a logistic regression analysis adjusting for covariates of baseline OCS dose, region, and treatment. The model will be used to estimate the odds ratio for the treatment difference and associated p-value and 95% confidence limit.

When strong control of type I error is required for making inferences for the pre-defined secondary endpoints, multiplicity will be controlled using a hierarchical, closed testing procedure. The hierarchy of endpoints will proceed from the primary endpoint to each of the secondary endpoints in the order they are listed above.

2. INTRODUCTION

2.1. Study Rationale

HES is a group of rare hematologic disorders without a known cause in which eosinophils are overproduced in the bone marrow for prolonged periods of time. The sustained overproduction of eosinophils in the bone marrow results in high blood eosinophil levels (eosinophilia). When activated eosinophils from the bloodstream infiltrate various tissues, they cause inflammatory tissue damage and dysfunction. HES is only diagnosed when organ damage and/or dysfunction are present. The current definition and diagnosis of HES in patients uses the following criteria: (1) blood eosinophilia of >1,500 eosinophils/µL on 2 examinations (at an interval ≥1month, except in case of life-threatening organ-damage when diagnosis can be made immediately) and/or tissue eosinophilia; (2) organ damage and/or dysfunction attributable to tissue eosinophilia; and (3) exclusion of other disorders or conditions as the major reason for organ damage [Valent, 2012].

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2.2. Background

HES is a heterogeneous group of chronic inflammatory disorders characterized by persistent eosinophilia (elevated blood eosinophil counts) and diverse organ involvement, punctuated by flares of disease worsening. Inadequate HES treatment can lead to profound end-organ damage and increased mortality. Given the clinical heterogeneity of HES, clinicians use diverse classes of medications (such as high doses of OCSs), most of which are not approved to treat HES, have detrimental side effects, and may not result in complete remission of disease.

HES Classification

The ability to distinguish different HES variants is critical for optimal patient management because the clinical manifestations and response to treatment vary considerably depending on the etiology of eosinophilia [Klion, 2009]. The three most common types of HES are myeloproliferative (M-HES), lymphocytic (L-HES) and undefined [Wechsler, 2012]. M-HES is a clinically defined variant characterized by an extreme male predominance, pathologic evidence of eosinophil-related tissue damage and tissue fibrosis, elevated serum tryptase levels, and myeloproliferative features, including splenomegaly, anemia, thrombocytopenia, bone marrow hypercellularity with reticulin fibrosis, and increased numbers of atypical mast cells [Klion, 2009]. Identification of L-HES rests upon recognition of distinct helper T cell subsets (Th1 and Th2) and clonal overgrowth of specific cytokine-producing cells, particularly production of interleukin-5 (IL-5) by TH2 cell clones. The most prevalent T cell clone associated with lymphocytic HES appears to be the $CD3^{-}CD4^{+}$ clone [Roufosse, 2007].

The identification of the FIP1L1-PDGFRα (F/P) fusion tyrosine kinase genetic translocation in the majority of patients with M-HES led to a dramatic improvement in prognosis for these patients due to response to imatinib (a tyrosine kinase inhibitor) treatment. While the prevalence of M-HES has not been reported, the prevalence of the F/P mutation in the total HES patient population was found to be between 11% and 18% [Ogbogu, 2009; Helbig, 2010]. Therefore, for the majority of HES patients no definitive genetic basis underlying their disease has been identified.

Although patients with L-HES typically do not show the same high incidence of life-threatening end-organ damage compared with M-HES, L-HES patients are at higher risk for developing peripheral T-cell lymphomas [Gleich, 2009]. Reported estimated incidence rates vary widely due to the small sample population from "rare", to 5% up to 14-25% [Valent, 2012; Simon, 1999; D'Souza, 2012]. In a study of F/P negative HES patients, 21% were diagnosed with L-HES [Roufosse, 2013]. In a retrospective study of 21 French patients with $CD3^{-}CD4^{+}$ L-HES and negative for the F/P mutation, 1 lymphoma occurred (5%) during the mean follow-up duration after HES diagnosis of 6.9±5.1 years [Lefèvre, 2014].

Signs and Symptoms of HES

Although over the past three decades HES has become a chronic and less fatal disease, the morbidity associated with the disease or caused by the currently available therapy has a substantial negative impact on day-to-day functioning and quality of life.

The signs and symptoms of HES vary widely depending on specific organ involvement. The most common reported clinical manifestations of HES are:

- Constitutional: fever, night sweats, weakness, malaise, weight loss, myalgia;
- Dermatologic: pruritus, dermatitis, angioedema;
- Pulmonary: asthma, persistent non-productive cough, dyspnea;
- Gastrointestinal: abdominal pain, vomiting, diarrhea;
- Cardiac/thromboembolic: congestive heart failure, mitral regurgitation, intracardiac thrombus, myocardial ischemia, arrhythmias.

For example, one large retrospective study reported that out of 188 HES patients, 37% had dermatologic, 25% had pulmonary and 14% had gastrointestinal manifestations [Ogbogu, 2009]. Another retrospective study found similar end-organ manifestations as mentioned above and also reported that all of the 88 HES patients had constitutional manifestations [Helbig, 2010]. Additionally, echocardiographic and clinical cardiac/thromboembolic manifestations were reported in 49% of 49 HES patients [Ommen, 2000]. In another report, cardiac involvement was less prevalent at initial evaluation (5%, N=188), but becomes more prevalent (20%) over a period of up to 5 years [Ogbogu, 2007].

Many patients have two or more organ systems affected [Ogbogu, 2009; Helbig, 2010]. In the GSK CUP, where eligible patients include those with life-threatening disease and documented failure to standard HES therapies, 82% (N=199) had a history of more than two organ systems involved at presentation. It is also noted that as the disease progresses, clinical manifestations may change.

Current Therapies and Unmet Medical Need

The goal of HES treatment is to reverse or delay progression of any further organ damage caused by activated eosinophils. The current approach is based on reduction of blood eosinophilia, reduction of active inflammation, suppression of the immune response, and treatment of disease-specific and/or treatment-related complications. SoC therapy for patients with HES includes glucocorticosteroids (for F/P negative or F/P positive with cardiac involvement at diagnosis) or imatinib (for F/P positive) as first-line therapy and cytotoxics (e.g., hydroxyurea, cyclophosphamide) or immunomodulators (interferon alpha [INFα], cyclosporine, immunoglobulin) as second-line agents [Roufosse, 2010]. Clinical responses to these therapies, however, are incomplete or inadequate in over 80% of HES patients (among those negative for F/P mutation).

The discovery of the F/P mutation in patients with myeloproliferative HES and its response to imatinib has improved survival and quality of life in this subpopulation [Klion, 2009; Wechsler, 2012]. For the majority of patients however, the only currently available treatment options are limited to chronic high doses of corticosteroids, IFNα, and cytotoxic agents such as hydroxyurea and cyclophosphamide. The efficacy of these agents, even in combination, is not always adequate and side effects with long-term use are significant. Additional agents with increased efficacy and decreased toxicity are therefore greatly needed.

Although not approved for use in HES, corticosteroids are used in clinical practice as first-line treatment for most patients with HES due to lack of available options [Ogbogu, 2009; Helbig, 2010]. The therapeutic strategy is to start with a moderate to high dose (≥40mg/day prednisone or equivalent) and taper very slowly while monitoring the blood eosinophil count closely. Using this approach, most patients (85%, N=141) will respond initially to steroid therapy based on a decrease of eosinophil count to normal range and symptomatic improvement. However, many HES patients (72%, N=179) will need to be maintained on low steroid doses (median 10mg/day) for long periods of up to 20 years since discontinuation of corticosteroids leads to eosinophilia and symptomatic recurrence in most patients [Klion, 2009; Ogbogu, 2009; Helbig, 2010].

The initial response to corticosteroid treatment is often positive, however long-term use is associated with significant and commonly reported side effects, including truncal obesity, moon facies, buffalo hump, increased blood pressure, weight gain, muscle atrophy, hyperglycemia, delayed wound healing, cataracts and glaucoma, peptic ulcers, and increased risk of infection [Poetker, 2010]. Therefore, with chronic use, the toxicities of steroid therapy become limiting, patient adherence diminishes, and additional or alternative corticosteroid-sparing therapies must be used [Roufosse, 2013]. The chronic use of corticosteroids is often discontinued (42%, N=179) or used in combination therapy (33%, N=179) due to toxicity or failure in the majority of HES patients [Ogbogu, 2009].

In the absence of targeted approved therapies for HES, several second line agents have been used based on empirical observational evidence of benefit. Commonly used second-line therapies include chemotherapeutic agents such as hydroxyurea, IFNα, and other cytotoxics (e.g., cyclosporine, vincristine, methotrexate, busulfan). These second-line agents are effective (defined as a decrease of eosinophil count and symptomatic improvement) only in a small number of HES patients, are associated with significant toxicities, have a slow onset of therapeutic effect, and confer an increased risk of patients developing malignancy. For example, the most commonly used second-line agent, hydroxyurea, is rarely useful as a single agent and its side effects and lack of efficacy result in discontinuation in the majority of patients (77%, N=64) [Ogbogu, 2009].

As described herein, due to the significant tolerability issues related to long-term use of corticosteroids and other chemotherapeutics, new alternative therapies with a positive risk:benefit profile are needed.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To demonstrate the efficacy of mepolizumab compared with placebo based on maintenance of control of HES symptoms during the treatment period.	• Proportion of subjects who experience an HES flare during the 32-week study treatment period
Secondary	
• To demonstrate supportive evidence of the benefit of	• Time to first HES flare

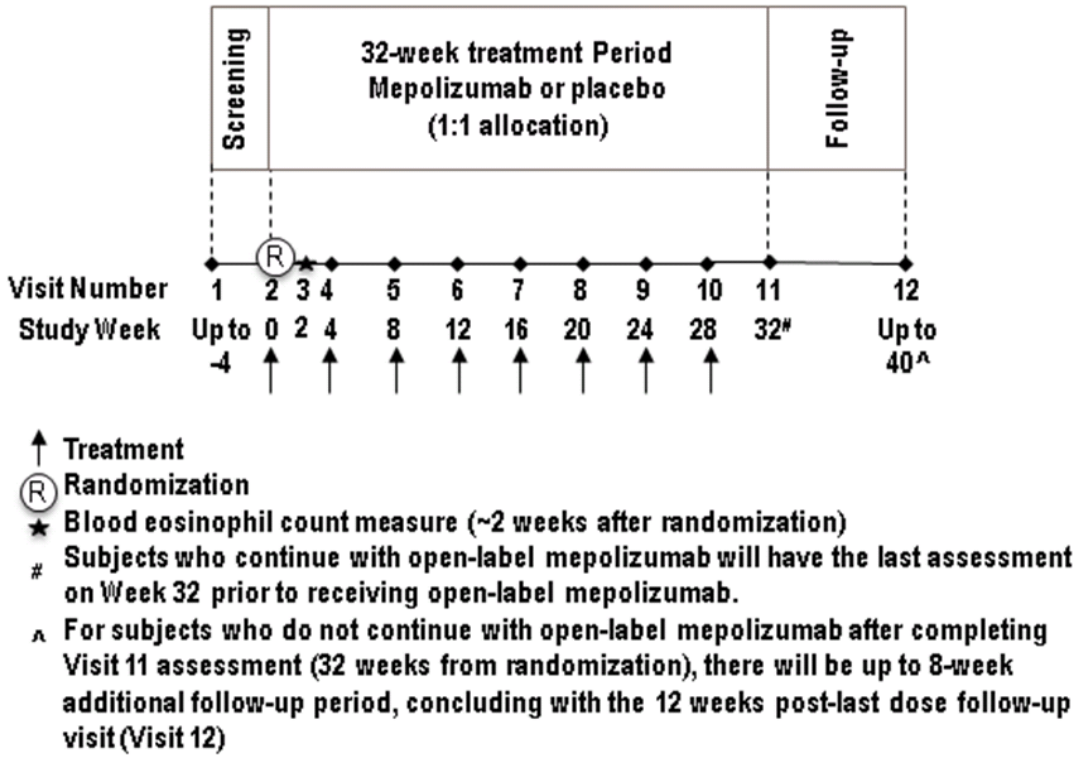
Objectives	Endpoints
mepolizumab compared with placebo based on other measures of efficacy.	• Proportion of subjects who experience an HES flare during Week 20 through Week 32 • Rate of HES flares • Change from baseline in fatigue severity based on Brief Fatigue Inventory (BFI) item 3 (worst level of fatigue during past 24 hours) at Week 32
Exploratory	
• To investigate mepolizumab compared with placebo with respect to additional measures of efficacy.	• Proportion of subjects who receive blinded active OCS due to an elevated blood eosinophil level that meets the pre-defined threshold during the 32-week study treatment period • Lung function tests (FEV_1, FVC, and ratio) • Echocardiogram
• To investigate the efficacy of mepolizumab compared with placebo with respect to patient and clinician reported symptoms, health status, and disease impact.	• Change from baseline in HES symptom severity based on HES Daily Symptoms (HES-DS) at Week 32 • Change from baseline in the BFI total and domain scores at Week 32 • Proportion of subjects with a favorable response as measured by clinician- and subject-rated overall response to therapy score (RTS) at Week 32 • Change from baseline in Subject-rated symptom severity (SSR) at Week 32 • Change from baseline in Modified Memorial Symptom Assessment Scale-Short Form (MSAS-SF) responses at Week 32 • Change from baseline in physical function (Patient Reported Outcome Measurement Information System [PROMIS] physical function items) at Week 32 • Change from baseline in sleep (PROMIS sleep items) at Week 32

Objectives	Endpoints
• To characterize the patient burden of HES.	• SF-36 v2 • Healthcare resource utilization (HCRU) • Work Productivity and Activity Impairment Index – General Health (WPAI-GH) v2 • Steroid perception questionnaire
• To investigate the pharmacokinetics (PK) of mepolizumab.	• Plasma concentration of mepolizumab
• To investigate the pharmacodynamics (PD) of mepolizumab.	• IL-5 levels (serum free and total) • Blood eosinophil levels
Safety	
• To evaluate the safety of mepolizumab compared with placebo in subjects with HES receiving standard of care treatment over a 32-week study treatment period	• Adverse events including local injection site reactions and systemic reactions (e.g., hypersensitivity) • Vital signs • 12-lead ECG • Hematological and clinical laboratory tests • Immunogenicity (anti-drug antibody)

4. STUDY DESIGN

4.1. Overall Design

Figure 1 Study schematic



This is a 32-week treatment period, randomized, double-blind, placebo-controlled, parallel group, multicentre study of mepolizumab in adolescent and adult subjects with severe HES receiving SoC therapy (Figure 1).

4.2. Treatment Arms and Duration

- The study is comprised of a screening period of up to approximately 4 weeks followed by a 32-week study treatment period and up to 8-week additional follow-up period (12 weeks after the last dose of study treatment).

- Approximately 80 subjects who are able to maintain a stable regimen of HES therapy for the 4 weeks prior to Visit 2 will be randomized in a 1:1 ratio to receive either 300 mg mepolizumab *or* placebo SC every 4 weeks while continuing their HES therapy. The sample size may be increased up to a maximum of 120 subjects in total (Section 9.2.3). The same regimen of HES therapy will be maintained throughout the 32-week study treatment period unless there is worsening of symptom(s) that requires an increase in therapy. A reduction in dose for safety reasons, with return to the original dosing regimen if possible, is permitted in consultation with the GSK Medical Monitor.

- The final dose of study treatment will be administered at Visit 10 (Week 28) with completion of the study treatment period achieved at the next 4-weekly visit. At Visit 11 (Week 32), subjects will complete the end-of-treatment assessment (4 weeks after the last dose).

- Subjects who withdraw from study treatment prematurely should continue in the study per protocol (including HES flare-related assessments) until 32 weeks from randomization.

- For subjects whose last dose of study treatment is on Visit 9 (Week 24) or Visit 10 (Week 28) *and* who do not continue with open-label mepolizumab after completing Visit 11 assessment (32 weeks from randomization), there will be up to 8-week additional follow-up period, concluding with the 12 weeks post-last dose follow-up visit (Visit 12).

- Subjects will be eligible to be considered to receive open-label mepolizumab 300 mg SC every 4 weeks after *either*:

  i. Completion of the treatment period in the 200622 study

  or

  ii. If the subject was withdrawn from study treatment prematurely during the 200622 study, but continued in the study per protocol (including HES flare-related assessments) until 32 weeks from randomization.

- Subject management during the study will be according to routine medical care, i.e., subjects will be instructed to contact their investigator for evaluation or seek emergency care as necessary when they experience worsening of symptoms as per their usual practice. The investigator will use the HES Core Assessments (Section 7.3.2) to assess for the presence of a HES flare (unscheduled 'Flare' visit in Section 7.1).

- Investigators, participating subjects, and GSK study personnel will be blinded to absolute blood eosinophil counts, total white blood cell counts, and white blood count differentials (%) from randomization (Visit 2) until completing the 32-week period from randomization. Blood eosinophil-unblinded GSK personnel/delegates not involved with other aspects of study conduct will monitor the absolute blood eosinophil count results and trigger blinded OCS treatment to treat an eosinophilia when the blood eosinophil count reaches a pre-defined threshold (Section 6.4).

- An IDMC will be utilized in this study (Section 10.8).

4.3. Type and Number of Subjects

Subjects entering the study must have experienced at least two HES flares within the past 12 months and have a blood eosinophil count of 1000/μL or higher during screening. Historical HES flares for the study entry criteria are defined as documented HES-related worsening of clinical symptoms or blood eosinophil counts requiring an escalation in treatment. In addition, at least one HES flare within the past 12 months must not be

related to a decrease in HES therapy during the 4 weeks prior to the flare. For further details on the study entry criteria, see Section 5.

Approximately 80 subjects will be randomized in the initial recruitment phase. The proportion of subjects that have an HES flare will be monitored and the total number of subjects randomized may be increased if the blinded overall rate is predicted to be <30%. The sample size may be increased up to a maximum of 120 subjects in total.

4.4. Design Justification

HES Therapy

This study is designed to evaluate the efficacy and safety of mepolizumab in adolescent and adult subjects with severe HES receiving SoC therapy. Allowing use of background SoC therapy supports inclusion of a placebo group contributing to a favorable benefit:risk profile for participating subjects. While permitting standard HES therapy during the study, an increase in the dose or addition of new therapy will not be allowed within 4 weeks prior to randomization. This requirement is to avoid randomizing subjects that are at risk of an imminent disease flare upon the start of study treatment. If a subject has worsening of symptom(s) and requires an increase in therapy after randomization (Section 7.3.1), the subject will be considered to be experiencing an HES flare.

Study Population

To demonstrate the efficacy of mepolizumab compared with placebo in subjects receiving standard HES therapy, the study will enroll subjects with severe HES. For identification of such a population, the study requires subjects to experience at least two HES flares within the past 12 months and have a blood eosinophil count of 1000/μL or higher during screening.

Overall, the study population describes a group of subjects considered likely to benefit from addition of mepolizumab to existing therapy. The study population will exclude patients with mild disease, since it is less likely that mepolizumab will show a clear benefit in this comparatively well-controlled population. Subjects with uncontrolled organ-threatening or life-threatening disease will also be excluded from the study (Section 5.2).

Study Treatment Duration

The total study treatment duration is 32 weeks. This length will provide adequate treatment duration to support the registration of mepolizumab for the indication under investigation. The duration of blinded study treatment is limited to 32 weeks to minimize the duration of time that investigators will be blinded from the blood eosinophil counts which are used in SoC to manage patients with HES.

Blood Eosinophil Blinding and Monitoring

The effect of mepolizumab on blood eosinophil counts is rapid, readily observable, and dramatic and may lead to inadvertent unblinding of the treatment assignment. Therefore,

in this study, investigators, participating subjects, and GSK study personnel will be blinded to absolute blood eosinophil counts, total white blood cell counts, and white blood count differentials (%) from randomization (Visit 2) to the end of the study (Section 6.4). Since initiating treatment based on an increase in eosinophil levels alone (without clinical symptoms) is part of SoC for HES patients, blood eosinophil-unblinded GSK personnel/delegates not involved with other aspects of study conduct will monitor the absolute eosinophil count results and trigger blinded OCS treatment to treat an eosinophilia flare. This is to ensure that subjects will not be placed at undue risk during the study, while maintaining the treatment blind.

Definition of a Disease Flare for the Primary Endpoint

Clinical manifestations in HES patients vary widely depending on specific organ involvement. This variability, combined with the lack of a validated biomarker, leads to persistent challenges in defining appropriate endpoints for disease characterization. The pragmatic approach proposed for this Study 200622 is modeled after severe asthma study MEA112997 [Pavord, 2012] and EGPA study MEA115921 (ClinicalTrials.gov Identifier. NCT02020889). In the severe asthma study, clinically significant asthma *exacerbations* were defined as "validated episodes of acute asthma requiring treatment with oral corticosteroids, hospital admission, or a visit to an emergency department" [Pavord, 2012]. In the EGPA study, disease *relapse* is defined as worsening or persistence of active disease since the last visit characterized by active vasculitis, active asthma symptoms, or active nasal and/or sinus disease warranting an increase in OCS therapy, or an increased dose or addition of immunosuppressive therapy, or hospitalization related to EGPA worsening. In this study, disease *flare* (HES flare) is defined as (1) an HES-related clinical manifestation based on a physician-documented change in clinical signs or symptoms resulting in the need for therapy adjustment (increase in OCS dose of at least 10mg/day or any increase in or addition of any cytotoxic/ immunosuppressive HES therapy) or (2) receipt of two or more courses of blinded active OCS during the study treatment period. The primary objective of the study is to demonstrate maintenance of control of HES symptoms during the treatment period as evident by the absence of HES flares.

HES Core Assessments to Monitor Disease Activities and Identify HES Flares during the Study

The clinical presentation of HES covers a wide variety of end-organ manifestations. In an effort to assess the clinical manifestations in the most commonly affected organ systems in patients with HES, the **HES Core Assessments** (Section 7.3.2) will be utilized by the investigators to characterize the disease at baseline and also to monitor the changes during the treatment period. This core assessment is the product of collective input from a panel of experts in the field and will provide the consistent framework for the investigators to assess an HES flare. The HES Core Assessments will be used to record the subject's clinical manifestations, but ultimately investigators will use their clinical judgment to determine if a subject is experiencing an HES flare.

4.5. Dose Justification

A dose of mepolizumab 300 mg administered SC every 4 weeks has been selected for investigation in this study. The dose selected is lower than the 750mg IV administered every 4 weeks previously investigated in a HES study (MHE100185). The dose selection was guided by information observed during the uncontrolled phase of an open-label extension HES study MHE100901 during which dosing interval was tailored (4 to 12 weeks) according to individual patient disease and response, including blood eosinophil count assessment [Roufosse, 2013].

In support of the dose selection, a dose-response meta-analysis for blood eosinophil reduction (a proxy marker of pharmacology), including data from sixteen studies and various eosinophilic conditions, albeit dominated by asthma, was carried out [GlaxoSmithKline Document Number 2015N238375_00]. Results highlighted differences between severe asthma and HES populations and confirmed the effects of OCS on blood eosinophil suppression in both diseases. Dose response models confirmed that baseline blood eosinophil count is an important determinant of overall response, with both location and maximum achievable drug inhibition being baseline-dependent. Inversion of the dose response showed that to achieve clinically meaningful target absolute blood eosinophil counts in patients with HES, doses higher than the therapeutic severe asthma dose of 100 mg SC are required. Although HES experts recognise that there is no universal blood eosinophil level or degree of suppression cut-off at which clinical benefit would be expected in all HES patients, considering that the current therapeutic option aims to maintain blood eosinophils as low as possible, it is not unreasonable to target a level within a normal range, i.e., <500 cells/µL and ideally between 200-300 cells/µL in the majority of HES patients. Acknowledging the limitations of extrapolation outside the range of data included in the dose-response model (to adjust for the effects of concomitant OCS treatment), it is predicted that patients with a Baseline blood eosinophil count between 1000 (minimal level required at Baseline in the proposed study) and 8000 cells/µL would achieve a blood eosinophil count between 100-500 cells/µL following a SC dose of mepolizumab 300 mg every 4 weeks [Figure 17 of GlaxoSmithKline Document Number 2015N238375_00]. Further analysis shows however that there will be limited additional benefit beyond this dose.

This dose should also be able to prevent bursts of blood eosinophils, which are triggered by external factors not very well understood and/or following OCS reduction as part of SoC in clinical practice, and subsequently prevent flare.

The selection of the 4-week dosing interval is supported by mepolizumab half-life of approximately three weeks, the dose response meta-analysis, also based on a dosing interval of every four weeks, and the consistent maintenance of pharmacological effect over this 4-week dosing interval at doses of mepolizumab 75 mg IV/100 mg SC and higher (MEA112997) [Pavord, 2012].

Mepolizumab has been studied in patients with HES at doses three-fold higher than proposed in this study for durations of up to 11 years. During this time no apparent safety signal has been detected and no clinically meaningful trends in hematology or clinical chemistry have been noted. Data from mepolizumab treatment over a 10-fold

range (75 to 750 mg IV every 4 weeks) in patients with severe asthma also have not shown any apparent increase in adverse events or laboratory abnormalities and hence an absence of response and dose-response to increasing doses of mepolizumab. Of note a 300 mg SC mepolizumab dose is currently under investigation in an ongoing randomized, placebo-controlled study in patients with EGPA (MEA115921), a disease which shares many similarities with HES with regards to blood eosinophil levels at the time of diagnosis and also multi-organ involvement. Therefore, in addition to this placebo-controlled study assessing 300 mg SC dose of mepolizumab for the treatment duration of 32 weeks, Study MEA115921 will provide one-year safety data at 300 mg SC that may also be concomitantly administered with immunosuppressive therapies.

Taken together, the above information suggests a mepolizumab dose of 300 mg SC (delivered 3x100mg SC injections) every four weeks could provide clinical benefit in the HES patient population targeted in the HES Study 200622, and has therefore been selected for investigation for a treatment duration of 32 weeks.

4.6. Benefit:Risk Assessment

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

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Investigative Medicinal Product (IMP): Mepolizumab		
Pre-Clinical and Clinical Findings		
Risk of Systemic Reactions (e.g., hypersensitivity) and Local Injection Site Reactions	• In the placebo-controlled severe asthma studies both acute and delayed systemic reactions including hypersensitivity have been reported following administration of mepolizumab with incidence rates similar between mepolizumab and placebo-treated subjects (6% in the mepolizumab [all doses combined] group and 3% in the mepolizumab [100 mg SC/75 mg IV] combined group as compared with 5% in the placebo group). The most common symptoms reported with any systemic reaction included headache, rash, pruritus, fatigue, and dizziness. • In the placebo-controlled severe asthma studies an increase in the incidence of local injection site reactions has been observed with SC administration of mepolizumab compared with placebo (8% vs. 3%). There have been no reports of severe reactions. Pain, erythema, swelling, itching, and burning sensation were the most common symptoms reported. • 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 AEs (SAEs) by GSK Medical Monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team. • Specific case report form (CRF) pages utilized for targeted collection of systemic and local reactions data. • Utilization of anaphylaxis diagnostic criteria as outlined by the 2006Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (see Section 12.6). • Subjects are monitored in clinic for 1 hour for the 1st three administrations following dosing, then follow monitoring policies for the center. • An IDMC will be utilized during study.
Potential Risk of Immunogenicity	• Biopharmaceutical products may elicit anti-drug antibody (ADA) and neutralizing antibodies (NAB), which have the potential to modulate pharmacokinetics (PK),	To characterize the potential risk of immunogenicity: • Blood samples are collected in clinical studies for detection

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	pharmacodynamics (PD) or produce adverse reactions. However, humanized and fully human antibodies are less immunogenic than mouse or chimeric monoclonal antibodies. • In the placebo controlled severe asthma studies low incidence (6% 100 mg SC and 2% all IV doses) and low titer of ADA and neutralizing antibodies have been reported. To date there have been no apparent association with adverse events, loss of disease control and/or markedly altered PK or PD profiles associated with anti-mepolizumab antibodies in any subjects. • Immunogenicity data reported to date across the mepolizumab development program are summarized in the IB; see Section 5.4. 'Clinical Immunogenicity' and a summary of immunogenicity findings in the 'Other Potentially Clinically Relevant Information for the Investigator' section located in Section 6 titled 'Summary of Data and Guidance for the Investigator'.	of both ADA and NAB. • PK/PD assessments will be conducted. • For subjects who develop anti-mepolizumab antibodies systematic review of AE/SAE data at the end of the study (after unblinding) will be conducted.
Potential risk for adverse cardiovascular (CV) effects	• Mepolizumab binding was restricted to human lymphoid tissues in an immunohistochemistry tissue binding study suggesting a low likelihood of non-pharmacologic effects on CV function. • No AEs concerning cardiac conduction or repolarization evident in cynomolgus monkeys at doses at least 10-fold in excess of humans dosed at 10 mg/kg or 750 mg. • No clinically relevant trends observed in electrocardiogram (ECG) data in humans.	• Daily monitoring of SAEs by GSK Medical Monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team. • CV monitoring for study includes: o Enhanced baseline collection of CV risk factors & functional status; o Baseline evaluation of clinical symptoms of ischemic heart disease, if clinically indicated; o Use of GSK standard CRFs to collect additional

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	• In study **MHE100185** HES subjects received mepolizumab 750 mg IV every 4 weeks for up to 36 weeks, cardiac events were reported by 7% of subjects in both mepolizumab and placebo arm s. There was 1 death, due to cardiac arrest in the mepolizumab group not considered related to mepolizumab treatment. This subject had severe HES with multiple cardiovascular complications and concurrent renal failure. Other cardiac disorder AE occurred is palpitation (2 subjects in the mepolizumab group and 1 subject in the placebo group). The following events reported in the placebo arm only: cardiovascular disorder, arterial dilatation, ventricular dysfunction and ventricular hypertrophy. • In study **MHE100901** (open-label extension [OLE] study to MHE100185 above), subjects received mepolizumab 750 mg IV for up to 67 months, 1 fatal and 2 non-fatal SAEs reported due to cardiac failure, none considered related to mepolizumab. • In study **MHE104317** (compassionate use) 7% of patients reported SAEs of cardiac disorders. 3 SAEs reported, 1 secondary to CHF, 1 due to cardiac arrest, & 1 due to MI, all were considered unrelated to mepolizumab. **Severe Asthma:** • In Study MEA112997, a numeric imbalance in the number of serious cardiac events was observed for mepolizumab (7 subjects: 2/153 on 75 mg IV [3 events: myocardial ischemia, acute myocardial infarction, coronary artery thrombosis], 1/152 on 250 mg IV [1 event: coronary artery insufficiency] and 4/156 on 750 mg IV [4 events: myocardial	data on selected CV events (i.e., myocardial infarction, hospitalization for unstable angina and congestive heart failure, arterial thrombosis, pulmonary embolism and deep vein thrombosis). • An IDMC will be utilized during study.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	ischemia, atrial fibrillation, myocardial infarction and supraventricular tachycardia]) compared with placebo (1 of 155 subjects reported atrial flutter). This imbalance was not replicated in subsequent Phase III placebo-controlled studies, MEA115588 and MEA115575, and it was not observed previously in other controlled asthma trials or in other populations studied such as HES. • In the OLE studies, cardiovascular events were similar in frequency and type with those reported from the placebo-controlled severe asthma (PCSA) studies. • Cardiovascular events in the severe asthma program are summarized under AESI section of the IB.	
Potential risk of alterations in immune response, potentially leading to increase in infections	• This is a theoretical concern with biologics; however, critical review of preclinical toxicity data and pharmacological properties of mepolizumab suggests that the risk for potential immunotoxicity is low. • No evidence of increased incidence of infections in any preclinical studies. • Murine data demonstrate that IL-5 antagonism is unlikely to influence cellular or humoral immunity, particularly in response to parasitic infections. • No mepolizumab-related effects on lymphocyte immunophenotyping in monkeys or humans, including T-cell activation, distribution of CD4/CD8 subtypes or Th1/Th2 cytokine patterns, B-cells, NK cells or γδ-T-cells. • Across all PCSA, the frequency of subjects with infections	• Eosinophils may be involved in the immunological response to some helminth infections. Subjects with recent parasitic (helminth) infections will be excluded from the study or required to be adequately treated for helminth infections before initiation of study treatment. If a subject becomes infected whilst receiving study treatment and does not respond to anti-helminth treatment, temporary discontinuation of study treatment should be considered in consultation with GSK Medical Monitor. • Daily monitoring of SAE by GSK Medical Monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team • An IDMC will be utilized during study.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	was similar between placebo (239/412 or 58%), mepolizumab 100 mg SC (136/263 or 52%) and mepolizumab 75 mg IV (209/344 or 61%). • In the OLE studies, rates of infections, including all infections, serious and opportunistic infections, were similar to those from the PCSA studies. • 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' HES subsection (for very common infections of nasopharyngitis, upper respiratory tract infection (URTI), rhinitis and bronchitis reported in other patient populations) sections located in Section 6 titled 'Summary of Data and Guidance for the Investigator'.	
Potential risk of alterations in immune response potentially leading to increase in malignancies	• Non-clinical and clinical experience to date does not support a role for mepolizumab in the development of malignancies. No evidence of defective tumor surveillance in IL-5 or eosinophil-deficient mice. Mepolizumab is not believed to possess an inherent carcinogenic potential or increase the susceptibility to tumor formation secondary to significant immunosuppres-sion, and there is no evidence to date that mepolizumab has produced immunosuppression in animals. • Reports of malignancies in the overall mepolizumab program (including asthma, HES, other eosinophil-driven diseases & healthy subjects) were similar across treatment groups and are those types common in the general population with a frequency rate of <1% at all individual doses and all doses of	• Subjects with a history of lymphoma or current lymphoma will be excluded from the study. • Exclusion of subjects with current malignancy or previous history of cancer in remission for less than 12 months prior to randomization (Visit 2). Subjects that had localized carcinoma (i.e., basal or squamous cell) of the skin which was resected for cure will not be excluded. • Daily monitoring of SAEs by GSK Medical Monitor; regular systematic review of AE/SAE data from this study by a GSK safety review team • An IDMC will be utilized during study.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	mepolizumab combined. A review of a well established cohort of patients with hyperoesinophilia including those with HES at the Mayo clinic showed that 5.1% developed hematologic malignancy over 13-year period; the median time the malignancy developed was 10 months after the onset of hypereosinophilia. T-cell derived malignancies were most commonly diagnosed [Jin, 2015]. • Malignancies, including lymphoma, reported to date across the mepolizumab program (severe asthma and HES) are summarized in the IB; see also 'Special Warnings and Special Precautions for Use' section located in IB Section 6 titled 'Summary of Data and Guidance for the Investigator'.	
Potential risk for exaggerated response of symptoms upon cessation of treatment	• No apparent rebound eosinophilia observed in monkeys treated with mepolizumab. • Across the PCSA program, post-treatment AEs of asthma did not appear to occur at a significantly greater incidence following cessation of treatment with mepolizumab compared with placebo.	• Daily monitoring of SAEs by GSK Medical Monitor; regular systematic review of AE/SAE data from ongoing studies by a GSK safety review team • An IDMC will be utilized during study.
Study Procedures		
Blinding eosinophil counts	• This study is a double-blind study which will be used to support approval of the use of mepolizumab in the treatment of HES. Unblinding eosinophil counts would compromise the integrity of the study.	• An IDMC will be utilized during study. • Blood eosinophil-unblinded GSK personnel/delegates not involved with other aspects of study conduct will monitor the absolute eosinophil count results and trigger blinded OCS treatment to treat an eosinophilia flare (Section 6.4).

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
		Investigators, participating subjects, and GSK study personnel will be blinded to absolute blood eosinophil counts, total white blood cell count, and white blood count differentials (%) from randomization to the end of the study.

4.6.2. Benefit Assessment

Study 200622 is a 32-week treatment period, randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of mepolizumab in the treatment of HES in adolescent and adult subjects receiving SoC therapy.

Data from three completed studies support the clinical utility/proof-of-concept of mepolizumab in the treatment of HES having demonstrated the use of mepolizumab to allow for a safe reduction of corticosteroid dose while maintaining clinical stability (MHE100185 [Rothenberg, 2008] and CRT112446 [Stein, 2008]) and safety (MHE100901 [Roufosse, 2013]) in subjects with HES. In addition, the interim review of the mepolizumab HES compassionate use program (MHE104317 as well as named patient supply [MHE112562 and 112000]) with over 200 patients (data cut-off date of 23 September 2013) demonstrated that mepolizumab is well tolerated and provides long-term clinical benefit to some patients with HES [GlaxoSmithKline Document Number ZM2006/00080/04; Duncan, 2015]. Furthermore, mepolizumab has also demonstrated clinical benefit in other conditions where eosinophilia is considered to play an important part in the pathology, e.g., severe asthma [Haldar, 2009; Nair, 2009; Pavord, 2012], EGPA [Kim, 2010] and EoE [Stein, 2006].

In addition, subjects will attend monthly visits and therefore may benefit from the additional disease monitoring and interaction with health care professionals.

Data obtained from Study 200622 will provide a robust clinical evaluation of the efficacy and safety of mepolizumab in the treatment of HES. It is planned to use the study results and supporting data as the basis for global regulatory submissions for mepolizumab for the treatment of HES.

4.6.3. Overall Benefit:Risk Conclusion

Data from mepolizumab preclinical and clinical development support the ability of mepolizumab to inhibit IL-5, and consequently treat conditions associated with eosinophilia, such as HES. To date, the safety profile of mepolizumab has been favorable. Furthermore, there are no safety concerns with mepolizumab to date that would preclude investigation in HES. The Sponsor therefore maintains that investigation of the efficacy, safety and tolerability of mepolizumab is justified in Study 200622.

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 (IP) or other study treatment that may impact subject eligibility is provided in the IB [GlaxoSmithKline Document Number CM2003/00010/10].

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

5.1. Inclusion Criteria

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

INFORMED CONSENT
1. Capable of giving signed informed consent/assent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

AGE
2. 12 years of age or older, at the time of signing the informed consent/assent

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
3. Subjects who have been diagnosed with HES for at least 6 months at randomization (Visit 2). HES diagnosis is based on signs or symptoms of organ system involvement and/or dysfunction that can be directly related to: • blood eosinophilia of >1,500 eosinophils/μL on at least two occasions, and/or • tissue eosinophilia documented prior to Visit 2 without a discernible secondary cause (e.g., drug hypersensitivity, parasitic helminth infection, human immunodeficiency virus [HIV] infection, non-hematologic malignancy). Tissue eosinophilia is defined as a history of one or more of the following: • The percentage of eosinophils exceeds 20% of all nucleated cells in bone marrow sections. • In the opinion of a pathologist, tissue infiltration by eosinophils is extensive (massive) when compared with the normal physiologic range, compared with other inflammatory cells, or both. • A specific stain directed against an established eosinophil granule protein (e.g., major basic protein) reveals extensive extracellular deposition of eosinophil-derived proteins indicative of local eosinophil activation [Valent, 2012].
4. A history of two or more HES flares within the past 12 months prior to screening (Visit 1). *Historical HES flares* are defined as documented HES-related worsening of clinical symptoms or blood eosinophil counts requiring an escalation in therapy. At least one HES flare within the past 12 months must not be related to a decrease in HES therapy during the 4 weeks prior to the flare.
5. Subjects must have blood eosinophil count ≥1000 cells/μL present in the sample collected during screening (within 4 weeks prior to randomization).
6. Subjects must be on a stable dose of HES therapy for the 4 weeks prior to randomization (Visit 2). HES therapy includes but is not limited to oral

corticosteroid (OCS), immunosuppressive, and cytotoxic therapy.

SEX

7. Male or female

A female subject is eligible to participate if she is not pregnant (as confirmed by a negative urine human chorionic gonadotrophin [hCG] test), not lactating, and at least one of the following conditions applies:

a. Females of non-reproductive potential (FNRP) defined as:

- Post-menopausal women (including all women over 60 years of age, see below), OR

  Pre-menopausal females with one of the following procedures documented and no plans to utilize reproductive techniques (e.g., in vitro fertilization or donor embryo transfer:

  - Bilateral tubal ligation or salpingectomy
  - Hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
  - Hysterectomy
  - Bilateral Oophorectomy (surgical menopause)

- Post-Menopause
  - Females 60 years of age or older
  - Menopause is the phase associated with complete cessation of menstrual cycles and implies the loss of reproductive potential by ovarian failure. This typically occurs around 50 years of age, although it may occur earlier or later. A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile, e.g., age appropriate, >45 years, in the absence of hormone replacement therapy (HRT) or medical suppression of the menstrual cycle (e.g., leuprolide treatment).
  - In questionable cases for women < 60 years of age, a blood sample with simultaneous follicle stimulating hormone and estradiol falling into the central laboratory's postmenopausal reference range is confirmatory (these levels need to be adjusted for specific laboratories/assays) [Kronenberg, 2008; Strauss, 2004].
  - Females under 60 years of age, who are on HRT and wish to continue, and whose menopausal status is in doubt, are required to use a highly effective method to avoid pregnancy, as outlined in the protocol. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT.

Following confirmation of their post-menopausal status, they can resume use of HRT during the study without use of a highly effective method to avoid pregnancy. If laboratory values for FSH and estradiol are drawn and the results do not confirm menopause on a potential subject that otherwise met the specifications for being post-menopausal defined above without question, the subject may still enrol in the study as a FNRP if approved by the GSK Medical Monitor and the safety physician.

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 Section 12.5) from 30 days prior to the first dose of study medication and until 4 months after the last dose of study treatment.

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

5.2. Exclusion Criteria

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

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Life-threatening HES or life-threatening HES co-morbidities: Imminently life-threatening HES disease severity such that the likelihood of death is high unless the course of the disease is interrupted within 12 weeks prior to randomization (Visit 2).
2. Other concurrent medical conditions that may affect the subject's safety: Subjects who have known, pre-existing, *clinically significant* endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, hematological, respiratory or any other system abnormalities that are not associated with HES and are uncontrolled with standard treatment.
3. Eosinophilia of unknown clinical significance
4. 12-lead ECG finding: QTc > 450 msec *or* QTc > 480 msec in subjects with bundle branch block An abnormal ECG finding from the 12-lead ECG conducted at Visit 1 if considered to be clinically significant and would impact the subject's participation during the study based on the evaluation of the Investigator. NOTE: 12-lead ECG results at screening (Visit 1) with the over-read by the centralized independent cardiologist must be received prior to assessing eligibility at Visit 2 by the Investigator.
5. Subjects with documented history of any clinically significant cardiac damage prior to screening (Visit 1) that, in the opinion of the investigator, would impact the

subject's participation during the study.

6. Liver abnormality/disease:
   - ALT >2.5xULN *or* ALT>5xULN if documented HES with liver manifestations
   - 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).

     NOTE: Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice, or cirrhosis.

     NOTE: Chronic stable hepatitis B and C (e.g., presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment) are acceptable if subject otherwise meets entry criteria.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA

7. Clinical diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA)
8. Malignancy:
   - Subjects with a history of *or* current lymphoma
   - Subjects with current malignancy or previous history of cancer in remission for less than 12 months prior to randomization (Visit 2). Subjects that had localized carcinoma (i.e., basal or squamous cell) of the skin which was resected for cure will not be excluded.
9. FIP1L1-PDGFRα Status: Subjects who test positive for the FIP1L1-PDGFRα fusion tyrosine kinase gene translocation.

   Blood sampling is required for all subjects at screening (Visit 1) for this test unless the documented result is available.
10. Infection:
    - Subjects with chronic or ongoing active infections requiring systemic treatment, as well as subjects who have experienced clinically significant infections due to viruses, bacteria, and fungi within 4 weeks prior to randomization (Visit 2).
    - Subjects with a pre-existing helminthes infestation within 6 months prior to randomization (Visit 2).
11. Subjects with a known immunodeficiency (e.g., HIV), other than that explained by the use of OCS or other therapy taken for HES.
12. Other laboratory abnormalities: Evidence of clinically significant abnormality in the hematological, biochemical or urinalysis screen from the sample collected at screening (Visit 1), that could put the subject's safety at risk by participating in the

study, as judged by the investigator

CONCOMITANT MEDICATIONS
13. Subjects who have previously received mepolizumab in the 4 months prior to randomization (Visit 2). 14. Subjects receiving any of the following: • Intravenous or subcutaneous corticosteroids in the 4-week period prior to randomization (Visit 2). • Any other monoclonal antibodies within 30 days or 5 half-lives, whichever is longer, of randomization (Visit 2). 15. Other investigational product/clinical study: • Subjects who have received treatment with an investigational agent (biologic or non-biologic) within the past 30 days or 5 drug half-lives whichever is longer, prior to randomization (Visit 2). The term "investigational" applies to any drug not approved for sale in the country in which it is being used or investigational formulations of marketed products • Subjects who are currently participating in any other interventional clinical study

CONTRAINDICATIONS
16. Subjects who are not responsive to OCS based on clinical response or blood eosinophil counts 17. Subjects with any history of hypersensitivity to any monoclonal antibody (including mepolizumab) or any steroid or steroid-containing product.

RELEVANT HABITS
18. Subjects with a known or suspected history of alcohol or substance abuse at screening (Visit 1) which in the opinion of the investigator could interfere with the subject's proper completion of the protocol requirement.

5.3. Screening/Baseline/Run-in Failures

A subject will be assigned a subject number at the time when the informed consent form (ICF) is signed.

A subject who is assigned a subject number, but does not complete any Visit 1 procedures will be considered a **pre-screen failure**. A minimal set of pre-screen failure information including Demography and any SAEs will be collected.

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and SAE.

For both pre-screen and screen failures, HES diagnosis, HES flares and HES medications taken within the 12 months prior to Visit 1 will be collected.

Re-screening of subjects will be allowed only upon approval by the GSK Medical Monitor.

5.4. Withdrawal/Stopping Criteria

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

Withdrawal from study treatment

Subjects who discontinue study treatment prematurely (for any reason) should, where possible, continue in the study per protocol (Refer to Section 7.1 – Visits 3-11 for subjects who prematurely discontinue study treatment) until 32 weeks after randomization, including the collection of biological samples for laboratory assessments approximately 4 weeks and 12 weeks after the last dose of study treatment as well as daily eDiary completion. Subjects will be considered to receive open-label mepolizumab after 32 weeks lapse from randomization, completing 'Visit 11 for subjects who prematurely discontinue study treatment' (Section 4.1). If a subject's last dose of study treatment was on Visit 9 (Week 24) and the subject does not continue with open-label mepolizumab after completing Visit 11 assessments (32 weeks from randomization), there will be an additional 8-week follow-up period, concluding with the 12 weeks post-last dose follow-up visit (Visit 12).

Reasons for premature discontinuation of study treatment must be captured in the CRF, e.g., AE, lack of efficacy, protocol deviation, pregnancy, investigator discretion, consent withdrawal, lost to follow-up, study termination.

If a subject experiences an organ-threatening or an life-threatening event, the investigator should discuss study treatment continuation with the GSK Medical Monitor.

Subjects will be withdrawn from study treatment for any of the following reasons:

- Meet the **liver chemistry stopping criteria** (Section 5.4.1)
- Meet **QTc stopping criteria** (Section 5.4.2)

- Use **prohibited medication** (i.e., as noted in Exclusion Criteria # 13, 14, & 15, and Section 6.10.2, Prohibited Medications and Non-Drug Therapies) that cannot be safely discontinued while maintaining the subject's health.
- **Treatment code unblinded**: Subjects must be discontinued from study treatment if the treatment code is unblinded by the Investigator or treating physician. The primary reason for withdrawal from study treatment (the event or condition which led to the unblinding) will be recorded in the CRF.
- **Pregnancy**: Any female subject who becomes pregnant.

Following withdrawal from study treatment, investigators and participating subjects should, where possible, continue to be blinded to absolute blood eosinophil counts, total white blood cell counts, and white blood count differentials (%) until completing the 32-week period from randomization. The subject's blood eosinophil count will be monitored and blinded OCS will be triggered according to the protocol during this time (Section 6.4).

Withdrawal from study

For this study there are no pre-determined protocol-specific study withdrawal criteria. Every effort should be made by the investigator to keep the subject in the study. However, subjects are free to withdraw consent to participate in the study at anytime. The investigator may also, at his or her discretion, withdraw a subject from further study participation. Subjects who are withdrawn from the study will not be replaced.

Reasons for withdrawal from the study must be captured in the CRF, e.g., consent withdrawn, lost to follow-up, study terminated, etc.

In the event of early withdrawal (EW) from the study, every effort should be made to have the subject return to the clinic for an EW visit (including the collection of biological samples for laboratory assessments approximately 4 weeks after the last dose of study treatment) as well as the last follow-up visit approximately 12 weeks after the last dose of study treatment, and return all study-related materials.

Following withdrawal from the study, investigators and participating subjects should, where possible, continue to be blinded to absolute blood eosinophil counts, total white blood cell counts, and white blood count differentials (%) for a period of 4 weeks after the last study treatment.

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.

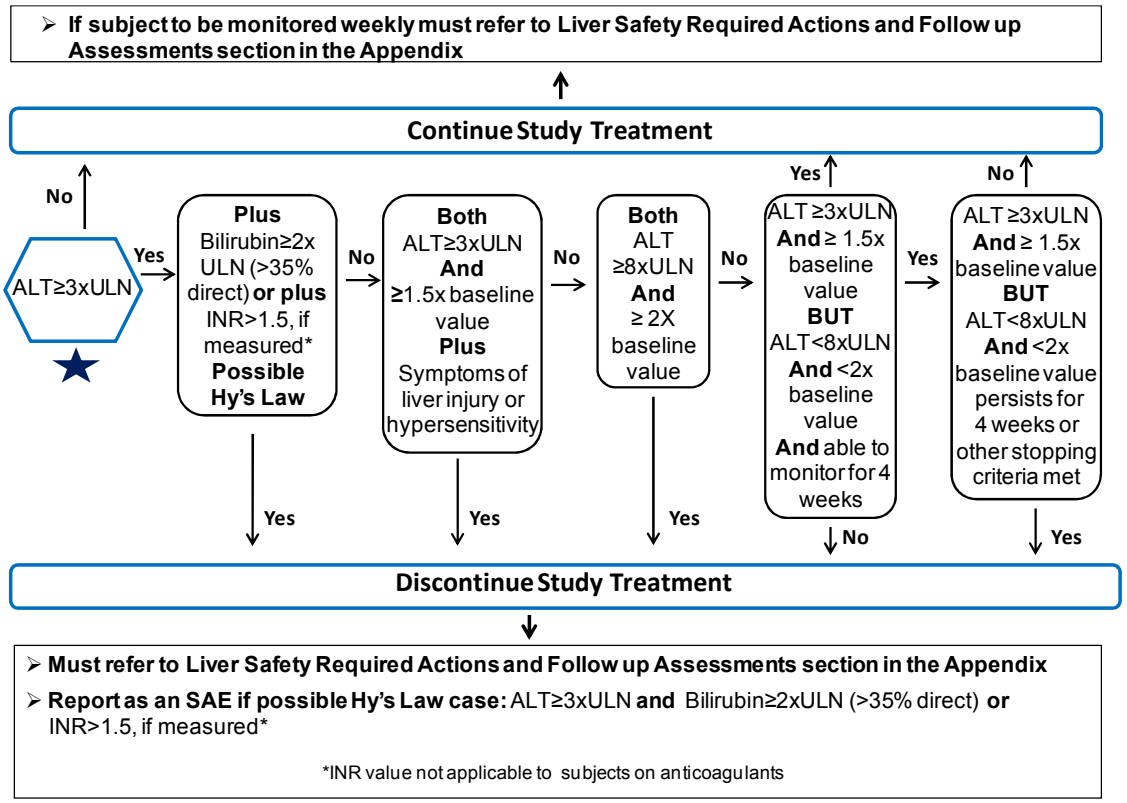
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact 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".

5.4.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria (Section 12.2) 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

Figure 2 Phase III-IV Liver Stopping and Monitoring Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Section 12.2.

5.4.1.1. Study Treatment Restart or Re-challenge

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

5.4.2. 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 single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

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

- QTc > 500 msec OR Uncorrected QT > 600 msec
- Change from baseline of QTc > 60 msec]

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

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

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

5.5. Subject and Study Completion

A subject is considered to have completed the study when finishing the end-of-treatment visit (Visit 11) 32 weeks after randomization. If a subject's last dose of study treatment is on Visit 9 (Week 24) or Visit 10 (Week 28) *and* the subject does not continue with open-label mepolizumab after completing Visit 11 assessments (32 weeks from randomization), the subject is considered to have completed the study when finishing up to 8-week additional follow-up period, concluding with the 12 weeks post-last dose follow-up visit (Visit 12).

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

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

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

	Study Treatment
Product name:	SB240563 (mepolizumab)
Formulation description:	Mepolizumab 100 mg vial for injection contains target quantities of 10.3 mg sodium phosphate dibasic heptahydrate, 0.96 mg polysorbate 80 and 230.4 mg xucrose per vial.
Dosage form:	Lyophilized powder for injection reconstituted with Sterile Water for Injection, just prior to use.
Unit dose strength(s)/Dosage level(s):	3 vials (100mg/vial) per administration
Route of Administration	3 SC injections per administration
Dosing instructions:	Subjects will be dosed with three 100 mg SC injections every 4 weeks. Injections should be administered into the abdomen, upper arm, or thigh.
Physical description	Mepolizumab will be provided as a lyophilized cake in sterile vials for individual use.

If a subject becomes infected with helminths while receiving study treatment and does not respond to anti-helminth treatment, temporary discontinuation of study treatment should be considered in consultation with GSK Medical Monitor.

Mepolizumab

Mepolizumab is a humanized IgG antibody (IgG1, kappa) with human heavy and light chain frameworks. Mepolizumab will be provided as a lyophilized cake in sterile vials for single use. The vial will be reconstituted with Sterile Water for Injection just prior to use. Further details of dose preparation and administration can be found in the IB [GlaxoSmithKline Document Number CM2003/00010/10] and the unblinded reference manual.

Mepolizumab will be provided by GSK as open-label product to the unblinded site staff. Unblinded site staff are required for this study. Unblinded site staff will be responsible for receipt, storage, reconstitution, and labelling, and accountability of IP.

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

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

Blinded OCS

GSK will provide blinded OCS. Each bottle will have a unique identifier number, and contain either 5 mg OCS (prednisolone or prednisone capsules) or matching placebo capsules. Refer to Section 6.4 for dispensing.

6.2. Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software to receive **either**:

Mepolizumab:	*or*	Placebo (0.9% sodium chloride):
Three 100 mg SC injections administered every 4 weeks (8 administrations)		Three SC injections administered every 4 weeks (8 administrations)

Due to potential differences in standards of care between regions, the randomization will be stratified by region.

An unblinded site staff member will be assigned to the study to prepare the appropriate medication according to the study subject's treatment assignment. Subjects eligible to enter the study will be assigned to treatment randomly through an interactive response technology (IRT).

Subjects will be monitored during SC administration and for 1 hour after the first three administrations and then follow monitoring policies for the center. Such monitoring will include general safety monitoring including monitoring for both systemic reactions (e.g., hypersensitivity) and local site reactions. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study treatment, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the subject including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the patient to another facility for additional care if appropriate.

6.3. Treatment Blinding

Once prepared mepolizumab and placebo will be identical in appearance and will be administered by a blinded member of the site staff. The blinding of those involved in the evaluation of the study, i.e., physician, nurse and subject will be maintained at all times.

This will be a double- blind study and the following will apply.

- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the GSK Medical Monitor or appropriate GSK study personnel to discuss options before unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
- The date and reason for the unblinding must be fully documented in the CRF.

A subject will be withdrawn from study treatment if the subject's treatment code is unblinded by the investigator or treating physician. The primary reason for discontinuation of study treatment (the event or condition which led to the unblinding) will be recorded in the CRF (Section 5.4).

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

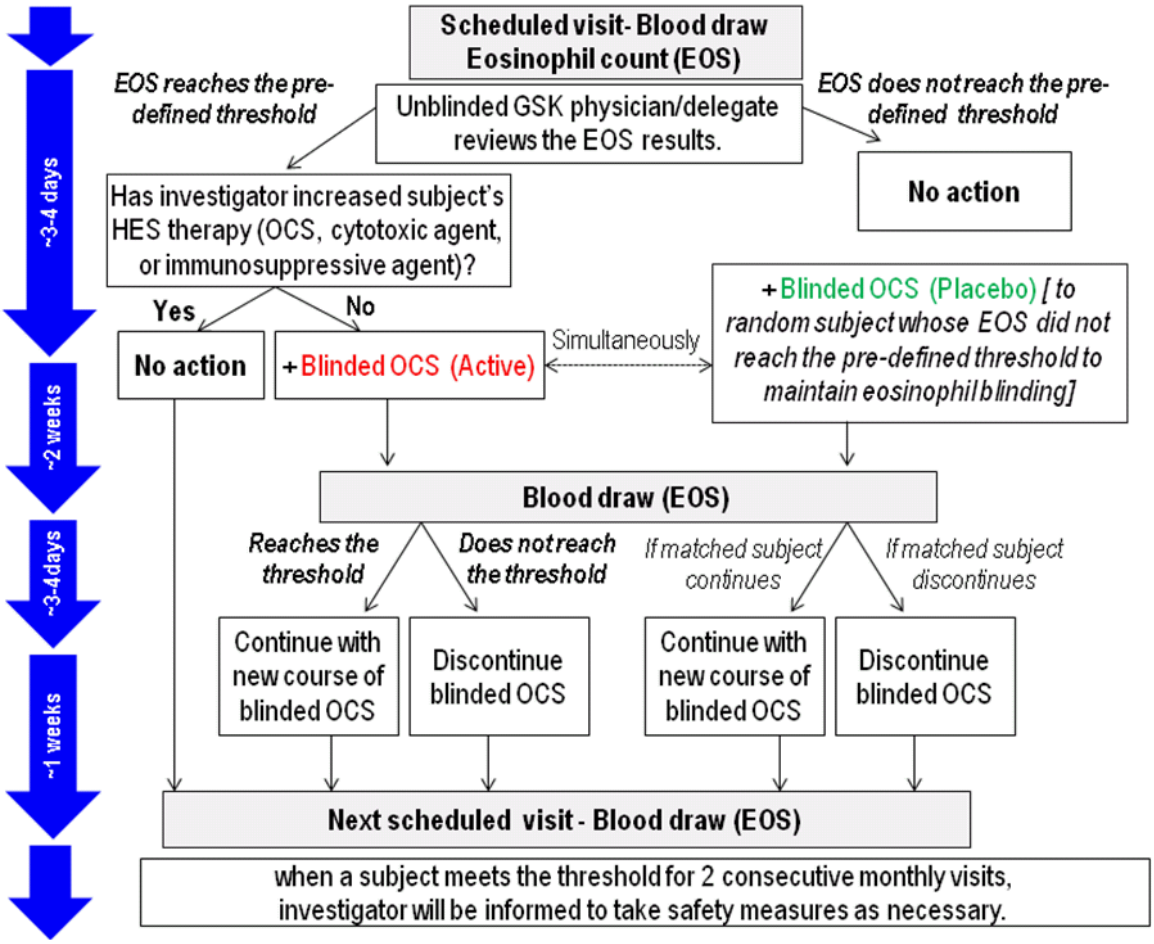
6.4. Blood Eosinophil Blinding

Investigators, GSK personnel involved in the study, and subjects will be blinded to the results of absolute blood eosinophil counts, total white blood cell counts, and white blood count differentials (%). Subjects that have an increase in blood eosinophils above the predetermined threshold will be instructed to take OCS capsules. In order to maintain the blind, this treatment will be with blinded OCS capsules.

All subjects will be provided 2 bottles of blinded OCS capsules, one containing 5mg OCS capsules (active OCS treatment) and a second one containing matching placebo capsules (placebo OCS treatment). These will be dispensed to each subject at each scheduled clinic visit and as needed. Subjects will also have blood drawn at each visit to assess the blood eosinophil count (Hematology assessment in Table 4).

A brief schematic of the trigger alert system is shown in Figure 3.

Figure 3 Blood eosinophil blinding and blinded OCS trigger schematic



Blood eosinophil-unblinded GSK personnel/delegates not involved with other aspects of study conduct will review the results from the central laboratory for absolute blood eosinophil count. If a pre-specified threshold blood eosinophil level (i.e., 2 x Baseline value [randomization] *or* Baseline value + 2500 cells/µL) is reached (eosinophilia flare), blood eosinophil-unblinded GSK personnel/delegates will communicate with the investigator to initiate blinded OCS treatment from one of the bottles provided (active treatment) unless the subject's HES therapy (OCS, cytotoxic agent, or immunosuppressive agent) has already been increased due to a symptom flare within the past 2 weeks. The subject will take the blinded OCS from the assigned bottle for ~2 weeks. A subject who does not reach the pre-specified blood eosinophil threshold with a similar blood draw date will be selected to initiate a placebo treatment in a blinded manner, to maintain study blood eosinophil blinding.

The dosing regimen for a course of blinded OCS is as shown in Table 1.

Table 1 A course of blinded OCS regimen

Days	Dose (mg/day)	Number of 5mg capsules/day
1-3	40	8
4-6	20	4
7-9	10	2
10- Until notified regarding whether to discontinue *or* start a new course of blinded OCS regimen Otherwise, until the next scheduled clinic visit	5	1

Approximately 2 weeks after the scheduled clinic visit, the blood eosinophil count will be assessed again for the subject who started blinded OCS (both active and placebo). The subject who has taken active blinded OCS will be instructed to continue with a new course of blinded OCS regimen from Day 1 (i.e., 40mg) until the next scheduled clinic visit if the blood eosinophil count is at or above the threshold unless the subject's HES therapy (OCS, cytotoxic agent, or immunosuppressive agent) has been increased due to a symptom flare since the initiation of the current course of blinded OCS, and discontinue if the blood eosinophil count is below the threshold. For subjects taking placebo-blinded OCS, continuation/discontinuation of blinded OCS will be determined depending on the continuation/discontinuation of their matched subject on active-blinded OCS as described in Figure 3.

A subject whose blood eosinophil count is at or above the threshold while receiving blinded placebo OCS will be re-evaluated when the subsequent test result from the scheduled clinical visit is available to determine whether blinded active OCS should be initiated.

A subject who starts blinded OCS based on the 2 weeks post-randomization (Visit 3) blood eosinophil count (both the active OCS and the matched placebo OCS subjects) will continue taking the blinded OCS until they return to the next scheduled clinic visit (Visit 4).

In the event that a subject has a blood eosinophil count that reaches the pre-defined threshold to trigger blinded active OCS for 2 consecutive monthly scheduled clinic visits, blood eosinophil-unblinded GSK physician/delegates will inform the investigator so that the investigator can take further measures as necessary.

Subjects who have to travel a great distance to the study site will be given an option to have a between-clinic visit blood draw locally and ship the sample to the central laboratory.

6.5. Packaging and Labeling

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

6.6. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for preparation of mepolizumab or placebo will be detailed in the unblinded reference manual.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the Study Reference Manual (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, GSK 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.

Mepolizumab must be stored in a secure area under the appropriate physical conditions for the product, which includes storage in a refrigerator or at a temperature of 2-8°C and protected from light. Maintenance of a temperature log (manual or automated) is required. Access to study treatment will be limited to the investigator's authorized unblinded site staff. Maintenance of a temperature log (manual or automated) is required. Study treatment must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

6.7. Compliance with Study Treatment Administration

Study treatment will be subcutaneously administered to subjects at the site. Administration will be documented in the source documents and reported in the CRF.

Compliance with blinded OCS will be based on pill counts at the time of dispense and collection of the bottles. These will be documented in the source documents and reported in the CRF.

6.8. Treatment of Study Treatment Overdose

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

In the event that mepolizumab is administered more than as detailed in the protocol in terms of dose or frequency, the investigator should contact the GSK Medical Monitor immediately.

6.9. Treatment after the End of the Study

Subjects who complete the protocol-specified assessments for the 32-week period from randomization (Section 4.3) will be evaluated, and if eligible, may be enrolled into an extension study to receive open-label mepolizumab.

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.

6.10. Concomitant Medications and Non-Drug Therapies

6.10.1. Permitted Medications and Non-Drug Therapies

Use of standard HES therapy including OCS, immunosuppressive or cytotoxic therapy (e.g., hydroxyurea, IFNα, cyclosporine, imatinib, methotrexate, azathioprine) will be permitted during the study. As specified in Inclusion Criterion #6, subjects must be on a stable dose of HES therapy for the 4 weeks prior to randomization (Visit 2) [Section 5.1]. The same regimen of HES therapy must be maintained throughout the 32-week study treatment period unless there is worsening of symptom(s) that requires an increase in therapy. If a subject has worsening of symptom(s) and requires an increase in therapy after randomization, the subject will be considered to be experiencing a flare (Section 7.3.1). Once the subject regains disease control, the investigator is encouraged, as medically appropriate, to adjust the dose of HES therapy back to the level prior to the disease worsening.

A reduction in standard HES therapy dose for safety reasons, with return to the original dosing regimen when possible, is permitted in consultation with the GSK Medical Monitor.

Additional therapies required to treat non-HES related medical conditions during the study are permitted in consultation with the GSK Medical Monitor and must be prospectively captured in the CRF.

6.10.2. Prohibited Medications and Non-Drug Therapies

Initiation of new medications or herbal remedies which may alter the course of HES or interact with the study treatment is prohibited within their specified timeframe and throughout the study (Visit 0 to Visit 11 inclusive) with the exception of HES therapy to treat an HES flare (Section 7.3.1).

In addition, the following medications will be prohibited:

- Any investigational agents (biologic or non-biologic) within the 30 days or 5 drug half-lives whichever is longer, prior to screening (Visit 1), and until Visit 11. The term "investigational" applies to any drug not approved for sale in the country in which it is being used or investigational formulations of marketed products.
- Any other biologic agents (except for IFNα): within 30 days or 5 half-lives, whichever is longer, of screening (Visit 1), and until Visit 11.

In the event that the use of a prohibited medication is identified by the study site, the investigator must use clinical judgment in balancing protocol compliance (discontinuing the medication) and subject safety. The investigator should assess whether the medication is required or likely to be required to maintain subject's health in control. The investigator also should assess whether the medication can be stopped after subject's health is re-established.

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).

The following points must be noted:

- Subject-completed assessments are done at the beginning of a visit in Section 7.1 in the order presented in the electronic device.
- Blood draws are done after vital signs and prior to dosing of study treatment.
- The timing and number of planned study assessments, including safety, PK, and PD assessments may be altered during the course of the study based on newly available data to ensure appropriate monitoring.
- The institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

7.1. Time and Events Table

Table 2 Time and Events Table

Procedures	Pre-screen	Screen	Randomi-zation	Double-blinded treatment period												Additional follow-up
Study visit	0	1	2	3	4	5	6	7	8	9	10	11 End-of-treatment	Flare[19]	3-11 for subjects who prematurely discontinue study treatment[20]	EW	12
Study week		Up to ~4 weeks (wks)	0	2 (± 5 days)	4 ±1 wks	8 ±1 wks	12 ±1 wks	16 ±1 wks	20 ±1 wks	24 ±1 wks	28 ±1 wks	32 ±1 wks				~12 wks after last dose ±1 wks
Informed consent[1]	X															
Demography	X															
Medical history		X														
History of HES (diagnosis/flares) and treatment (past 12 months)	X															
CV history/risk factors		X														
Inclusion/exclusion		X	X													
Parasite screening[2]		X														
Efficacy and PRO assessments																
Subject-RTS[3]					X	X	X	X	X	X	X	X			X	
SSR[2]			X		X	X	X	X	X	X	X	X	X			
Modified MSAS-SF[3]			X		X	X		X		X		X	X		X	
PROMIS sleep and physical function scales[2]			X		X	X		X		X		X				
SF-36 v2[3]			X		X	X	X	X	X	X	X	X	X	X		
WPAI-GH v2[3]			X		X	X	X	X	X	X	X	X	X		X	
Steroid perception questionnaire[3]			X													
HES Core Assessments (clinician assessment) /Flare detail			X		X	X	X	X	X	X	X	X	X	X	X	
Clinician-RTS					X	X	X	X	X	X	X	X			X	

Procedures	**Pre-screen**	**Screen**	**Randomi-zation**	**Double-blinded treatment period**											**Additional follow-up**
Study visit	0	1	2	3	4	5	6	7	8	9	10	11 End-of-treatment	Flare[19]	3-11 for subjects who prematurely discontinue study treatment[20]	EW	12
Study week		Up to ~4 weeks (wks)	0	2 (± 5 days)	4 ±1 wks	8 ±1 wks	12 ±1 wks	16 ±1 wks	20 ±1 wks	24 ±1 wks	28 ±1 wks	32 ±1 wks				~12 wks after last dose ±1 wks
HCRU			X		X	X	X	X	X	X	X	X			X	
Spirometry			X			X		X		X		X	X			
Echocardiogram[4]		X										X	X			
Safety assessments																
Physical examination[5]		X	X		X	X	X	X	X	X	X	X	X			
Height and weight[6]		X	X					X				X			X	
Concomitant meds including maintenance OCS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[7]		X	X		X	X	X	X	X	X	X	X	X		X	
ECG		X										X	X			
AEs			X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments[8]																
Hematology[9]		X	X	X	X	X	X	X	X	X	X	X	X	X	X[21]	
Chemistry[10]		X			X	X	X	X	X	X	X	X	X	X[21]	X[21]	
Troponin		X			X	X	X	X	X	X	X	X	X	X[21]	X[21]	
Pregnancy test[11]		X	X		X	X	X	X	X	X	X	X		X[21]	X[21]	
Aldolase		X			X	X	X	X	X	X	X	X	X			
Lipoproteins (fasting)[12]		X														
Urinalysis[13]		X										X		X[21]	X[21]	
Hep B & C serology[14]		X														
F/P status[15]		X														
T-cell profile		X										X		X[21]	X[21]	
Total IgE			X													

Procedures	**Pre-screen**	**Screen**	**Randomi-zation**	**Double-blinded treatment period**												**Additional follow-up**
Study visit	0	1	2	3	4	5	6	7	8	9	10	11 End-of-treatment	Flare[19]	3-11 for subjects who prematurely discontinue study treatment[20]	EW	12
Study week		Up to ~4 weeks (wks)	0	2 (± 5 days)	4 ±1 wks	8 ±1 wks	12 ±1 wks	16 ±1 wks	20 ±1 wks	24 ±1 wks	28 ±1 wks	32 ±1 wks				~12 wks after last dose ±1 wks
PK					X			X				X		X[21]	X[21]	X[21]
PD (IL-5)			X									X	X			
Immunogenicity (Anti-drug antibody)			X					X				X		X[21]	X[21]	X[21]
Genetics[16]			X													
Sample collection for biomarker sub-study[17]			X									X	X	X[21]	X[21]	
Investigational product & other study treatment																
Study treatment administration[18]			X		X	X	X	X	X	X	X					
Dispense/collect blinded OCS			X	X	X	X	X	X	X	X	X	X		X	X	
Interactive Response Technology (IRT)/electronic CRF (eCRF)/electronic Diary (eDiary)																
Register visit on IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete eCRF		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense (D) /collect (C) eDiary[22]		D										C		C for Visit 11	C	
Review eDiary			X	X	X	X	X	X	X	X	X	X		X	X	

EW: Early withdrawal

1. Pre-screen visit to obtain informed consent can occur on the same day as Visit 1, but informed consent must be obtained prior to starting Visit 1 procedures.
2. 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.
3. Subject-completed assessments are done at the beginning of a visit.
4. Echocardiogram is performed to support CV assessment at screening and at the end of study treatment for all subjects. Echocardiogram at Visit 1 is required unless there is a documented result within the previous 6 months from Visit 1.
5. Findings during physical examination related to HES will be recorded in the HES Core Assessments/flare detail.
6. Height to be measured at screening only.
7. Vital sign measurements will include temperature, systolic and diastolic blood pressure and pulse rate.
8. During the treatment period, all laboratory samples (Table 4) should be obtained **pre-dose**.
9. Refer to Section 6.4 for additional blood draw between the scheduled clinical visits for subjects who will administer blinded OCS.
10. Clinical chemistry will include analytes and liver chemistry monitoring.
11. Negative urine pregnancy test result must be confirmed prior to dosing in women of reproductive potential.
12. Lipoprotein (fasting) included in clinical chemistry. Subject must be in a fasting state. If the subject has not fasted, he/she may return to the clinic to collect this sample.
13. Urine tests are done using dipstick. If found abnormal, the urine sample will be sent to the central laboratory for further testing.
14. If test was performed within 3 months prior to randomization, testing at screening is not required.
15. F/P test is required if no documented results are available.
16. Informed consent for optional sub-studies (e.g., genetics research) must be obtained before collecting a sample. Genetic sample collection is recommended at Visit 2, but may be drawn at any time after the subject is consented and randomized.
17. Sample collection for the optional biomarker sub-study should be done after obtaining a written consent.
18. The date and time of the administration of study treatment will be recorded in the CRF. For safety monitoring requirement, refer to Section 6.2.
19. Assessments will be collected when possible depending on the clinical status during worsening of symptoms between scheduled clinic visits to evaluate for an HES flare. Spirometry for a respiratory flare, and troponin, echocardiogram, & ECG for a CV flare will be performed (Selective assessments depending on the type of flare are noted in the table with the gray shade). Echocardiogram will be performed only if there is a change in HF classification (see Section 12.7) and/*or* the investigator determines that there is a need for assessment. When attending the clinic visit at the time of a suspected HES flare is not possible, the investigator should make every effort to evaluate the subject via telephone and complete the HES Core Assessments (Section 7.3.2).
20. Subjects who prematurely discontinue study treatment will continue to attend 4-weekly scheduled clinic visit and complete these assessments. Blood samples for hematology will be collected at these visits for blinded blood eosinophil monitoring (Section 6.4). All other laboratory assessments are completed at 4 and 12 weeks after the last dose only as noted in footnote #21.
21. Approximately 4 weeks after the last dose of study treatment, every attempt should be made to collect urine and blood samples for laboratory assessments. In addition, all subjects will be brought in for an additional follow-up visit 12 weeks after the last dose, including the collection of a blood sample for measurement of anti-drug antibodies and PK, unless the subject receives open-label mepolizumab according to the protocol criteria at that time.
22. Subjects will complete BFI and HES daily symptoms (HES-DS) in the eDiary on a daily basis. Subjects must complete the eDiary for at least 7 days prior to randomization. Subjects who prematurely discontinue study treatment will continue daily eDiary completion and return the eDiary at Visit 11 for EW.

7.2. Screening and Critical Baseline Assessments

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

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

Medical/medication history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

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

PRO questionnaires should be completed by subjects before any other assessment at a clinic visit.

Evaluation of medical history relating to the subject's HES at screening includes:

- Date of diagnosis and/or approximate duration since diagnosis
- Requirement for therapy (e.g., immunosuppressive or cytotoxic therapy) including OCS for the management of their HES during 12 months prior to screening (Visit 1)
- Number and type(s) of HES flares (including organ systems affected and the type of interventions) experienced during the 12 months prior to screening (Visit 1). Refer to Section 5.1 for the definition of a historical HES flare (Inclusion Criterion #4).
- Documentation of any of the following complications of HES: gangrene, massive pulmonary hemorrhage or respiratory failure requiring ventilator support, congestive cardiac failure, renal failure requiring dialysis, cerebrovascular accident.

At randomization (Visit 2), the HES Core Assessments will be completed to establish the baseline characteristics of subjects' HES. Throughout the treatment period, the same set of the assessments will be utilized to monitor changes in their disease activity for major organ systems affected by HES. Further information can be found in Section 7.3.2.

7.3. Efficacy

7.3.1. HES flare

An HES flare is defined as *either*

a) An HES-related clinical manifestation based on a physician-documented change in clinical signs or symptoms resulting in the need for either of the following:

- An increase in the maintenance OCS dose by at least 10mg/day for 5 days

- An increase in or addition of any cytotoxic and/or immunosuppressive HES therapy

or

b) Receipt of two or more courses of blinded active OCS during the treatment period.

The start date for an HES flare meeting flare endpoint definition 'a)' will be defined as the date of therapy escalation confirmed by the investigator attributable to an HES-related clinical manifestation. The start date for an HES flare meeting flare endpoint definition 'b)' will be defined as the date of the blood draw at which the second course of blinded active OCS was triggered via scheduled blood sampling for eosinophil monitoring.

When a subject experiences an HES flare as defined in 'a)' above, the investigator will monitor the change in disease control per routine medical care (e.g., follow-up call) and record the resolution of the flare including the end date. Investigators are encouraged, as medically appropriate, to return the subject's treatment regimen to the baseline (randomization) after the flare has resolved.

An increase in blood eosinophils only (without any other clinical manifestations) during the study may trigger an alert which will result in administration of additional blinded OCS (active treatment) [Section 6.4]. When a subject receives the second course of blinded active OCS during the 32-week treatment period, the subject will be considered to be experiencing a flare. Subsequently, the date of the first blood draw at which blood eosinophil count is below the threshold to trigger blinded active OCS will be the resolution date. Each subsequent course of blinded active OCS beyond 14 days from the resolution date of the preceding flare will be considered as an additional flare (e.g., 3 courses of blinded active OCS are considered as 2 flares, 4 courses of blinded active OCS are considered as 3 flares, etc.).

For subjects who reduce the dose of HES therapy after randomization for safety reasons (Section 4.1), the increase in HES therapy used to define an HES flare will be the change from the dose at randomization.

In the event of disease worsening for which the investigator suspects an HES flare between scheduled clinic visits, when possible, the subject will return to the clinic to have the unscheduled 'Flare' visit assessment completed as described in the Time and Events Table (Section 7.1). When attending the clinic visit at the time of a suspected HES flare is not possible, the investigator should make every effort to evaluate the subject via telephone and complete the HES Core Assessments (Section 7.3.2). If an escalation of therapy is initiated by a non-study physician, the investigator should confirm that the escalation in therapy is attributable to an HES-related clinical manifestation.

Investigators will be required to record details pertaining to the HES flare event in the CRF from randomization (Visit 2) until study completion at Week 32 or Early Withdrawal (EW). This should include details regarding the clinical symptoms resulting in the flare with detail of the required intervention(s), e.g., OCS dose increase, *or* addition or escalation of immunosuppressive or cytotoxic therapy. In addition, all other

relevant clinical, laboratory or other diagnostic investigations required to confirm the flare must be captured in the CRF.

7.3.2. HES Core Assessments (Clinician Assessment)

Clinical evaluation by the investigator will be guided by the HES Core Assessments (Table 3), consisting of clinical signs and symptoms that reflect the heterogeneous nature of HES observed in clinical practice. During the study, the investigator will evaluate subjects at each clinic visit using the HES Core Assessments and determine whether worsening of signs/symptoms supports an increase in HES therapy. In addition, to further characterize the basis for determination of flare and increase in therapy, the investigator will prepare a narrative for each HES flare.

The HES Core Assessments will characterize each subject's clinical manifestations at baseline and monitor for changes throughout the study. The investigator will be asked to rule out other possible etiologies for the change in clinical symptoms, such as an infection, prior to diagnosing an HES flare. For the "others" category in Table 3, specific components of the physical exam will be used as part of the baseline core assessments and throughout the study to monitor for the presence or absence of changes in exam findings. Findings of the HES Core assessments will be recorded in the electronic device.

Table 3 HES Core Assessments

Symptoms	Assessment
Constitutional	
Fatigue Pain (including but not limited to muscle, joint, general pain) Angioedema (swelling under the skin)	Each symptom rated using a 0-3 scale
Dermatologic	
Rash Itch Hives Others (specify)	Each symptom rated using a 0-3 scale
Gastrointestinal	
Average number of vomiting a day in the past week Average number of diarrhea a day in the past week Average number of stools a day in the past week Abdominal pain Difficulty in swallowing food	Each symptom rated using a 0-3 scale

Symptoms	Assessment
Respiratory	
Breathing symptoms such as shortness of breath and wheezing	0-3 scale
Dyspnea (shortness of breath)	0-3 scale
Cough	0-3 scale
Sinus-related symptoms: Nasal congestion Sinus headache/facial pain/pressure Postnasal drip (drainage down the back of the throat) Purulent rhinorrhea (discoloured & thick nasal discharge) Ear fullness	Each symptom rated using a 0-3 scale
Cardiovascular	
Heart failure classification for functional capacity	Classes I-IV
Heart failure classification for objective assessment	Classes: A-D
Neurologic	
Sensory Motor Cognitive and Mental status change	Each symptom rated using a 0-3 scale
Others	
Vascular, venous, arterial, loss of pulse, splinter hemorrhage, renal failure, splenomegaly, other (specify)	Each identified symptom rated using a 0-3 scale

0-3 scale symptom score: 0 for not present or no impact, 1 for present but minimal impact, 2 for significant impact on daily activities, 3 for incapacitating

7.3.3. Spirometry

Spirometry will be conducted at the visits specified in the Time and Events table (Table 2). Spirometry instrument and training will be provided by a vendor.

Prior to the randomization visit (Visit 2) and any visit where spirometry is assessed, subjects should withhold short-acting beta$_2$-agonists (SABAs) for at least 6 hours and long-acting beta$_2$-agonists (LABAs) for approximately 12 hours to minimize the effect of medications on spirometry.

Due to diurnal variation associated with lung function, when possible, spirometry should be performed at the same time of day (± 1 hour) as at the randomization (Visit 2) assessment.

7.3.4. Echocardiogram

Subjects who have a documented echocardiogram result within 6 months of Visit 1 will not require a screening echocardiogram. When a CV flare is suspected during the study treatment period (based on a change in the HF class [see Section 12.7] and/or investigator's judgment), an echocardiogram will be performed when possible.

7.3.5. Healthcare Resource Utilization (HCRU)

All unscheduled HES-related healthcare utilization (Section 7.1) will be recorded in the CRF including telephone contacts, specialist nurse visits, visits to a physician's office, home visits (day and night time), outpatient visits, visits to urgent care, visits to the emergency department, and hospitalizations associated with the subject's worsening of symptoms. Hospitalization data should be categorized by ward type (e.g., intensive care unit [ICU] and usual care). Hospital length of stay in each type of ward will also be recorded.

The HCRU worksheet used by the subject to record all healthcare contacts experienced since the last visit will be presented to the investigator (or designee) at the clinic visits. 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. The investigator (or designee) should ask the subject if any of the healthcare contacts that are recorded on the worksheet were due to a worsening of HES symptom. The investigator can refer to his/her records to verify or supplement information given by the subject, if necessary.

7.4. Safety

Planned timepoints for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional timepoints for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

Safety assessments include:

- Adverse Events including systemic reactions (e.g., hypersensitivity) and local site injection-related reactions (*AEs of special interest*)

  NOTE: Systemic reactions can be allergic or non-allergic in nature and are typically mild to moderate in intensity, generally develop within several hours of the injection but also may have a delayed onset (i.e., days). Anaphylaxis is the most severe form of hypersensitivity reactions. Both AEs of special interest, local injection site reactions and systemic reactions, will have additional information (i.e., corresponding symptoms) collected via AE and SAE pages in the eCRF. In addition, the information whether an event met the diagnostic criteria for anaphylaxis as

outlined by the Second Symposium on Anaphylaxis ([Sampson, 2006], see Section 12.6), and in Section 12.6 will be collected on the AE and SAE CRF pages.

- Hematological and clinical chemistry parameters
- Vital signs (pulse rate and systolic and diastolic blood pressure)
- Presence of anti-drug antibodies to mepolizumab

The following safety endpoints will be derived:

- Change from baseline in systolic blood pressure
- Change from baseline diastolic blood pressure
- Change from baseline in pulse rate
- 12-lead ECG to derive the following endpoints:
  - Mean change from baseline in the QTcF (QT interval corrected by Fridericia's method)
  - Mean change from baseline in QTcB (QT interval corrected by Bazett's method)
  - Maximum change from baseline for QTcF and QTcB.

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

The definitions of an AE or SAE can be found in Section 12.4.

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 the follow-up contact (see Section 7.4.1.3), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Section 12.4.6.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Section 12.4.5.

7.4.1.2. Method of Detecting AEs and SAEs

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

- "How are you feeling?" *or* **"**How does your child seem to feel?"
- "Have you had any (other) medical problems since your last visit/contact?" *or* "Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?" *or* "Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?"

7.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 7.4) 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 5.4). Further information on follow-up procedures is given in Section 12.4.3.

7.4.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 12.4.3 and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

7.4.1.5. Regulatory Reporting Requirements for SAEs

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

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ 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.

7.4.2. Pregnancy

- Details of all pregnancies in female subjects that occur from the first dose of study treatment and until at least 4 months post-last dose of study treatment will be collected.
- 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 Section 12.5.2.

7.4.3. Physical Exams

- A complete physical examination will include, at a minimum, assessment of the ENT, Cardiovascular, Respiratory, Gastrointestinal, Skin, and Neurological systems. Height (at screening only) and weight will also be measured and recorded (Section 7.1). Physical exam includes assessment of symptoms/signs noted as physician assessment in Section 7.3.2. Findings during physical examination related to HES will be recorded in the HES Core Assessments/Flare details.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.4.4. Vital Signs

Vital signs will be measured prior to blood draws in a sitting position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate.

7.4.5. Electrocardiogram (ECG)

- Details of the cardiac monitoring procedures will be provided by the centralized cardiology service provider.
- All sites will use standardized ECG equipment provided by a centralized external vendor.
- Recordings will be made at timepoints outlined in Section 7.1. Collection shortly after a meal or during sleep should be avoided since QT prolongation can occur at these times. All ECG measurements will be made with the subject in a supine

position having rested in this position for approximately 5 minutes before each reading.

- Paper ECG traces will be recorded at a standard paper speed of 25 mm/sec and gain of 10 mm/mV, with a lead II rhythm strip. There will be electronic capture and storage of the data by a validated method, with subsequent transfer to the central laboratory for manual reading and calculation of the electrocardiographic parameters. Paper traces are required to be maintained at the site with other source documents.
- The investigator, a designated sub-investigator, or other appropriately trained site personnel will be responsible for performing each 12-lead ECG. The investigator must provide his/her dated signature on the original paper tracing, attesting to the authenticity of the ECG machine interpretation.
- All ECGs will be electronically transmitted to an independent cardiologist (contracted by GSK) and evaluated. The independent cardiologist, blinded to treatment assignment, will be responsible for providing measurements of heart rate, QT intervals and an interpretation of all ECGs collected in this study. A hard copy of these results will be sent to the investigator. The investigator must provide his/her dated signature on the confirmed report, attesting to his/her review of the independent cardiologist's assessment to support the decision regarding the continuation or discontinuation of study treatment based on the ECG results (Section 5.4.2).
- A single 12-lead ECGs will be obtained at each timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 5.4.2 for QTc stopping criteria and additional QTc readings that may be necessary.

7.4.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 4, must be conducted in accordance with the laboratory manual, and Protocol Time and Events Schedule (Section 7.1). Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), the results must be recorded in the CRF unless the central laboratory results are available in time to support medical intervention. The investigator should make every effort to maintain the blinding to subject's blood eosinophil level.

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

All study-required laboratory assessments will be performed by a central laboratory.

NOTE: Local laboratory results are only required in the event that the central laboratory results are not available in time for either a treatment and/or response evaluation to be performed. If a local sample is required it is important that the sample for central analysis is obtained at the same time. Additionally if the local laboratory results are used to make either a treatment or response evaluation, the results must be entered into the CRF.

All blood samples should be taken after measuring vital signs and **prior to administration of study treatment** (for dosing visits).

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 4.

Table 4 Clinical Laboratory Parameters

Routine Clinical Chemistry	**Routine Hematology**
Sodium	Hemoglobin
Potassium	Red cell count
Chloride	Platelet count
Calcium	*Total white cell count*#
Phosphorous inorganic	White cell differentials:
Glucose	Neutrophil (absolute and *differential [%]*#)
Protein, total	Lymphocytes (absolute and *differential [%]*#)
Albumin	Monocyte count (absolute and *differential [%]*#)
CPK, total	Eosinophil count (*absolute*# and *differential [%]*#)
Creatinine	Basophil count (absolute and *differential [%]*#)
Urea nitrogen	Mean Corpuscular Volume (MCV)
Lactic dehydrogenase	Mean Corpuscular Hemoglobin (MCH)
Bilirubin, direct	Mean Corpuscular Hemoglobin Concentration (MCHC)
Bilirubin, indirect	**Urinalysis**
Bilirubin, total	Protein Qualitative
Aspartate amino transferase (AST)	Glucose
Alanine amino transferase (ALT)	Ketones
Gamma glutamyl transaminase (GGT)	Occult Blood
Alkaline phosphatase	Microscopic: WBC and RBC
Lipoproteins	**Other laboratory parameters**
Cholesterol, total	F/P status
High density lipoprotein, Cholesterol, direct	CD3, CD4, CD8
Low density lipoprotein, calculation	Hepatitis B surface antigen (HBsAg)
Very low density lipoprotein, calculation	Hepatitis C antibody
	Total IgE
	Troponin
	Aldolase
	Urine pregnancy test

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 5.4.1 and Section 12.2.
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or ethics committee.
3. Refer to Section 6.4 regarding the results that will not be sent to the investigators for blinding from the blood eosinophil counts [i.e., *absolute blood eosinophil counts, total white blood cell counts and white blood count differentials (%)*[#]].

7.5. Pharmacokinetics

7.5.1. Blood Sample Collection

Blood samples for determination of mepolizumab plasma concentration will be collected at the timepoints indicated in Section 7.1, Time and Events Table. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional timepoints to ensure thorough PK monitoring.

Processing, storage and shipping procedures are provided in the laboratory manual.

7.5.2. Sample Analysis

Plasma analysis will be performed under the control of PTS-DMPK/Scinovo, GSK. Concentrations of mepolizumab will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site.

7.6. Pharmacodynamic Markers

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

- Blood samples will be collected for measurement of serum free and total (free IL-5 and mepolizumab-bound IL-5) IL-5 levels at the visits specified in the Time and Events table (Section 7.1).

7.7. Immunogenicity

Blood samples will be collected prior to dosing at visits specified in the Time and Events Table (Section 7.1). Samples will be analysed for the presence of anti-mepolizumab antibodies.

7.8. T-cell profile

Patients with lymphoproliferative HES or those with an abnormal T-cell phenotype are at an increased risk of developing T-cell lymphoma as part of the natural history of the disease. The risk benefit ratio in these patients should be considered prior to initiation and/or continuation of treatment with mepolizumab [GlaxoSmithKline Document Number CM2003/00010/10].

Subjects with a history of *or* current lymphoma, malignancy, or previous history of cancer in remission for less than 12 months prior to randomization will be excluded from the study. In addition, T-cell profiling (including CD3, CD4, and CD8) will be performed during screening and at the end of study treatment.

7.9. F/P status

The FIP1L1-PDGFRα (F/P) fusion tyrosine kinase gene is a consequence of an interstitial chromosomal deletion [Cools, 2003] and detected in a subset of patients with HES (Section 2.2).

A blood sample will be collected at Screening (Visit 1) to determine the F/P status for every subject unless the documented result is available. Subjects who have the F/P fusion tyrosine kinase gene translocation (F/P positive) are excluded from this study (see Section 5).

7.10. Biomarker Sub-study

With the subject's consent, blood samples will be collected during this study and will be used for the biomarker sub-study. In addition, the samples may be used for the purposes of measuring novel biomarkers to identify factors that may influence HES, and/or potentially medically related conditions (e.g., T-cell lymphoma), as well as the biological and clinical responses to study treatment. If relevant, this approach will be extended to include the identification of biomarkers associated with adverse events.

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with HES conditions that are medically related to HES, and/or the action of study treatment may be identified by application.

All samples will be retained for a maximum of 15 years after the last subject completes the trial.

7.11. Genetics

Information regarding genetic research is included in Section 12.3.

7.12. Patient-Reported Outcomes (PROs)

Daily Electronic Diary

The electronic diary (eDiary) will be dispensed at the screening visit and will be completed at home by the subject on a daily basis. Subjects should complete the eDiary at approximately the same time each day. Subjects must complete the eDiary for at least 7 days before randomization.

Completion of PRO Questionnaires

PRO questionnaires are to be administered at the beginning of the visits specified in Section 7.1 in the order presented in the electronic device. To avoid biasing responses, 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 to avoid influencing the subject's response. Adequate time must be allowed to complete all items on the questionnaires, and if necessary, the subject must be encouraged to complete any missing items.

7.12.1. Brief Fatigue Inventory

The Brief Fatigue Inventory (BFI) is a tool developed for the rapid assessment of fatigue severity for use in both clinical screening and clinical trials [Mendoza, 1999]. The BFI has 9 items. The subject should rate their average and worst fatigue levels over the previous 24 hours using a numeric rating scale anchored with 0 (no fatigue/interference) and 10 (as bad as you can imagine/completely interferes) numeric rating scales. The subject will complete one item of the BFI daily and the full BFI every 7 days at home on the eDiary.

7.12.2. HES Daily Symptoms (HES-DS)

The HES Daily Symptoms (HES-DS) include 6 constitutional and organ system-specific symptoms commonly reported by patients with HES. At the randomization study visit, the subject will identify up to three symptoms that are most bothersome to him/her. Each of the 7 symptoms will be rated daily at home on the eDiary. Each item has a 11-point numeric rating scale with 0 indicating that the symptom is not present and 10 indicating symptom is worst imaginable. The symptoms will be rated each evening recalling the worst symptom experience over the previous 24 hours.

7.12.3. Clinician- and Subject-Rated Overall Response to Therapy Score (RTS)

The clinician and the subject will rate the response to therapy (the investigator and the subject should complete the assessment independently) at the visits specified in the Time and Events schedule (Section 7.1). The subject should complete the Subject-RTS as the first procedure at the study visit prior to study procedure or examinations by a clinician. Clinician-RTS will be completed at the end of their subject evaluation. This is an overall evaluation of response to treatment using a 7-point rating scale. This rating scale uses the following definitions:

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

7.12.4. Subject-Rated Symptom Severity (SSR)

The subject will rate overall severity of symptoms at the visits specified in the Time and Events schedule (Section 7.1). This is an overall evaluation of symptom severity using a 5-point rating scale of none, mild, moderate, severe and very severe.

7.12.5. Modified Memorial Symptom Assessment Scale-Short Form (MSAS-SF)

The Memorial Symptom Assessment Scale (MSAS) was developed to measure physical and psychological symptom prevalence, severity and distress across a range of cancers [Chang, 2000; Portenoy, 1994]. The MSAS provides a total, physical and psychological score of symptom burden based on ratings of symptom frequency and distress. A modified version of the MSAS was developed based on the symptoms described in literature and confirmed in qualitative interviews with 26 patients with HES. The MSAS has a recall period of the previous 7 days.

7.12.6. Patient Reported Outcome Measurement Information System (PROMIS) Physical Function and Sleep

The Patient Reported Outcome Measurement Information System (PROMIS) is a psychometrically validated, dynamic system to measure PROs efficiently in study participants with a wide range of chronic diseases and demographic characteristics based on calibrated item banks (sets of well-defined and validated items), and includes concepts such as pain, fatigue, physical function, depression, anxiety and social function. These calibrated item banks can be used to derive short forms (typically requiring 4-10 items per concept), or computerized adaptive testing (typically requiring 3-7 items per concept for more precise measurement) [Reeve, 2007].

To support assessment of physical function and sleep, short-form assessments of these concepts have been developed. The PROMIS physical function (14 items) and sleep scales (2 items) have a recall of 7 days and 5-point response scales, and will be completed at study visits as defined in Section 7.1.

7.12.7. SF-36 V2

The SF-36 v2 is a health status survey with 36 questions [Maruish, 2011]. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based

physical and mental health summary measures and a preference-based health utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-36 v2 has proven useful in differentiating the health benefits produced by a wide range of different treatments.

The SF-36 v2 assesses eight health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. The survey was constructed for self-administration by persons 14 years of age and older.

The SF-36 will be completed with a 4-week recall at a scheduled clinic visits as specified in Section 7.1, to support assessment of overall change in health-related quality of life (HRQoL). The SF-36 will be completed with a 1-week recall at an unscheduled 'Flare' visit, to provide an assessment of the impact of flare on HRQoL.

7.12.8. Work Productivity and Activity Impairment Index – General Health (WPAI-GH) V2

The WPAI-GH v2 is a self or interviewer administered tool comprised of 6 questions which address absenteeism, presenteeism (reduced effectiveness while working), overall work productivity loss (absenteeism plus presenteeism), and activity impairment. This validated tool captures data from the past 7 days. WPAI-GH outcomes are scored as impairment percentages, with a higher percentage indicating greater impairment and less productivity [Reilly, 1993].

7.12.9. Steroid Perception Questionnaire

The use of maintenance oral corticosteroids can have many and diverse adverse effects. The steroid perception questionnaire was developed to better assess the subjects perception of the adverse effects associated with the use of daily OCS including physical and mood impacts. In this study, HES therapy including a stable dose of OCS will be maintained throughout the 32-week study treatment period unless there is worsening of symptom(s) that requires an increase in therapy. Therefore, the questionnaire will be implemented at Randomization (Visit 2) only to characterize burden of OCS in this population of patients with HES.

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.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The primary efficacy endpoint is the proportion of subjects who experience an HES flare during the 32-week study treatment period. This study is designed to test the superiority of mepolizumab versus placebo. The primary analysis will test the following hypothesis:

- **Null hypothesis**: no difference between mepolizumab relative to placebo for the proportion of subjects who experience an HES flare during the 32-week study treatment period.
- **Alternative hypothesis**: the proportion of subjects who experience an HES flare during the 32-week study treatment period is smaller for mepolizumab compared to placebo.

Significance tests will be performed at the two-sided 5% level (one sided 2.5%).

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

This study is designed to test the superiority of mepolizumab versus placebo.

The primary efficacy endpoint is the proportion of subjects who experience an HES flare during the 32-week study treatment period. The power calculation assumes that 60% of subjects on placebo will experience an HES flare during the 32-week study treatment period. With a two-sided 5% level of significance and a sample size of 40 randomized subjects per arm, the null hypothesis will be rejected if the observed proportion of patients with an HES flare on placebo is 60% and on mepolizumab is 35% or less. If the true population proportion of subjects who would experience an HES flare during the 32-week study treatment period on placebo is 60% and on mepolizumab is 22%, the study has 90% power for demonstrating a statistically significant result for this assumed true population effect.

This endpoint is novel, and has not explicitly been used in clinical trials of HES. There is therefore little previous data on which to base estimates of the number of subjects who will experience an HES flare during the 32-week study treatment period.

9.2.2. Sample Size Sensitivity

If either the actual percentage of subjects on placebo who experience an HES flare during the 32-week study treatment period or the impact of mepolizumab is different from the values assumed in Section 9.2.1, the power to detect a change in the proportion of subjects who experience an HES flare during the 32-week study treatment period will be affected. Due to the uncertainty in the number of subjects who will experience an HES flare during the 32-week study treatment period, a blinded sample size re-estimation is planned (see Section 9.2.3).

9.2.3. Sample Size Re-estimation or Adjustment

While the estimate of 60% of placebo subjects and 22% of mepolizumab subjects having an HES flare during the 32-week study treatment period is felt by clinical experts to be reasonable for this population, the proportion of subjects who have an HES flare will be monitored, blinded to treatment, and if the blinded overall proportion is predicted to be <30% the sample size may be increased up to a maximum of 60 subjects per group (total 120 subjects). The planned increase to sample size will depend on the observed blinded overall proportion of subjects as follows:

Blinded overall proportion[1] (%)	N per group
≥30	40 (no increase)
27.5 – 30	45
25-<27.5	50
<25	60

[1]Proportion of subjects who have an HES flare during the 32-week study treatment period.

The decision to increase the sample size will be made when at least 30 subjects per arm have been randomised. The blinded overall proportion of subjects who have an HES flare will be calculated based on the HES flare data available in the CRF. This will include all HES flares meeting flare endpoint definition 'a)' in Section 7.3.1. The number of HES flares due to flare endpoint definition 'b)' is expected to be small, therefore in order to maintain the blood eosinophil blinding, HES flares due to subjects receiving two or more courses of blinded active OCS will not be included in the calculation of the blinded overall proportion.

9.3. Data Analysis Considerations

All pre-specified analyses will be described in a full reporting analysis plan (RAP) which will be finalized prior to unblinding.

The study will be unblinded once the final subject has completed the Week 32 visit plus the safety follow-up visit (if applicable), all queries for data collected up to this time are resolved and the clinical study database is frozen.

9.3.1. Analysis Populations

Intent-to-Treat Population:

The intent-to-treat (ITT) population will consist of all subjects who are randomized. This will constitute the primary population for all analyses of efficacy measures.

Per Protocol Population:

The Per Protocol (PP) population will consist of all subjects in the ITT population not identified as full protocol deviators with respect to criteria that are considered to impact the primary efficacy analysis. The decision to exclude a subject from the PP population or exclude part of their data from the PP population analyses will be made prior to

breaking the blind. The PP population will be used for a supplementary analysis of the primary endpoint.

Safety Population:

The Safety Population will consist of all subjects who are randomized and who receive at least one dose of trial medication. Randomized subjects will be assumed to have received study treatment unless definitive evidence to the contrary exists. This will constitute the primary population for all analyses of safety measures.

PK Population:

The PK population is defined as all subjects in the ITT population who received at least one dose of study medication and for whom at least one PK sample was obtained, analyzed and was measurable. This will be the primary population for assessing PK.

PD Population:

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

9.3.2. Treatment Comparisons

All treatment comparisons are between mepolizumab and placebo.

9.3.3. Multiple Comparisons and Multiplicity

In order to provide strong control of type I error when making inferences for the pre-defined secondary endpoints, multiplicity will be controlled using a hierarchical, closed testing procedure.

The hierarchy of endpoints is defined as follows:

1. Proportion of subjects who experience an HES flare during the 32-week study treatment period (primary endpoint)
2. Time to first HES flare
3. Proportion of subjects who experience an HES flare during Week 20 through Week 32
4. Rate of HES flares
5. Change from baseline in fatigue severity based on BFI item 3 (worst level of fatigue during past 24 hours) at Week 32

When strong control of type I error is required, each endpoint in the hierarchy will be formally tested for confirmatory evidence of statistical significance only if all preceding tests are statistically significant.

9.3.4. Interim Analysis

As described in Section 10.8, an external Independent Data Monitoring Committee (IDMC) will periodically review unblinded safety data from the study, in accordance with the IDMC Charter. The safety data analyses for the IDMC reviews will be performed by an independent statistical analysis data center (SDAC). There are no circumstances under which IDMC review of the data would lead to a recommendation to stop for efficacy of mepolizumab. Other than the procedures described in Section 6.3, all personnel having direct responsibility for the conduct of the study will remain blinded to treatment groups for all data until the database is frozen.

9.4. Key Elements of Analysis Plan

9.4.1. Efficacy Analyses

The study is designed to continue to collect data on HES flares for subjects who prematurely discontinue from their randomized treatment. All data on HES flares collected for these subjects will also be included in the primary analysis. For subjects who withdraw prematurely from study treatment and for whom collection of data on HES flares is not possible, it will be assumed for the primary endpoint that they are treatment failures, i.e., that they experience a flare following study withdrawal. This strategy corresponds to a de facto estimand of treatment effect. Sensitivity analyses will be performed to examine the potential impact of the missing data.

Primary endpoint

The primary efficacy endpoint will be compared between treatments using a Cochran-Mantel-Haenszel test stratified by baseline OCS dose (0-≤20mg/day and >20mg/day prednisolone/prednisone or equivalent) and region.

The analysis will be supplemented with a logistic regression analysis adjusting for covariates of baseline OCS dose, region, and treatment. The model will be used to estimate the odds ratio for the treatment difference and associated p-value and 95% confidence limit.

Sensitivity analyses to assess the impact of missing data will be performed as follows:

- Subjects withdrawing from the study prematurely prior to reporting an HES flare, with the primary reason for treatment withdrawal reported as AE or Lack of Efficacy, will be assumed to experience an HES flare. Subjects withdrawing from the study prematurely with any other reason for treatment withdrawal will be included as having a flare if one is recorded prior to study withdrawal, and as not having a flare if no flare is recorded prior to study withdrawal.

- Observed data analysis. Subjects withdrawing from the study prematurely will be included as having a flare if one is recorded prior to study withdrawal, and as not having a flare if no flare is recorded prior to study withdrawal.

Secondary endpoints

Time to first HES flare

The time to first HES flare will be calculated from the date of randomization and the start date of the HES flare (see Section 7.3.1). Time to first HES flare will be analyzed using a log-rank test stratified by baseline OCS dose and region. This analysis will be supplemented by a Cox proportional hazards regression model allowing for covariates of baseline OCS dose and region. The hazard ratio will be derived along with 95% confidence limits. Cumulative event rates will be calculated using the Kaplan-Meier method. Subjects who withdraw prematurely from randomized treatment will continue to be monitored for HES flares. If a subject withdraws prematurely from the study and collection of data on flares is not possible, the event time will be censored at the time point at which they withdrew from the study. Sensitivity analyses to assess the impact of missing data will be performed with full details provided in the Reporting and Analysis Plan (RAP).

Proportion of subjects who experience an HES flare during Week 20 through Week 32

An HES flare during Week 20 through Week 32 will be defined as an HES flare starting or ongoing on or after the date of the Week 20 visit up to and including the date of the Week 32 visit. Subjects withdrawing from the study prematurely, prior to reporting an HES flare during Week 20 through Week 32, will be assumed to experience a flare during Week 20 through Week 32.

The proportion of subjects who experience an HES flare during Week 20 through Week 32 will be analyzed in the same way as the primary endpoint, using a Cochran-Mantel-Haenszel test stratified by baseline OCS dose and region. The analysis will be supplemented with a logistic regression analysis adjusting for covariates of baseline OCS dose, region and treatment.

Sensitivity analyses to assess the impact of missing data will be performed with full details provided in the RAP.

Rate of HES flares

The rate of HES flares will be calculated for each subject as the number of observed HES flares divided by the time (expressed in years) between randomisation and either the week 32 visit date if available, or otherwise the study withdrawal date. The number of observed HES flares will be calculated for each subject as the number of unique starting dates for HES flares. To be considered as a separate episode of HES flare, the start date of an HES flare must be at least 14 days apart from the resolution date of the preceding HES flare. See Section 7.3.1 for detailed definitions of flare start and resolution dates. For subjects withdrawing prematurely from the study during the 32 week treatment period, all data up to the time of study withdrawal will be used to calculate the rate of HES flares. Sensitivity analyses to assess the impact of missing data will be performed with full details provided in the RAP.

The rate of HES flares will be compared between treatment groups using a stratified Wilcoxon Rank Sum test, stratified by baseline OCS dose and region. This analysis will be supplemented by an analysis using a negative binomial generalised linear model with a log link-function. The model will include terms for treatment group, region, baseline OCS dose and observed time (as an offset variable). The estimated mean rates per year, treatment ratio and confidence limits will be presented.

Change from baseline in fatigue severity based on BFI item 3 (worst level of fatigue during past 24 hours) at Week 32

The change from baseline in fatigue severity (worst level of fatigue during past 24 hours) at week 32 will be calculated using the mean of the 7 daily assessments of BFI item 3 up to and including the date of the week 32 visit as the week 32 assessment, and the mean of the 7 daily assessments of BFI item 3 up to and including the date of randomisation as the baseline assessment. Subjects withdrawing prematurely from the study during the 32 week treatment period will be assumed to have the largest (i.e., worst) value observed for any subject for the change from baseline BFI item 3 at week 32. Sensitivity analyses to assess the impact of missing data will be performed with full details provided in the RAP.

The change from baseline in fatigue severity at week 32 will be compared between treatment groups using a stratified Wilcoxon Rank Sum test, stratified by baseline fatigue severity ("severe" defined as BFI item 3 >=7, and "not severe" defined as BFI item 3<7) and region.

9.4.2. Safety Analyses

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

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

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

Immunogenicity will be summarized using appropriate descriptive statistics.

9.4.3. Pharmacokinetic Analyses

Blood samples will be collected to determine mepolizumab plasma concentrations (Section 7.5). Sparse blood sampling is being implemented in this study. The mepolizumab plasma concentrations from this study will be evaluated using the population PK model developed based on previous mepolizumab data collected during

mepolizumab clinical development. The analysis will be conducted using an appropriate software and will allow the determination for example of the population and/or individual systemic exposure, apparent volume of distribution and apparent clearance as well as characterize the between- and within subject variability. The effect of subjects' characteristics such as, for example, body weight, age, gender, serum creatinine on mepolizumab systemic exposure will also be explored in order to explain the inter-subject variability in drug exposure. Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively.

Further details of the analysis will be described in the RAP.

9.4.4. Pharmacodynamic Analyses

Ratio to baseline in blood eosinophil count will be compared between treatments using a mixed model repeated measures analysis adjusting for the covariates of baseline blood eosinophil count, baseline OCS dose and region. Values below the lower limit of quantification will be imputed as half the lower limit of quantification prior to analysis. Data will be log-transformed prior to analysis. Visit will be fitted as a categorical variable with the effect of treatment group and baseline eosinophil count varying at each visit (i.e., visit by baseline and visit by treatment group interactions will also be included in the model).

9.4.5. Other Analyses

Full details of the analyses to be performed on all exploratory endpoints will be given in the RAP.

If genetic analysis is warranted, a separate research analysis plan will be drafted (Section 12.3).

If biomarker analysis is warranted, a separate research analysis plan will be drafted (Section 7.10).

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.
- 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 CRF will serve as the source document.

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

- 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.

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

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

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

10.8. Independent Data Monitoring Committee

An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety data in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter.

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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
ANCA	anti-neutrophil cytoplasmic antibodies
AST	Aspartate transaminase
BP	Blood pressure
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CRF	Case Report Form
C-RTS	Clinician-rated overall Response to Therapy score
CUP	Compassionate Use Program
CV	Cardiovascular
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic diary
EGPA	Eosinophilic Granulomatosis with Polyangiitis
EoE	Eosinophilic Esophagitis
EW	Early Withdrawal
FAAN	Food Allergy and Anaphylaxis Network
FRP	Female of reproductive potential
FEV_1	Forced Expiratory Volume in one second
FISH	Fluorescence in situ hybridization
F/P	Fip1-like1-Platelet Derived Growth Factor Receptor α (FIP1L1-PDGFRa)
FSH	Follicle stimulating hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GI	Gastrointestinal
GSK	GlaxoSmithKline
HBsAg	Hepatitis B Surface Antigen
hCG	human chorionic gonadotrophin
HCRU	Healthcare resource utilization
HCV	Hepatitis C Virus
HES	Hypereosinophilic Syndrome
HF	Heart failure
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography

HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICU	Intensive care unit
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL	Interleukin
INFα	Interferon alpha
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent-to-Treat
IV	Intravenous(ly)
LABA	Long-acting $beta_2$-agonist
LDH	Lactate dehydrogenase
L-HES	Lymphocytic hypereosinophilic syndrome
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
M-HES	Myeloproliferative hypereosinophilic syndrome
MSAS-SF	Memorial Symptom Assessment Scale-Short Form
MSDS	Material Safety Data Sheet
msec	millisecond
NAB	Neutralizing antibodies
NIAID	National Institute of Allergy and Infectious Disease
NYHA	New York Heart Association
OCS	Oral corticosteroid
OLE	Open-label extension
PCR	Polymerase chain reaction
PCSA	Placebo-controlled severe asthma
PD	Pharmacodynamics
PEF	Peak expiratory flow
PK	Pharmacokinetics
PMS	Post marketing surveillance
PP	Per protocol
PRO	Patient reported outcome
PROMIS	Patient Reported Outcome Measurement Information System
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red blood cell

RNA	Ribonucleic acid
RTS	Response to Therapy Score
SABA	Short-acting beta$_2$-agonist
SAE	Serious Adverse Event
SC	Subcutaneous(ly)
SDAC	Statistical analysis data center
SOC	System Organ Class
SoC	Standard of care
SRM	Study reference manual
SSR	Subject-Rated Symptom Severity
URTI	Upper respiratory tract infection
WBC	White blood cell
Wks	Weeks

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.2. Appendix 2: Phase III-IV liver chemistry stopping and monitoring criteria, and required actions and follow-up assessments

Phase III-IV liver chemistry stopping criteria

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT absolute	**Both** ALT ≥ 8xULN **and** ≥ 2X baseline value
ALT Increase	**Both** ALT ≥ 3xULN **and ≥** 1.5x baseline value that 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	**Both** ALT ≥ 3xULN **and ≥** 1.5x baseline value **and** cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	**Both** ALT ≥ 3xULN **and ≥** 1.5x baseline value 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 SAE data collection tool if the event also meets the criteria for an SAE[2]**.** • Perform liver event follow up assessments. • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below). • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted**. • If restart/rechallenge **not allowed or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments. **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend. • 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 1 week of the liver event[6]. • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN. • Obtain complete blood count with differential to assess eosinophilia. *Note: To ensure investigators remain blinded to eosinophil count, as for all other blood count tests after randomization, sites will only be sent absolute lymphocyte, monocyte, neutrophil, and basophil counts. The*

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. **For All other criteria:** • 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.	*complete blood count with differential (including eosinophil count will be available after the subject's treatment has been unblinded.* • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form. • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form. • **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins) • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). NOTE: not required in China. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms

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

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

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN and ≥ 1.5x baseline value **but** ALT <8x ULN and < 2x baseline value **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, after 4 weeks of monitoring, ALT <3xULN and <1.5 X baseline value, and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline

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12.3. Appendix 3: Genetic Research

Genetics – Background

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

Genetic Research Objectives and Analyses

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

- Response to medicine, including mepolizumab or any concomitant medicines;
- HES 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 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 DNA extraction. A blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. If a subject initially declines to participate in genetic research and then changes their mind, a sample should be obtained at the earliest opportunity. 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 inability to utilize the original sample.

The genetic sample is labeled (or "coded") with the same study specific number as 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 purposes 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 clinical study or after completion of the clinical study and may be analyzed during the clinical study or stored for future analysis.

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

Screen and Baseline Failures

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

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

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

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

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

12.4.1. Definition of Adverse Events

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

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

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

condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.4.2. Definition of Serious Adverse Events

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

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

a. Results in death

b. Is life-threatening

NOTE:

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

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

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

d. Results in disability/incapacity

NOTE:

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

• This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.
Refer to Section 12.2 for the required liver chemistry follow-up instructions

12.4.3. Definition of Cardiovascular Events

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

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

12.4.4. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.
- Subject-completed PRO questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the PRO questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

12.4.5. Evaluating AEs and SAEs

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort

and not interfering with everyday activities.

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

Assessment of Causality

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

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests

or investigations, histopathological examinations or consultation with other health care professionals.

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

12.4.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

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

12.5. Appendix 5: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

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

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

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011])
4. Injectable progestogen [Hatcher, 2011]
5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011]
7. Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

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

12.5.2. 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 Section 12.4.6. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

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

12.5.3. References

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12.6. Appendix 6: Anaphylaxis Criteria

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

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

12.7. Appendix 7: Classification of Heart Failure

Physicians usually classify patients' heart failure according to the severity of their symptoms [American Heart Association, 2014]. The table below describes the most commonly used classification system, the NYHA Functional Classification. It places patients in one of four categories based on how much they are limited during physical activity.

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
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.

Class	Objective assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

For Example:

- A patient with minimal or no symptoms but a large pressure gradient across the aortic valve or severe obstruction of the left main coronary artery is classified: Function Capacity I, Objective Assessment D.
- A patient with severe anginal syndrome but angiographically normal coronary arteries is classified: Functional Capacity IV, Objective Assessment A.

12.8. Appendix 8: Country Specific Requirements

No country-specific requirements exist.