TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	Study 205050: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Investigate the Efficacy and Safety of Mepolizumab Administered Subcutaneously in Subjects with Moderate to Severe Atopic Dermatitis

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Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2015N268158_00	2016-AUG-25	Original
2015N268158_01	2016-DEC-26	Amendment No. 1
Protocol amendment 1 includes recommendations from the US Food and Drug Administration (FDA) and other clarifications.		
2015N268158_02	2017-JUN-22	Amendment No. 2
Protocol amendment 2 includes: - The addition of administrative interim analyses to enable review of subject efficacy and safety data summaries. - Minor clarifications regarding: collection of ECGs in triplicate for all ECG time points; general order of study procedures; checks for BSA and EASI eligibility utilizing eCRF auto calculated totals at Screening and Baseline visits. - Increase in anticipated number of subjects screened from approximately 75 subjects to approximately 140 subjects (no change in target number of subjects randomized). - Reminders inserted into the study schematic and Time and Events tables, indicating no IP dose will be administered at Week 16 and Week 20. - Removed requirement for subject data entry into the Daily Sign and Symptom Severity Diary for at least 7 consecutive days immediately prior to the Baseline visit.		

SPONSOR SIGNATORY

Angelo Secci, MD Senior Medical Director Dermatology TA, R&D	Date

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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

Regulatory Agency Identifying Number(s): IND 129605

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol 205050: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Investigate the Efficacy and Safety of Mepolizumab Administered Subcutaneously in Subjects with Moderate to Severe Atopic Dermatitis

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

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

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

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

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Rationale

Interleukin-5 (IL-5) is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Elevated levels of serum IL-5 and peripheral blood eosinophils have been implicated in the pathogenesis of atopic dermatitis (AD). Mepolizumab (SB-240563; NUCALA®) is a humanized monoclonal antibody (IgG1, kappa, mAb) that binds to human interleukin-5 (hIL-5) and blocks it from binding to the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibits signaling. Mepolizumab neutralizes IL-5 leading to a reduction in the production and survival of eosinophils which may be therapeutic in subjects with AD.

Mepolizumab has been approved for the treatment of severe eosinophilic asthma in several regions and countries including the United States (US), Canada, European Union, Japan and Taiwan.

The purpose of this randomized, double-blind study is to investigate the efficacy and safety of mepolizumab (100 mg subcutaneous [SC] administered every 4 weeks) compared with placebo over a 16-week treatment period in adult subjects with moderate to severe AD.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	**Primary**
• To determine the efficacy of mepolizumab SC in subjects with moderate to severe AD	• Proportion of subjects who achieve treatment success defined as an Investigator's Global Assessment (IGA) score of 0 or 1 and at least a 2-grade improvement at Week 16.
Secondary	
• To estimate the efficacy of mepolizumab SC	• Mean percentage change in Eczema Area and Severity Index (EASI) score from baseline to each study visit. • Proportion of subjects with an IGA score of 0 or 1 and at least a 2-grade improvement at each study visit.
• To describe the safety and tolerability of mepolizumab SC	• Incidence, frequency, and nature of adverse events (AEs) including local injection site reactions and systemic reactions. • Change from baseline in laboratory parameters (hematology and chemistry) and frequency of clinically significant abnormal test results. • Change from baseline in vital signs and frequency of clinically significant abnormal results. • Immunogenicity as measured by anti-mepolizumab antibodies.

Objectives	Endpoints
Exploratory	
• To further estimate the efficacy of mepolizumab SC	• Proportion of subjects with ≥50% improvement in EASI from baseline to each study visit. • Proportion of subjects with ≥75% improvement in EASI from baseline to each study visit. • Mean change in percent of total body surface area (% BSA) affected from baseline to each study visit. • Mean change in weekly average of daily itch/pruritus numeric rating scale [NRS] score (based on Item #1 of Daily Sign and Symptom Severity Diary) from baseline to Week 16. • Mean change in weekly average of daily itch/pruritus NRS score (based on Item #1 of Daily Sign and Symptom Severity Diary) from baseline to each study visit.
• To evaluate disease flare/relapse during and after treatment with mepolizumab SC	• Proportion of subjects who have an IGA score of 3 or 4 after achieving an IGA score of 0 or 1 and at least a 2-grade improvement during the Treatment and Follow-up Periods. • Proportion of subjects who have an increase in EASI score of ≥25% from baseline during the Treatment and Follow-up Periods.
• To characterize the relationship between efficacy and blood eosinophil counts	• Proportion of subjects who have an IGA score of 0 or 1 and at least a 2-grade improvement at each study visit by baseline blood eosinophil count. • Mean percentage change in EASI score from baseline to each study visit by baseline blood eosinophil count. • Mean percentage change in EASI score compared to change in blood eosinophils at each visit.
• To investigate the pharmacokinetics (PK) of mepolizumab in subjects with moderate to severe AD	• Plasma concentration of mepolizumab
• To investigate the pharmacodynamics of mepolizumab in the blood and in AD lesional skin biopsies	• Ratio to baseline in blood eosinophil counts • IL-5 levels (serum free and total) • Levels of circulating biomarkers in the blood including IgE, eosinophilic cationic protein (ECP), and levels of chemokines such as thymus and activation-regulated chemokine (TARC) • Gene expression biomarkers in skin biopsies
• To describe the effect of mepolizumab SC on Patient-reported Outcomes (PROs)	• Change over time in Daily Sign and Symptom Severity Diary • Change over time in Patient Global Impression of Severity and Patient Global Impression of Change

Overall Design

This is a multicenter, randomized, double-blind, placebo-controlled, 2-arm, parallel-group study that will investigate the efficacy and safety of mepolizumab SC in adult subjects with moderate to severe AD. At the Baseline visit on Day 1, subjects who meet all inclusion criteria including a screening blood eosinophil count ≥350 cells/μL and none of the exclusion criteria will be randomized in a ratio of 1:1 (mepolizumab 100 mg SC: placebo SC).

Treatment Arms and Duration

- This study will consist of 4 periods:
    - Pre-screening (up to 4 weeks)
    - Screening (1 to 2 weeks)
        - If an ineffective treatment is stopped for the purpose of study entry, informed consent should be obtained at the time the ineffective treatment is stopped. Note: For subjects who may need to stop treatment with a biologic, the total Pre-Screening and Screening period may last up to 20 weeks.
    - Treatment (16 weeks with the last dose of study treatment at Week 12)
    - Follow-up (4 weeks).
- The subject will participate in the study for a maximum total duration of approximately 26 weeks. (Note: Subjects who need to stop treatment with a biologic during the Pre-Screening Period may participate in the study for a maximum total duration of approximately 40 weeks).
- For at least 7 consecutive days immediately prior to the Baseline visit and throughout the Treatment and Follow-up Periods, subjects must apply a non-prescription, non-medicated (without an active ingredient) emollient twice daily. The same emollient will be used by the subject throughout the study.

    Note: In order to facilitate the assessment of AD at study visits, the subject must not apply the emollient within the 2-hour period preceding the study visit. If the emollient is applied less than 2 hours prior to the study visit, study procedures will be performed ≥2 hours after emollient application.
- Subject participation in the following exploratory sub-studies is voluntary and will require additional informed consent:
    1. Skin biopsy sub-study: skin biopsies (at pre-identified study centers only) to study the effect of mepolizumab on gene expression biomarkers in the skin.
    2. Genetics sub-study: to investigate the relationship between genetic variants, response to medicine and susceptibility, severity and progression of AD and related conditions.
- In order to maintain the blind, the results from the following laboratory assessments will be blinded during the study: PK, immunogenicity, IL-5, blood biomarkers, and

skin biopsy. Additionally, the following will be blinded from the Baseline visit until the end of the study: total white blood cell (WBC) count, absolute eosinophil count, and differential (%). Investigators will ensure that subjects and any physicians managing study subjects during the course of the study are informed of this requirement. Absolute neutrophil, lymphocyte, monocyte, and basophil counts will be provided.

- Subjects who experience a suspected AD flare/relapse between scheduled study visits in the Treatment and Follow-up Periods will return to the clinic for an unscheduled visit to determine if AD flare/relapse criteria are met. If AD flare/relapse is confirmed at the time of the unscheduled visit, the assessments of the unscheduled visit for flare/relapse will be completed. In the case of flare/relapse with intolerable AD symptoms where the use of prohibited medication is required, the subject will be permanently withdrawn from treatment and the procedures and visits described in the last two bullets of the **Treatment Period** (below) will apply. AD flare/relapse is defined as:
    - an IGA score of 3 or 4 after achieving an IGA score of 0 or 1 and at least a 2-grade improvement, OR
    - an increase in EASI score of ≥25% from Baseline.

Pre-screening/Screening Periods

Pre-Screening Period: Prohibited Medications Prior to Screening:

- Selection and modification of the subject's medications prior to study participation is based on the physician's judgment according to sound medical practice and principles and each subject's needs. Effective medications and treatments should not be changed merely for the purpose of enabling the subject's participation in the study.
- Informed consent should be obtained prior to performing any study assessments or procedures.
- Certain medications and treatments are prohibited prior to the Screening visit and throughout the study in order to allow for the evaluation of mepolizumab as monotherapy for AD and to eliminate the possible confounding effects of the specified medications/treatments on the evaluation of the study endpoints.
- Subjects who have used prohibited concomitant medications or non-drug therapies will complete a Pre-screening period.
- Assessments for the Pre-screening Visit will be completed up to 4 weeks prior to the Screening Visit.

Screening Period:

- The Screening Period will begin once the subject meets the criteria for prohibited concomitant medications and non-drug therapies. The Screening Period will last from a minimum of 1 week to a maximum of 2 weeks prior to the Baseline visit.
- For subjects who have not used a prohibited medication or non-drug therapy the assessments for the Pre-Screening and Screening Periods will be combined. The total

time to complete the combined Pre-Screening and Screening assessments will be a minimum of 1 week to a maximum of 2 weeks prior to the Baseline visit.

For All Subjects:

- Results of the blood eosinophil count obtained at the Screening visit, after requirements regarding previous use of prohibited medication and non-drug therapies are met, will be used to determine eligibility (≥350 cells/μL) and therefore must be available prior to randomizing the subject.

- At the Screening visit, site personnel will train subjects on the use of the electronic Daily Sign and Symptom Severity Diary. Subjects will complete the Daily Sign and Symptom Severity Diary starting at the Screening Visit and throughout the life of study Site personnel will receive automated alerts based on subject data entry throughout life of study. Subjects for whom an alert is received will be re-educated on the importance of completing their diary. Every effort will be made to re-educate those subjects who continue to not complete their diary (see SRM for information regarding monitoring).
- The results of all laboratory assessments must be available prior to randomization in order to determine the subject's eligibility. The Screening Period may be extended beyond 2 weeks, if needed, to obtain the results of all laboratory assessments.

Treatment Period

- The Treatment Period will begin with the Baseline visit on Day 1. Study visits will also occur at Week 4, Week 8, Week 12, and Week 16.
- At the Baseline visit, eligible subjects will be randomized in a 1:1 ratio to receive either mepolizumab 100 mg SC or placebo SC.
- Study treatment will be prepared by a designated, qualified, unblinded member of the site staff who is independent of the protocol-defined study assessments.
- Study treatment will be administered by SC injection at the Baseline visit, Week 4, Week 8, and Week 12 (last dose) into the upper arm, abdomen, or thigh. Every effort should be made to inject each dose of study treatment into the same region of the body. Each SC injection will be administered by a trained member of the site staff who is blinded to study treatment. Each subject will receive one 1 mL SC injection of study treatment at each visit where dosing is scheduled.
- Subjects will remain in the clinic for safety monitoring one hour after each administration of study treatment. Subjects will be observed for adverse events (AEs) including systemic reaction (i.e., allergic (type 1 hypersensitivity) reaction and other systemic reactions) and local injection site reactions.
- There are no planned dose adjustments during the study.
- The last dose of study treatment will be administered at Week 12. Study treatment will **not** be administered at Week 16. For those subjects randomized to mepolizumab, four doses will provide therapeutic coverage to Week 16 when efficacy assessments for the primary endpoint will occur. For this reason, the

Week 16 visit is considered to be part of the Treatment Period while also serving as the first follow-up visit (Post-Treatment Visit 1).

- Subjects who prematurely discontinue study treatment will be followed for 8 weeks after the last dose and will be scheduled for the following visits:
  - Early Withdrawal Visit (if the decision is made to prematurely discontinue study treatment <4 weeks after last dose of study treatment),
  - Post-Treatment Visit 1 (4 weeks after last dose of study treatment), and
  - Post-Treatment Visit 2 (8 weeks after last dose of study treatment).
- Subjects who are withdrawn from the study will complete an Early Withdrawal visit and then exit the study.

Follow-up Period

- Following completion of the Week 16 visit (Post-Treatment Visit 1), subjects will enter the Follow-up Period with a visit at Week 20 (Post-Treatment Visit 2, occurring 8 weeks after the last dose of study treatment).

Type and Number of Subjects

Approximately 140 adult subjects (ages 18 to 70 years) with moderate to severe atopic dermatitis will be screened to achieve approximately 56 randomized and 50 evaluable subjects.

Analysis

The primary endpoint will be the proportion of subjects who achieve treatment success defined as an IGA score of 0 or 1 and at least a 2-grade improvement at Week 16.

Sample size is based on the objective to characterize the clinical activity of mepolizumab in subjects with moderate-to-severe atopic dermatitis. In order to characterize this, we assume that a 40% IGA response rate in the mepolizumab group and a 10% IGA response in the placebo arm, as well as a at least 15 percentage point improvement over placebo, will constitute a clinically meaningful improvement.

Using Bayesian posterior probability and assuming a uniform prior from 0-1 for difference in response rate, 25 mepolizumab subjects (and 25 placebo subjects) will power the study to approximately 80% with predictive probability method and provide P (difference in response rate ≥15%|Data) greater than 70% if the true response rate is 40% for mepolizumab group and 10% for placebo group. The 80% credible intervals for the difference in response rate will be presented. No pair wise comparisons are planned.

Administrative and formal interim analyses may be performed. An administrative interim analysis may be performed to enable the review of subject efficacy and safety data. The formal interim analysis may be conducted to assess futility when approximately 50% of subjects have been randomized and completed the Week 8 visit.

The primary analysis will be performed on the Intent-to-Treat (ITT) population, with a supporting analysis of the per protocol (PP) population.

2. INTRODUCTION

2.1. Study Rationale

Interleukin-5 (IL-5) is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Elevated levels of serum IL-5 and peripheral blood eosinophils have been implicated in the pathogenesis of atopic dermatitis (AD). Mepolizumab (SB-240563; NUCALA®) is a humanized monoclonal antibody (IgG1, kappa, mAb) that binds to human interleukin-5 (hIL-5) and blocks it from binding to the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibits signaling. Mepolizumab neutralizes IL-5 leading to a reduction in the production and survival of eosinophils which may be therapeutic in subjects with AD.

Mepolizumab has been approved for the treatment of severe eosinophilic asthma in several regions and countries including the United States (US), Canada, European Union, Japan, and Taiwan.

The purpose of this randomized, double-blind study is to investigate the efficacy and safety of mepolizumab (100 mg subcutaneous [SC] administered every 4 weeks) compared with placebo over a 16-week treatment period in adult subjects with moderate to severe AD.

2.2. Brief Background

Atopic dermatitis is a common inflammatory skin condition characterized by chronic pruritus, lichenification, xerosis, erythematous papules and plaques. The cause of AD is multifactorial, with genetic and environmental factors, deficient skin barrier function, and impaired immune response being the most predominant factors [Guttman-Yassky, 2011a; Guttman-Yassky, 2011b]. The prevalence of AD is increasing, affecting up to 20% of children and 2–10% of adults in industrialized countries [Schneider, 2013; Shaw, 2011; Silverberg, 2013].

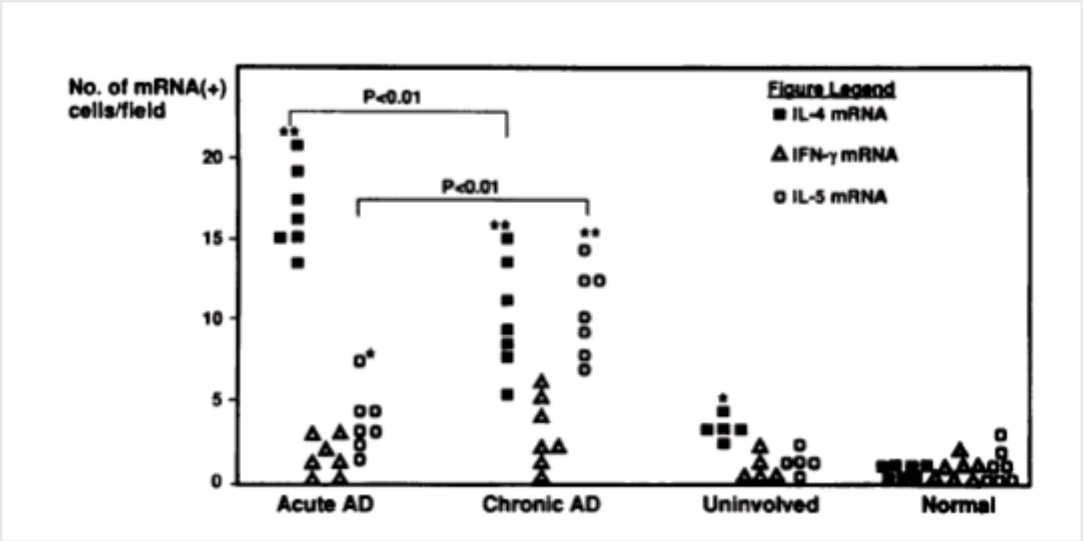
Atopic dermatitis, IL-5 expression and eosinophilia

AD is considered to be a type 2 helper T-cell (Th-2) mediated disease that results in over production of interleukin (IL)-4, IL-5, and IL-13. Elevated serum levels of IL-5 have been reported in patients with moderate and severe AD. In a study of 25 AD patients, elevated serum levels of IL-5 were detected in 22 patients compared to minimal to no detectable levels of IL-5 in normal controls. Serum levels of IL-5 decreased significantly with topical steroid treatment and a greater reduction in clinical severity (>40%) was associated with a greater decrease in IL-5 serum levels [Kondo, 2001].

IL-5 overproduction promotes the differentiation, activation, mobilization, and survival of eosinophils [Guttman-Yassky, 2011b]. In a study reported by Hamid et al., the number of activated eosinophils (EG2+) in the skin from both acute AD lesions (acute erythematous AD lesions <3 days onset) and chronic AD lesions (chronic lichenified AD

lesions >2 weeks duration) were significantly elevated compared to non-lesional skin and skin from normal controls [Hamid, 1994]. Expression of IL-5 messenger ribonucleic acid (mRNA) levels was higher in chronic AD lesions compared to acute AD lesions or uninvolved skin (Figure 1). As compared with normal control skin or uninvolved skin of patients with AD, acute and chronic skin lesions had significantly greater numbers of cells that were positive for IL-4 ($p<0.01$) and IL-5 ($p<0.01$) mRNA expressing cells. Chronic AD skin lesions had significantly fewer IL-4 mRNA-expressing cells ($p<0.01$), but significantly greater IL-5 mRNA ($p<0.01$) than acute AD lesions. These data indicate that, although acute and chronic AD lesions are associated with increased activation of IL-4 and IL-5 genes, initiation of acute skin inflammation in AD is associated with a predominance of IL-4 expression whereas maintenance of chronic inflammation is predominantly associated with increased IL-5 expression and eosinophil infiltration. In the transition from acute to chronic atopic disease, there is a rise in IL-5 expression in the activated eosinophils [Hamid, 1994].

Figure 1 In situ hybridization of AD skin lesions and normal skin, by using riboprobes for IL-4, IL-5, and interferon (IFN)-gamma



1. Republished with permission of American Society for Clinical Investigation [Hamid, 1994]; permission conveyed through Copyright Clearance Center, Inc.
2. *p <0.05 or **p<0.01, respectively, as compared to the same cytokine mRNA in normal skin.

In another study, chronic AD lesions showed evidence of activated eosinophils [Kiehl, 2001]. These results provide further evidence that tissue eosinophilia may be important for development of chronic AD.

Effective AD treatment has been shown to impact the number of eosinophils as well as the level of IL-5 in the peripheral blood and skin. For example, tacrolimus has been shown to decrease levels of IL-5 and activated eosinophils in the skin [Caproni, 2007]. In a study of 20 children with AD, a significant relationship between pre-treatment peripheral blood eosinophil counts and disease severity as measured by the severity score atopic dermatitis (SCORAD) index was observed ($p=0.0001$) [La Grutta, 2005]. All patients achieved a clinical remission after 1 to 2 week pulse treatments with a topical

corticosteroid (mometasone furorate) with a significant decrease in blood eosinophil counts ($p<0.0001$).

Mepolizumab

Mepolizumab (SB-240563) is a humanized monoclonal antibody (IgG1, kappa, mAb) that blocks human interleukin-5 (hIL-5) from binding to its receptor. Mepolizumab has been shown to reduce blood and tissue eosinophils and provide clinical benefit in subjects with severe eosinophilic asthma [Ortega, 2014a] and potential clinical benefit in subjects with hypereosinophilic syndrome [Rothenberg, 2008] and eosinophilic granulomatosis with polyangiitis [Kim, 2010; Menzella, 2015]. A cluster analysis showed that responses in patients with severe eosinophilic asthma were correlated with an elevated baseline blood eosinophil count [Ortega, 2014b]. To date, there have been no safety concerns identified with mepolizumab that would preclude further investigation in the patient populations under study in the clinical development program.

In 2002, a phase 2 study (SB240563/045) evaluated the efficacy of mepolizumab administered intravenously in adult subjects with moderate AD [Oldhoff, 2005; GlaxoSmithKline Document Number 2014N217948_00, 2014]. Mepolizumab (750 mg) or placebo was administered via two intravenous (IV) injections one week apart. The primary endpoint was the proportion of subjects with a Physician Global Assessment of Improvement (PGAI) score of "0=cleared", "1=almost cleared", or "2=marked improvement" at week 2. While there was a higher proportion of responders in the mepolizumab group (4/18 subjects=22.2%) compared to placebo (1/22 subjects=4.6%), the difference was not statistically significant ($p=0.115$). However, a Proportional Odds analysis for the PGAI at Week 2 (i.e., considering all six levels of response, PGAI 0-5) showed an odds ratio (90% confidence interval [CI]) of 3.6 (1.3, 10.2) in favor of mepolizumab which did achieve statistical significance ($p=0.0193$). Mepolizumab was well tolerated and no safety signals were observed. Statistical analysis of change from baseline in blood eosinophil counts at week 2 showed a mean difference (90% CI) between mepolizumab and placebo treatment groups of −489 (−648, −329) cells per microliter which was statistically significant ($p<0.001$). The limited clinical effect in the primary endpoint analysis may have been due to the short duration of the clinical study (2 weeks).

The scientific data implicating the role of IL-5 and eosinophils in the pathogenesis of AD provide the basis for the investigation of mepolizumab for the treatment of moderate to severe AD in a study with a longer treatment duration than the prior phase 2 study (SB240563/045).

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	**Primary**
• To determine the efficacy of mepolizumab SC in subjects with moderate to severe AD	• Proportion of subjects who achieve treatment success defined as an Investigator's Global Assessment (IGA) score of 0 or 1 and at least a 2-grade improvement at Week 16.
Secondary	
• To estimate the efficacy of mepolizumab SC	• Mean percentage change in Eczema Area and Severity Index (EASI) score from baseline to each study visit. • Proportion of subjects with an IGA score of 0 or 1 and at least a 2-grade improvement at each study visit.
• To describe the safety and tolerability of mepolizumab SC	• Incidence, frequency, and nature of adverse events (AEs) including local injection site reactions and systemic reactions. • Change from baseline in laboratory parameters (hematology and chemistry) and frequency of clinically significant abnormal test results. • Change from baseline in vital signs and frequency of clinically significant abnormal results. • Immunogenicity as measured by anti-mepolizumab antibodies.
Exploratory	
• To further estimate the efficacy of mepolizumab SC	• Proportion of subjects with ≥50% improvement in EASI from baseline to each study visit. • Proportion of subjects with ≥75% improvement in EASI from baseline to each study visit. • Mean change in percent of total body surface area (% BSA) affected from baseline to each study visit. • Mean change in weekly average of daily itch/pruritus numeric rating scale [NRS] score (based on Item #1 of Daily Sign and Symptom Severity Diary) from baseline to Week 16. • Mean change in weekly average of daily itch/pruritus NRS score (based on Item #1 of Daily Sign and Symptom Severity Diary) from baseline to each study visit.
• To evaluate disease flare/relapse during and after treatment with mepolizumab SC	• Proportion of subjects who have an IGA score of 3 or 4 after achieving an IGA score of 0 or 1 and at least a 2-grade improvement during the Treatment and Follow-up Periods. • Proportion of subjects who have an increase in EASI score of ≥25% from baseline during the Treatment and Follow-up Periods.

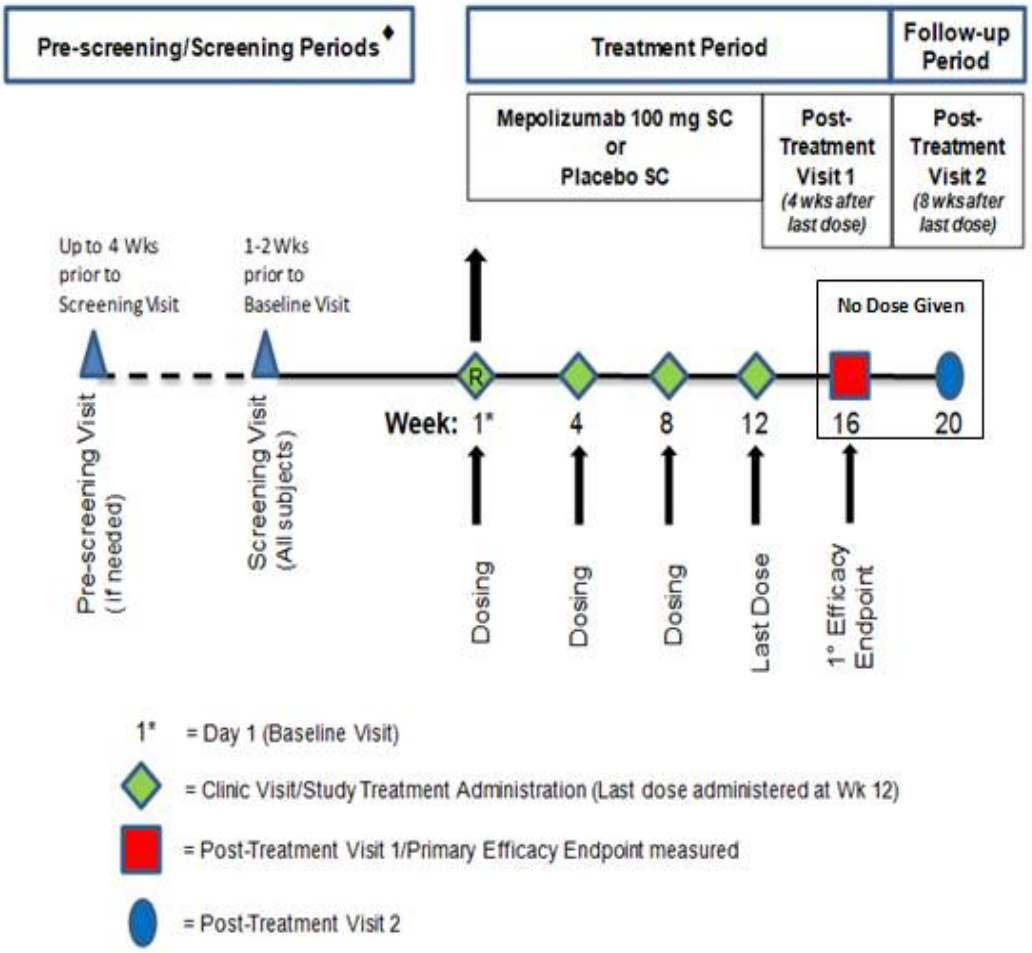
Objectives	Endpoints
• To characterize the relationship between efficacy and blood eosinophil counts	• Proportion of subjects who have an IGA score of 0 or 1 and at least a 2-grade improvement at each study visit by baseline blood eosinophil count. • Mean percentage change in EASI score from baseline to each study visit by baseline blood eosinophil count. • Mean percentage change in EASI score compared to change in blood eosinophils at each visit.
• To investigate the pharmacokinetics of mepolizumab in subjects with moderate to severe AD	• Plasma concentration of mepolizumab
• To investigate the pharmacodynamics of mepolizumab in the blood and in AD lesional skin biopsies	• Ratio to baseline in blood eosinophil counts • IL-5 levels (serum free and total) • Levels of circulating biomarkers in the blood including immunoglobulin (IgE), eosinophilic cationic protein (ECP), and levels of chemokines such as thymus and activation-regulated chemokine (TARC) • Gene expression biomarkers in skin biopsies
• To describe the effect of mepolizumab SC on Patient-reported Outcomes (PROs)	• Change over time in Daily Sign and Symptom Severity Diary • Change over time in Patient Global Impression of Severity and Patient Global Impression of Change

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, randomized, double-blind, placebo-controlled, 2-arm, parallel-group study that will investigate the efficacy and safety of mepolizumab SC in adult subjects with moderate to severe AD. At the Baseline visit on Day 1, subjects who meet all inclusion criteria including a screening blood eosinophil count ≥350 cells/μL and none of the exclusion criteria will be randomized in a ratio of 1:1 (mepolizumab 100 mg SC: placebo SC).

Figure 2 Study Schematic



Abbreviations: 1°= primary; R= randomize; SC= subcutaneous; wks=weeks

♦ If an ineffective treatment is stopped for the purpose of study entry, informed consent should be obtained at the time the ineffective treatment is stopped. Note: For subjects who may need to stop treatment with a biologic, the total Pre-Screening and Screening period may last up to 20 weeks (See Table 1 for prohibited period before the Screening Visit)

4.2. Treatment Arms and Duration

- This study will consist of 4 periods:
  - Pre-screening (up to 4 weeks)
  - Screening (1 to 2 weeks)
    - If an ineffective treatment is stopped for the purpose of study entry, informed consent should be obtained at the time the ineffective treatment is stopped. Note: For subjects who may need to stop

treatment with a biologic, the total Pre-Screening and Screening period may last up to 20 weeks.

- Treatment (16 weeks with the last dose of study treatment at Week 12)
- Follow-up (4 weeks).

- The subject will participate in the study for a maximum total duration of approximately 26 weeks (Note: Subjects who need to stop treatment with a biologic during the Pre-Screening Period may participate in the study for a maximum total duration of approximately 40 weeks).
- Subject participation in the following exploratory sub-studies is voluntary and will require additional informed consent:
  1. Skin biopsy sub-study: skin biopsies (at pre-identified study centers only) to study the effect of mepolizumab on gene expression biomarkers in the skin.
  2. Genetics sub-study: to investigate the relationship between genetic variants, response to medicine and susceptibility, severity and progression of AD and related conditions
- In order to maintain the blind, the results from the following laboratory assessments will be blinded during the study: PK, immunogenicity, IL-5, blood biomarkers, and skin biopsy. Additionally, the following will be blinded from the Baseline visit until the end of the study: total white blood cell (WBC) count, absolute eosinophil count, and differential (%). Investigators will ensure that subjects and any physicians managing study subjects during the course of the study are informed of this requirement. Absolute neutrophil, lymphocyte, monocyte, and basophil counts will be provided.

4.2.1. Pre-screening/Screening Periods

Pre-Screening Period: Prohibited Medications Prior to Screening:

- Informed consent should be obtained prior to performing any study assessments or procedures.
- Certain medications and treatments are prohibited prior to the Screening visit and throughout the study in order to allow for the evaluation of mepolizumab as monotherapy for AD and to eliminate the possible confounding effects of the specified medications/treatments on the evaluation of the study endpoints.
- Selection and modification of the subject's medications prior to study participation is based on the physician's judgment according to sound medical practice and principles and each subject's needs. Effective medications and treatments should not be changed merely for the purpose of enabling the subject's participation in the study. See Table 1 for a list of Prohibited Concomitant Medications and Non-Drug Therapies prior to the Screening visit. If an ineffective treatment is stopped for the purpose of study entry, informed consent should be obtained at the time the ineffective treatment is stopped.

- Subjects who have used prohibited concomitant medications or non-drug therapies will complete a Pre-screening period.
- Assessments for the Pre-screening period will be completed up to 4 weeks prior to the Screening Visit.

- **Screening Period:**
  - When the subject meets criteria listed in Table 1 for prohibited concomitant medications and non-drug therapies, the Screening Period will begin. The Screening Period will last from a minimum of 1 week to a maximum of 2 weeks prior to the Baseline visit.
  - For subjects who have not used a prohibited medication or non-drug therapy, the assessments for the Pre-Screening and Screening Periods will be combined. The total time to complete the combined Pre-Screening and Screening assessments will be a minimum of 1 week to a maximum of 2 weeks prior to the Baseline visit.

- **For All Subjects:**
  - Results of the blood eosinophil count obtained at the Screening visit, after requirements regarding previous use of prohibited medication and non-drug therapies (Table 1) are met, will be used to determine eligibility (≥350 cells/μL) and therefore must be available prior to randomizing the subject.
  - At the Screening visit, site personnel will train subjects on the use of the electronic Daily Sign and Symptom Severity Diary. Subjects will complete the electronic Daily Sign and Symptom Severity Diary starting at the Screening Visit and throughout the life of study. Site personnel will receive automated alerts based on subject data entry throughout life of study. Subjects for whom an alert is received will be re-educated on the importance of completing their diary. Every effort will be made to re-educate those subjects who continue to not complete their diary (see SRM for information regarding monitoring).
  - For at least 7 consecutive days immediately prior to the Baseline visit, all subjects must apply a non-prescription, non-medicated (without an active ingredient) emollient twice daily. Examples of acceptable emollients are provided in the Study Reference Manual (SRM). The same emollient will be used by the subject throughout the study. On study visit days, the subject must not apply the emollient within the 2-hour period preceding the study visit. See Section 6.10.1 for further details regarding emollient use.
  - The results of all laboratory assessments must be available prior to randomization in order to determine the subject's eligibility. The Screening Period may be extended beyond 2 weeks, if needed, to obtain the results of all laboratory assessments.

4.2.2. Treatment Period

- The Treatment Period will begin with the Baseline visit on Day 1. Study visits will also occur at Week 4, Week 8, Week 12, and Week 16.

- At the Baseline visit, eligible subjects will be randomized in a 1:1 ratio to receive either mepolizumab 100 mg SC or placebo SC.
- Study treatment will be prepared by a designated, qualified, unblinded member of the site staff who is independent of the protocol-defined study assessments (See Section 6.1).
- Study treatment will be administered by SC injection at the Baseline visit, Week 4, Week 8, and Week 12 (last dose). Each SC injection will be administered by a trained member of the site staff who is blinded to study treatment. See Section 6.1.1 for injection site instructions and study treatment administration details.
- Subjects will remain in the clinic for safety monitoring one hour after each administration of study treatment. Subjects will be observed for adverse events (AEs) including systemic reactions (i.e., allergic (type I hypersensitivity) reaction and other systemic reaction) and local injection site reactions (See Section 6.1.2).
- There are no planned dose adjustments during the study.
- The last dose of study treatment will be administered at Week 12. Study treatment will **not** be administered at Week 16. For those subjects randomized to mepolizumab, four doses will provide therapeutic coverage to Week 16 when efficacy assessments for the primary endpoint will occur. For this reason, the Week 16 visit is considered to be part of the Treatment Period while also serving as the first follow-up visit (Post-Treatment Visit 1).
- Subjects will continue to apply the same non-prescription, non-medicated (without an active ingredient) emollient twice daily. On study visit days, the subject must not apply the emollient within the 2-hour period preceding the study visit. See Section 6.10.1 for further details regarding emollient use.
- Subjects who prematurely discontinue study treatment will be followed for 8 weeks after the last dose and will be scheduled for the following visits (Section 5.4 and Table 3):
    - Early Withdrawal Visit (if the decision is made to prematurely discontinue study treatment <4 weeks after last dose of study treatment),
    - Post-Treatment Visit 1 (4 weeks after last dose of study treatment), and
    - Post-Treatment Visit 2 (8 weeks after last dose of study treatment).
- Subjects who are withdrawn from the study will complete an Early Withdrawal visit and then exit the study. See Section 5.4 and Table 3.

4.2.3. Follow-up Period

- Following completion of the Week 16 visit (Post-Treatment Visit 1), subjects will enter the Follow-up Period with a visit at Week 20 (Post-Treatment Visit 2, occurring 8 weeks after the last dose of study treatment).
- Subjects will continue to apply the same non-prescription non-medicated (without an active ingredient) emollient twice daily until the Week 20 visit. On study visit

days, the subject must not apply the emollient within the 2-hour period preceding the study visit. See Section 6.10.1 for further details regarding emollient use.

4.2.4. Unscheduled Visit for Flare/Relapse

- Subjects who experience a suspected AD flare/relapse between scheduled study visits in the Treatment and Follow-up Periods will return to the clinic for an unscheduled visit to determine if AD flare/relapse criteria are met. AD flare/relapse is defined as:
    - an IGA score of 3 or 4 after achieving an IGA score of 0 or 1 and at least a 2-grade improvement, OR
    - an increase in EASI score of ≥25% from Baseline.
- If AD flare/relapse is confirmed at the time of the unscheduled visit, the assessments of the unscheduled visit for flare/relapse (Table 4) will be completed.
- In the case of flare/relapse with intolerable AD symptoms where the use of prohibited medication is required (See Table 1) the subject will be permanently withdrawn from treatment.
- If the subject permanently withdraws from study treatment or withdraws from the study, the procedures and visits described in Section 5.4 and Table 3 will apply.

4.3. Type and Number of Subjects

Approximately 140 adult subjects (ages 18 to 70 years) with moderate to severe atopic dermatitis will be screened to achieve approximately 56 randomized and 50 evaluable subjects, assuming a drop-out rate of 10%.

4.4. Design Justification

The randomized, double-blind, placebo-controlled study design was selected to minimize the potential for subjective bias in assessing patient response. The inclusion of a placebo group will provide a control for comparison of safety and efficacy of mepolizumab in the AD patient population.

This study will investigate the efficacy of mepolizumab at a SC dose of 100 mg administered every 4 weeks in subjects with moderate to severe AD. Subjects with mild AD will be excluded because they can be adequately treated with topical therapies. Published data have indicated elevated blood eosinophil counts in patients with moderate to severe AD [Tremp, 2011; Hon, 2007; La Grutta, 2005; Yoshida, 2002]. An inclusion criterion of blood eosinophils ≥350 cells/μL has been selected based on data from Study SB240563/045 where approximately 70% of subjects had a baseline blood eosinophil count above this threshold. This inclusion criterion has therefore been selected to ensure the enrollment of subjects with meaningfully high blood eosinophil counts. The relationship between baseline blood eosinophil count and efficacy will be explored in this

study. In addition, the value of baseline biomarkers (ECP, IgE, and levels of chemokines such as TARC) as predictors of response will be evaluated.

The use of a non-prescription, non-medicated (without an active ingredient) emollient is required twice daily for the 7 consecutive days preceding the Baseline visit. Subjects whose disease is adequately managed by the non-prescription, non-medicated emollient during this 7-day period will not be eligible for the study. The requirement for the continued use of the concurrent non-prescription, non-medicated emollient throughout the remainder of the study ensures a consistent standard of care treatment for all subjects. Examples of acceptable emollients will be supplied in the SRM. The subject will use the same emollient throughout the study to ensure consistency. If the investigator determines it is in the best interest of the subject to initiate treatment with a prohibited medication or therapy, study treatment will be discontinued (if applicable), and the procedures and visits described in Section 5.4 and Table 3 will be performed.

The study will be conducted at multiple study centers to increase the generalizability of the study results.

4.5. Dose Justification

Mepolizumab pharmacology has been extensively investigated during clinical development across various eosinophilic conditions. In studies conducted in patients with severe eosinophilic asthma, efficacy was observed at doses of 75 mg IV or 100 mg SC administered every 4 weeks. Both doses provide similar exposure in terms of area under the curve (AUC) based on mepolizumab SC absolute bioavailability. Higher doses (up to 750 mg IV) were well tolerated but provided similar clinical benefit. Characterization of the dose-response relationship for blood eosinophil reduction in Study MEA114092 conducted in subjects with moderate/severe asthma and blood eosinophils >300 cells/μL identified approximately 100 mg SC (every 4 weeks) as the dose providing 90% of maximal blood eosinophil reduction (ID_{90}) [Pouliquen, 2015]. A confirmatory phase 3 trial in severe asthma with eosinophilic inflammation (Study MEA115588; Ortega, 2014a) confirmed 100 mg SC as an effective therapeutic dose, and therefore the translation of pharmacology into the clinical endpoint. Mepolizumab, at a dose of 100 mg SC administered once every 4 weeks, recently received regulatory approval in the treatment of patients with severe eosinophilic asthma. The dose selection for the AD program is also supported by the knowledge of mepolizumab pharmacology and is consistent with the dose justification approach taken in other mepolizumab follow-on indications.

Mean blood eosinophil count reported in the severe AD patient population varies greatly across publications (mean ranging from 292 to 1319 cells/μL across 5 publications of various sample sizes [Tremp, 2011; Jenerowicz, 2007; La Grutta, 2005; Hon, 2007; Yoshida, 2002]). This might reflect differences in concurrent therapies known to impact blood eosinophil count, such as steroids. In a publication reporting the results of four dupilumab studies in subjects with AD, mean baseline blood eosinophils reported across groups (with or without concurrent therapies) and studies ranged from 200 to 900 cells/μL [Beck, 2014].

In the previous phase 2 study of mepolizumab in subjects with moderate AD (Study SB240563/045), the median blood eosinophil count decreased from 432.5 to 88.5 cells/µL in the mepolizumab group and increased from 495 to 605 cells/µL in the placebo group from Day 0 to Day 14. Acknowledging the uncertainty around the true mean baseline blood eosinophil count in the targeted population in the absence of concurrent therapy, an assumed geometric mean baseline of 500 to 800 cells/µL was considered reasonable. Based on the established mepolizumab dose-response for blood eosinophil reduction, for such a geometric mean baseline range, a reduction to a predicted geometric mean absolute blood eosinophil count of 100 to 150 cells/µL would be anticipated with a 100 mg SC dose administered every 4 weeks [GlaxoSmithKline Document Number 2015N238375_00, 2015]. Based on the results of studies in other diseases (e.g., asthma), this magnitude of decrease in blood eosinophil level is anticipated to be therapeutic in moderate to severe AD subjects.

This study utilizes a Treatment Period of 16 weeks with study treatment administered at the Baseline visit, Week 4, Week 8, and Week 12. For those subjects randomized to mepolizumab, four doses will provide therapeutic coverage to Week 16. A 16-week Treatment Period is expected to be sufficient to reduce eosinophils in the skin and to assess clinical disease response to study treatment.

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with mepolizumab (SB-240563) can be found in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number CM2003/00010/12, 2016]. The following section outlines the key risks and risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [mepolizumab]		
Risk of Systemic Reactions, including allergic reactions	Biopharmaceutical products administered subcutaneously may elicit systemic (e.g. hypersensitivity) and local 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: • 54/915 subjects or 6% in the mepolizumab group [all doses combined] • 7/263 subjects or 3% in the mepolizumab 100 mg SC group • 12/344 subjects or 3% in the mepolizumab 75 mg IV group • 20/412 subjects or 5% in the placebo group. The most common symptoms reported with any systemic reaction included headache, rash, pruritus, fatigue, and dizziness. While rare, serious systemic reactions including anaphylaxis have been reported.	Daily monitoring of serious adverse events (SAEs) by medical monitor; regular systematic review of adverse event (AE)/SAE data from ongoing studies by a GlaxoSmithKline (GSK) study team and/or GSK Safety Review team. Customized AE and SAE case report form (CRF) utilized for targeted collection of information for systemic reaction adverse events. Use of Joint National Institute of Allergy and Infectious Diseases (US) (NIAID)/ Food Allergy and Anaphylaxis Network (FAAN) 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (See Appendix 2). Subjects are monitored in the clinic for 1 hour after each administration of study treatment. Subjects will be observed for adverse events (AEs) including systemic reactions (i.e., allergic (type I hypersensitivity) reaction and other systemic reactions) and local injection site

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Systemic reactions reported to date across the mepolizumab program are summarized in the IB 'Adverse Events of Special Interest' section; See also 'Special Warnings and Special Precautions for Use' section located in Section 6 titled 'Summary of Data and Guidance for the Investigator'.	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 patient including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the patient to another facility for additional care if appropriate.
Injection site reactions	In the placebo controlled severe asthma studies, the incidence of local injection site reactions with SC administration of mepolizumab was higher on mepolizumab 100 mg SC group (21/263 or 8%) compared to mepolizumab 75mg IV (10/344 or 3%) or placebo (13/412 or 3%). Symptoms included pain, erythema, swelling, itching, and burning sensation. Local injection site reactions reported to date across the mepolizumab program are summarized in the Adverse Events of Special Interest' section of the IB; See also 'Section 6 titled 'Summary of Data and Guidance for the Investigator'.	Daily monitoring of SAEs by medical monitor; regular systematic review of AE/SAE data from ongoing studies by GSK study team and/or GSK Safety Review Team. Customized AE and SAE CRF pages utilized for targeted collection of information for local injection site reaction adverse events.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential risk of immunogenicity	Biopharmaceutical products may elicit anti-drug antibody (ADA) and neutralizing antibody (NAB), which have the potential to modulate pharmacokinetic (PK), pharmacodynamic (PD) or produce adverse reactions. Mepolizumab has low immunogenic potential. Both incidence and titer data from completed studies demonstrate a low risk for loss of efficacy associated with AEs and/or altered PK/PD. Immunogenicity data reported to date across the mepolizumab development program are summarized in the IB; See Section 5.4 'Clinical Immunogenicity' and a summary of immunogenicity findings in Section 6 'Other Potentially Clinically Relevant Information for the Investigator'.	Blood samples will be collected for detection of both ADA and NAB. 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 of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Study visits and procedures may be a burden on the subject and may impact study completion. Study procedures may cause adverse events.	There is the potential for subjects to experience adverse events from the blood draws or electrocardiograms (ECGs). However, these are generally considered to be low risk procedures.	The protocol has been designed to minimize the burden to sites and subjects as much as possible while maintaining the integrity of the design to support the endpoints. All study procedures will be performed by appropriately trained study staff and subjects will be informed of the potential risks.
Scarring/discomfort/complications from skin biopsy	Subjects who consent to participate in the skin biopsy sub-study may experience discomfort, pain, bleeding, bruising, and/or scarring from the skin biopsy. Complications may occur such as infection or damage of the structures in the vicinity of the biopsy site (e.g., vessels and skin nerves).	Only sites with experience in skin biopsy sample collection will participate in the skin biopsy sub-study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other		
AD flare/relapse	Subjects may experience disease flare/relapse and need alternative treatment.	Subjects who experience an AD flare/relapse between scheduled study visits will return to the clinic for an unscheduled visit to determine if AD flare/relapse criteria are met (Table 4). In the case of flare/relapse with intolerable AD symptoms where the use of prohibited medication is required (See Table 1), the subject will be permanently withdrawn from treatment. If the subject permanently withdraws from study treatment or withdraws from the study, the procedures and visits described in Section 5.4 and Table 3 will apply.

4.6.2. Benefit Assessment

Subjects randomized to mepolizumab may experience improvement in their AD during the course of the study.

Mepolizumab has demonstrated clinical benefit in severe eosinophilic asthma [Ortega, 2014a].

4.6.3. Overall Benefit:Risk Conclusion

Data from mepolizumab preclinical and clinical development support the ability of mepolizumab to inhibit IL-5 leading to consistent reduction in blood eosinophils, and consequently, improvement in conditions associated with eosinophilia. To date, there are no safety concerns with mepolizumab that would preclude development in AD.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the mepolizumab Investigator's Brochure (IB) [GlaxoSmithKline Document Number CM2003/00010/12, 2016].

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:

AGE
• Between 18 and 70 years of age inclusive, at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
• AD diagnosed by the Eichenfield revised criteria of Hanifin and Rajka [Eichenfield, 2014] (Appendix 3). • Diagnosis of AD ≥2 years prior to the Screening visit. • An IGA score ≥3 at the Screening and Baseline visits (Appendix 4). • AD involvement of ≥10% BSA at the Screening and Baseline visits (Appendix 5). • EASI score ≥16 at the Screening and Baseline visits (Appendix 6).

- Absolute blood eosinophil count ≥350 cells/μL at the Screening visit.
- Applied the same non-prescription, non-medicated (without an active ingredient) emollient twice-daily for at least 7 days immediately before the Baseline visit.
- Recent history (≤6 months prior to the Screening visit) of inadequate response to a stable regimen of prescription topical medication or for whom prescription topical medications are not tolerated or where there is a concern for potential side effects, such as skin thinning or increased risk of hypothalamic-pituitary-adrenal [HPA] suppression; as well as, inadequate response to optimization of nonpharmacological measures such as moisturizers
  - **Note**: Inadequate response to a stable regimen of prescription topical medication (such as medium to high potency topical corticosteroids or topical calcineurin inhibitors) is defined as failure to achieve and maintain remission or low disease activity state (equivalent to an IGA score =0 [clear] to 2 [mild]) despite treatment for the recommended duration as per label or for the maximum duration recommended for the subject treatment, whichever is shorter.

SEX

- Male OR Female

Females:

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. Non-reproductive potential defined as:
   - Pre-menopausal females with one of the following:
     - Documented tubal ligation
     - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
     - Hysterectomy
     - Documented Bilateral Oophorectomy
   - Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment.

b. Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of

Reproductive Potential (FRP) (See Appendix 7) from 30 days prior to the first dose of study medication and until 16 weeks after the last dose of study medication.

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

INFORMED CONSENT
• Subject is able to give signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

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. Other types of eczema. 2. Any other concomitant skin disorder (e.g., generalized erythroderma such as Netherton's Syndrome, or psoriasis), pigmentation, or extensive scarring that in the opinion of the investigator may interfere with the evaluation of AD lesions or compromise subject safety. 3. Immunocompromised (e.g., lymphoma, acquired immunodeficiency syndrome, Wiskott-Aldrich Syndrome) or has a history of malignant disease within 5 years before the Baseline visit. **Note**: Subjects with successfully treated basal cell carcinoma (no more than 3 lesions), squamous cell carcinoma of the skin, or cervical carcinoma in situ, with no evidence of recurrence within the 3 years prior to the Baseline visit may participate in the study. 4. A positive history for human immunodeficiency virus (HIV) antibody. 5. Chronic or acute infection requiring treatment with oral or IV antibiotics, antivirals, anti-protozoals, or antifungals within 4 weeks before the Screening visit or anytime between the Screening and Baseline visits. Also See Section 6.10.2 and Table 1. 6. Superficial skin infections within 1 week before the Screening visit. 7. Known, pre-existing or suspected parasitic infection within 6 months before the Screening visit. 8. Other known or suspected conditions that could lead to elevated eosinophils, for example, hypereosinophilic syndromes including eosinophilic granulomatosis with polyangiitis (EGPA, also known as Churg-Strauss Syndrome), eosinophilic esophagitis, or severe asthma.

9. A history or ongoing serious illness or medical, physical, or psychiatric condition(s) that, in the investigator's opinion, may interfere with the subject's completion of the study. 10. ALT >2xULN 11. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). 12. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). 13. QTcF >450 msec or QTcF >480 msec in subjects with Bundle Branch Block. 14. Clinically significant abnormality in the hematological or biochemical screen, as judged by the investigator.

CONCOMITANT MEDICATIONS
15. Previously treated with mepolizumab or participated in a previous mepolizumab clinical study. 16. Prior treatment with any of the medications or treatments listed in Table 1 within the indicated periods before the Screening visit.
RELEVANT HABITS
17. Prolonged exposure to natural (e.g, sunlight) ultraviolet (UV) radiation within 4 weeks prior to the Baseline visit and/or intention to have such exposure during the study, which is thought by the investigator to potentially impact the subject's AD. 18. More than 2 visits per week to a tanning booth or parlor in the 4 weeks prior to the Baseline visit. 19. Onset of a new exercise routine or major change to a previous exercise routine within 2 weeks before randomization, or unwilling to maintain current level of physical activity throughout the length of participation in this study. 20. History of alcohol or other substance abuse within the last 2 years.

CONTRAINDICATIONS
21. Hypersensitivity to mepolizumab or any of its excipients.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
22. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. 23. Exposure to more than 4 investigational medicinal products within 12 months prior to the Baseline visit. 24. Subject is a member of the investigational team or his/her immediate family.

5.3. Screening/Baseline Failures

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 Serious Adverse Events (See Section 7.4.1.5).

Subjects who are screen failures may be re-screened one time.

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, behavioral or administrative reasons.

5.4.1. Early Withdrawal from Study Treatment

Subjects must **permanently discontinue study treatment** for any of the following reasons:

- Subject presents with worsening AD or any other condition that requires treatment with a prohibited medication.
- Subject experiences an adverse event(s) which is considered to be related to study treatment or study procedures and, in the investigator's judgment, is severe enough in nature to warrant treatment discontinuation.
- Subject experiences a cardiovascular or hematologic AE consistent with specific Common Terminology Criteria for AEs (CTCAE) version 4.02 Grade 2 (moderate) or higher (See SRM).
- The subject's randomized treatment assignment is unblinded by the investigator or treating physician.
- Subject becomes pregnant.
- Sponsor request (after discussion with the investigator), for reasons such as a significant protocol deviations or subject noncompliance.
- Study is terminated by the sponsor.
- Subject meets liver chemistry stopping criteria (See Section 5.4.4).
- Subject meets QTcF stopping criteria (See Section 5.4.5).

Subjects who permanently discontinue study treatment will be followed for 8 weeks after the last dose of study treatment. Every effort will be made by the investigator to encourage the subject to remain in the study to complete the two Post-Treatment visits providing that consent has not been withdrawn for subsequent visits.

If the decision is made to permanently discontinue study treatment less than 4 weeks after the last dose, an Early Withdrawal Visit will be scheduled as soon as is reasonably possible. Post-Treatment Visit 1 will then be scheduled 4 weeks after the last dose of study treatment, and Post-Treatment Visit 2 will be scheduled 8 weeks after the last dose of study treatment.

If the decision is made to permanently discontinue study treatment at a scheduled visit and approximately 4 weeks have elapsed since the last dose of study treatment, the procedures of Post-Treatment Visit 1 will be performed. Post-Treatment Visit 2 will be scheduled 8 weeks following the last dose of study treatment.

The investigator will record the primary reason for permanent discontinuation of study treatment and subsequent study withdrawal in the electronic Case Report Form (eCRF).

5.4.2. Early Withdrawal from Study

The subject must **discontinue study treatment and be withdrawn from the study** for the following reasons:

- Subject demonstrates significant noncompliance with the study procedures. (See the SRM for examples.)
- Subject is lost to follow-up.
- Subject withdraws consent to participate in the study. If specified by the subject, the investigator should document the reason for withdrawal of consent.
- Study is terminated by the sponsor.
- Sponsor request (after discussion with the investigator) for reasons such as a significant protocol deviations or subject noncompliance.

Subjects who are **withdrawn from the study** will be asked to return to the clinic for an Early Withdrawal Visit providing that consent has not been withdrawn for subsequent visits.

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. The investigator will record the primary reason for study withdrawal in the eCRF.

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".

5.4.3. Postponement of Study Treatment

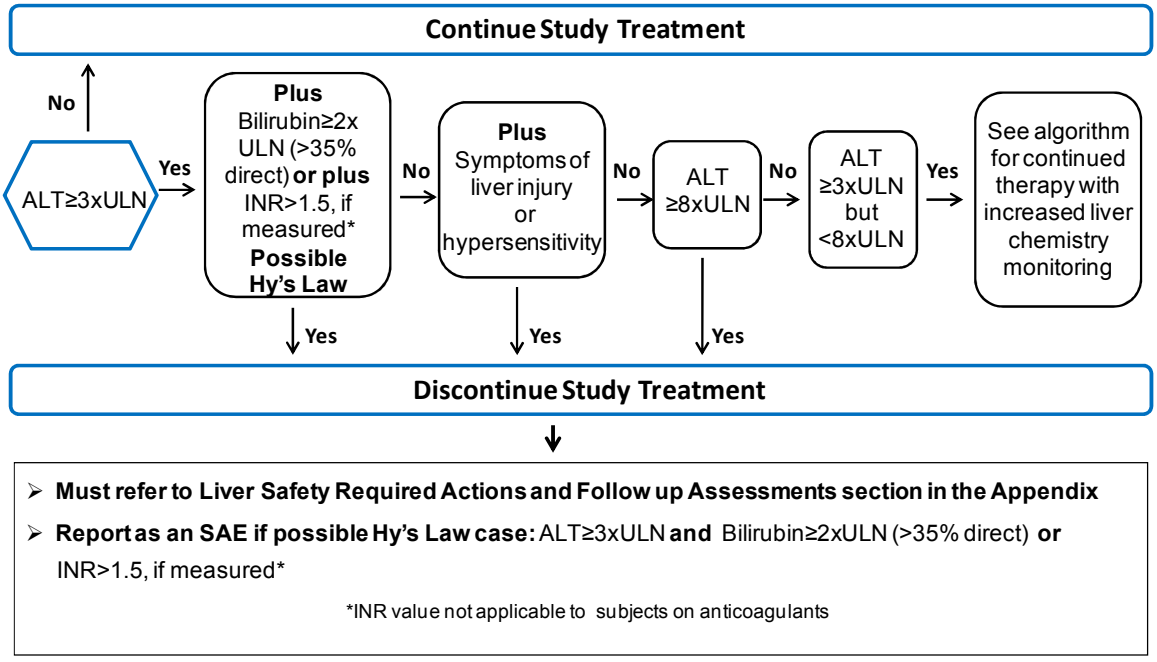
Administration of study dose and scheduled study visit assessments will be postponed during treatment for acute infection with oral or IV non-cytotoxic antibiotics, antivirals, anti-protozoals or antifungals. Upon completion of treatment of the acute infection, the postponed dose of study drug will be administered as soon as feasible but not further than 2 weeks from the originally planned visit schedule.

Successive administrations of study dose (if applicable) will resume as per the subject's originally planned visit schedule. If dose cannot be administered within 2 weeks from the original schedule, subjects must be discontinued from study treatment.

5.4.4. Liver Chemistry Stopping Criteria

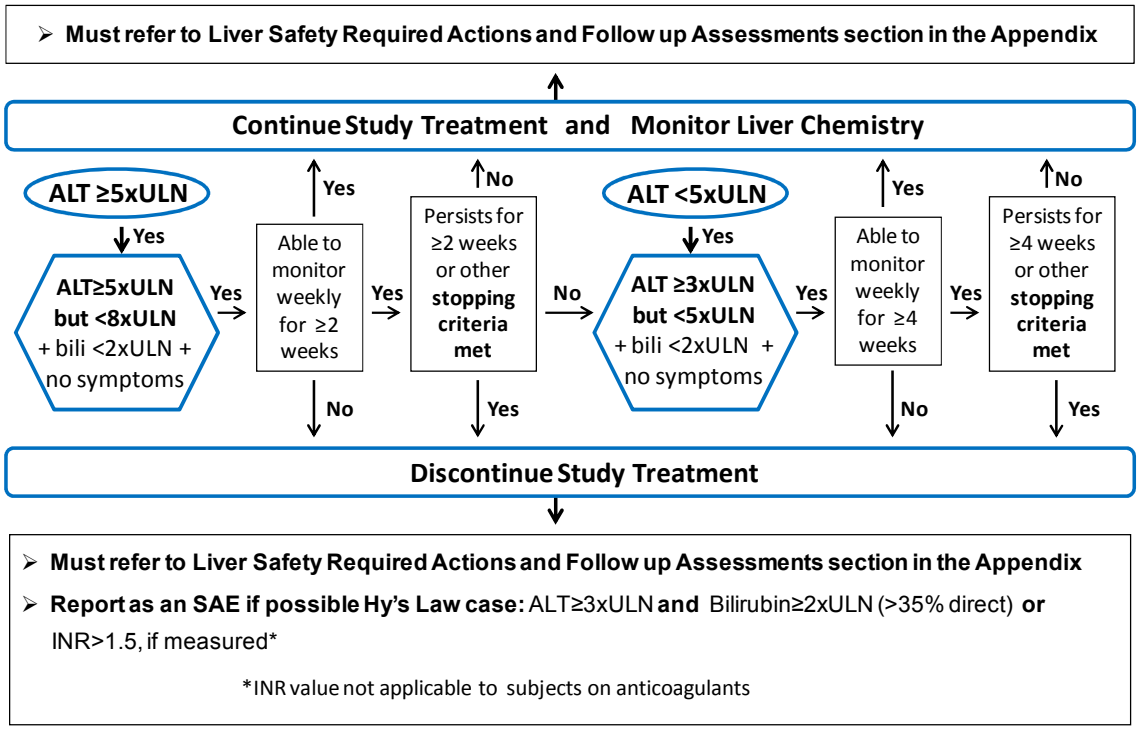
Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Figure 3 Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 8.

Figure 4 Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3xULN but <8xULN



Required Actions and Follow up Assessments for all subjects who meet liver chemistry stopping or increased monitoring criteria can be found in Appendix 8.

5.4.4.1. Study Treatment Restart or Rechallenge

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

5.4.5. QTcF Stopping Criteria

- The *same* QT correction formula *must* be used for *each individual subject* to determine eligibility for and discontinuation from the study. Note: QTcF will be utilized for this study. This formula may not be changed or substituted once the subject has been enrolled.
- The QTcF should be based on averaged QTcF 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:

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

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

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

Note: Unscheduled ECGs may be performed as clinically indicated during the study.

5.5. Subject and Study Completion

A subject will be considered to have **completed study treatment** if he/she receives all planned doses of study treatment through Week 12 and completes the Week 16 visit (final primary endpoint visit). A subject will be considered to have **completed the study** if he/she receives all planned doses of study treatment and completes the Week 16 (Post-Treatment 1) and Week 20 (Post-Treatment 2) visits.

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.

Mepolizumab (SB-240563) is a humanized immunoglobulin G (IgG) monoclonal antibody (IgG1, kappa) with human heavy and light chain frameworks. Mepolizumab will be provided as a lyophilized cake in sterile vials for individual use. The vial will be reconstituted with 1.2 mL Sterile Water for Injection, just prior to use yielding a 1 mL, 100 mg/mL extractable volume. The placebo in this study will be 0.9% sodium chloride solution and will be provided by the study site. Once prepared, mepolizumab and placebo will be identical in appearance. The mepolizumab 100 mg and placebo treatments will be delivered as 1 mL bolus subcutaneous injections.

Study treatment will be prepared by a designated, qualified, unblinded member of the site staff who is independent of the protocol-defined study assessments. Unblinded site staff cannot participate in blinded activities (e.g., may not transition to study coordinator role or other blinded role) at any point throughout the life of the study. They must not have

any contact with the study subjects. The unblinded site staff will be responsible for receipt, storage, reconstitution, labelling, and accountability of investigational product.

It is recommended that a second unblinded member of the site staff review the unblinded study treatment documentation to verify the treatment assignment prior to transferring blinded study treatment to blinded site staff for administration to the subject.

6.1.1. Study Treatment Administration

Blinded site staff will administer the study treatment into the subject's upper arm, abdomen, or thigh via SC injection at the following visits: Baseline, Week 4, Week 8, and Week 12. Ideally, study treatment should be injected into the same region of the body (e.g., upper arm) throughout the study. However, the injection site may be changed (e.g., from upper arm to thigh) based on the investigator's judgment and the reason documented in the source documents. The site of injection for each dose will be recorded in the eCRF.

The blinding of all those involved in the evaluation of the study treatment (e.g., physician/nurse as well as the subject) shall be maintained at all times; therefore, procedures must be in place at the study site to ensure that blinding is maintained.

Further details of study treatment preparation and administration can be found in the Investigator's Brochure [GlaxoSmithKline Document Number CM2003/00010/12, 2016], SRM, and unblinded pharmacy manual.

6.1.2. Observation Period

Subjects will remain in the clinic for safety monitoring 1 hour after each administration of study treatment. Subjects will be observed for adverse events (AEs) including systemic reaction (i.e., allergic (type I hypersensitivity) reaction and other systemic reactions) and local injection site reactions.

Systemic reactions will be evaluated for anaphylaxis using the diagnostic criteria for anaphylaxis as outlined by the Joint NIAID/FAAN Second Symposium on Anaphylaxis [Sampson, 2006] (See Appendix 2).

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 patient including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the patient to another facility for additional care if appropriate.

6.2. Treatment Assignment

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized at the Baseline visit in a ratio of 1:1 (mepolizumab 100 mg SC: placebo SC).

A description of each regimen is provided in the table below:

Mepolizumab	OR	Placebo (0.9% sodium chloride)
One 100 mg SC injection administered at the following visits: Baseline, Week 4, Week 8, and Week 12		One SC injection administered at the following visits: Baseline, Week 4, Week 8, and Week 12

Subjects will be assigned to study treatment via an interactive voice response system (IVRS) in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software. Once a randomization number has been assigned to a subject, it must not be re-assigned to a different subject.

6.3. Blinding

This will be a double-blind (sponsor open) study and the following will apply:

- GSK will utilize a blinded study team which will include a blinded study medical monitor and a blinded Operations and Science Lead. In addition, GSK will designate unblinded team members including an unblinded Medical Monitor and an unblinded Global Study Manager to respond to questions or issues involving study treatment assignment and preparation. The unblinded medical monitor may also review unblinded abnormal lab values for safety monitoring. Unblinded GSK study monitors will review unblinded study treatment documentation while blinded GSK study monitors will review blinded records. Procedures will be in place to ensure blinded GSK team members remain blinded.

- Formal Interim Analysis: A formal interim analysis may be performed to enable future planning and to assess futility. It is expected that GSK's study statistician, programmer, clinical scientist, project physician lead, and/or respective designee(s) will be unblinded to subject-level data for the subjects enrolled at the time the database is locked for the formal interim analysis. These persons will not share subject-level randomization assignments with anyone not involved in conducting the analyses. The protection of the study blind and the dissemination plan for summary level results of the interim analyses will be described in the RAP.

- Administrative Interim Analyses: Unblinded in-stream data summaries will be generated by a GSK study statistician and study programmer. The unblinded summaries will be provided to GSK senior manager(s) for their review of subject efficacy and safety data. The results and randomization assignments will only be shared with members involved in the review and conduct of the analysis.

- Study treatment will be prepared by a designated qualified, unblinded member of the site staff who is independent of the protocol-defined study assessments. Unblinded site staff cannot participate in blinded activities (e.g., may not

transition to study coordinator role or other blinded role) at any point throughout the life of the study. They must not have any contact with the study subjects.

- Once prepared, mepolizumab and placebo (0.9% sodium chloride solution provided by the site) will be identical in appearance.
- Blinded site staff will administer study treatment to the subject.
- Procedures must be in place at the study site to ensure that blinding is maintained.
- In order to maintain the blind, the results from the following laboratory assessments will be blinded during the study: PK, immunogenicity, IL-5, blood biomarkers, and skin biopsy. Additionally, the following will be blinded from the Baseline visit until the end of the study: total WBC count, absolute eosinophil count, and differential (%). Investigators will ensure that subjects and any physicians managing study subjects during the course of the study are informed of this requirement. Absolute neutrophil, lymphocyte, monocyte, and basophil counts will be provided.
- In the event that a local laboratory analyzes a hematology sample for a study subject after the Baseline visit, procedures must be in place at the site to ensure that the results of the total WBC count, absolute eosinophil count, and differential (%) remain blinded to the blinded site staff.
- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
- The date and reason for the unblinding must be fully documented in the CRF.
- A subject must permanently discontinue study treatment if that subject's treatment assignment is unblinded by the investigator or treating physician (Section 5.4). The subject will be encouraged to complete the Post-Treatment visits. The primary reason for study treatment discontinuation (the event or condition which led to the unblinding) will be recorded in the eCRF.
- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an

expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4. Packaging and Labeling

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

6.5. Preparation/Handling/Storage/Accountability

- A description of the methods and materials required for reconstitution of mepolizumab and preparation of placebo are described in Section 6.1 and the unblinded pharmacy manual.
- Unblinded site staff 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 authorized unblinded site staff.
- The unblinded site staff is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM and unblinded pharmacy manual.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.6. Compliance with Study Treatment Administration

Mepolizumab or placebo will be administered subcutaneously to subjects at the site by blinded site staff. Administration will be documented (including date and time) in the source documents and reported in the eCRF.

6.7. Treatment of Study Treatment Overdose

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

In the event that study treatment is administered more than as detailed in the protocol in terms of dose or frequency, the blinded GSK Medical Monitor should be notified.

6.8. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because: there is insufficient evidence of efficacy in this indication, the indication being studied is not life threatening or seriously debilitating, and other treatment options are available.

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.

6.9. Lifestyle Restrictions

Prolonged exposure to natural (e.g., sunlight) sources of UV radiation, which is thought by the investigator to potentially impact the subject's AD, is prohibited from 4 weeks prior to the Baseline visit and until the last follow-up visit. A subject who visits a tanning booth or parlor more than 2 times per week within the 4 weeks before the Baseline visit will not be eligible for inclusion in the study. Tanning booth or parlor use is prohibited from the Baseline visit through the Follow-up Period.

Subjects should maintain their baseline level of physical activity throughout the study.

6.10. Concomitant Medications and Non-Drug Therapies

All concomitant medications and non-drug therapies received by the subject during the study must be recorded in the source documents and eCRF.

6.10.1. Permitted Medications and Non-Drug Therapies

Subjects must apply a non-prescription, non-medicated (without an active ingredient) emollient twice-daily for at least 7 days immediately before the Baseline visit and throughout the Treatment and Follow-up Periods. Examples of acceptable emollients are provided in the SRM. The subject will apply the same emollient throughout the study.

In order to facilitate the assessment of AD at study visits, the subject must not apply the emollient within the 2-hour period preceding the study visit. If the subject applies an emollient less than 2 hours prior to the study visit, site personnel must wait at least 2 hours after the emollient was applied before conducting any study procedures.

Alternatively, the study visit may be rescheduled within the visit window specified in the Time and Events Tables (Section 7.1).

Other than the prohibited medications and non-drug therapies listed in Section 6.10.2, treatment with concomitant medications are permitted during the study if, in the opinion of the investigator, their use will not impact the study assessments. This includes treatment with oral contraceptives; nasal, inhaled, and intraocular corticosteroids for any duration. Oral or IV non-cytotoxic antibiotics, antivirals, anti-protozoals, or antifungals are permitted after the Baseline visit for the acute treatment of infections (for a duration no longer than indicated to treat the infection) See Section 5.4.3 for required postponement of study treatment during the use of oral or IV non-cytotoxic antibiotics, antivirals, anti-protozoals or antifungals.

6.10.2. Prohibited Medications and Non-Drug Therapies

The prohibited concomitant medications and non-drug therapies listed in Table 1 will not be used from the specified period before the Screening visit and thereafter for the duration of the study except as stated below.

After completing the Week 16 visit, or after Early Withdrawal from Treatment, subjects may use prohibited concomitant medications for the treatment of worsening AD. The use of topical therapies after the Week 16 or Early Withdrawal visit is preferred. The use of systemic therapies during this time is at the investigator's discretion.

The subject must permanently discontinue study treatment if the subject presents with worsening AD or any other condition that requires treatment with a prohibited medication prior to administration of the Week 12 dose of study treatment, and the procedures described in Section 5.4 and Table 3 will apply. If the subject takes a prohibited medication or uses a non-drug therapy for reasons other than worsening AD, the investigator should consult with the medical monitor to determine if the subject should be withdrawn from study treatment and/or the study.

Table 1 Prohibited Concomitant Medications and Non-Drug Therapies

Prohibited Medication or Non-Drug Therapy ***(Note: Examples are not all-inclusive.)***	**Prohibited period before the *Screening visit***
Allergen immunotherapy (desensitization therapy)	6 months
Biologic agents	12 weeks or 5 half-lives, whichever is longer (e.g., 18 weeks for omalizumab)
Other investigational products	30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer)
Oral or systemic glucocorticoids (e.g., hydrocortisone, cortisol, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, etc.)	4 weeks
Oral or systemic cytotoxic antibiotics (e.g., actinomycin, bleomycin, plicamycin, mitomycin, etc.)	4 weeks
Oral or systemic antimetabolites (e.g., methotrexate, azathioprine, mercaptopurine, etc.)	4 weeks
Oral or systemic alkylating agents (e.g., mechlorethamine, cyclophosphamide, melphalan, chlorambucil, ifosfamide, busulfan, etc.)	4 weeks
Mycophenolate: mycophenolate mofetil	4 weeks
Oral or systemic drugs acting on immunophilins (e.g., oral calcineurin inhibitors, cyclosporin, etc.)	4 weeks
Interferon-gamma	4 weeks
Adrenocorticotropic hormone analogs	4 weeks
Phototherapy (S*ee Section 6.9 for tanning booth/parlor restrictions*.)	4 weeks
Coal tar	4 weeks
Oral antihistamines	1 week
Topical immunomodulators (e.g., pimecrolimus, tacrolimus, etc.)	1 week
World Health Organization (WHO) group I-VII topical corticosteroids (e.g., betamethasone, clobetasol, desoximetasone, flurandrenolide, fluticasone, hydrocortiosone, traimcinolone, etc.)	1 week
Topical retinoids (e.g., tretinoin, tazarotene, adapalene, etc.)	1 week
Topical antibiotics	1 week
Antibacterial or antiseptic cleansing body wash/soap	1 week
Treatment of AD with a medical device (e.g., Atopiclair, PruMyx, EpiCeram, CeraVe, etc.)	1 week
Bleach baths	1 week
Wet wraps	1 week
Note: Selection and modification of the subject's medications prior to study participation is based on the physician's judgment according to sound medical practice and principles and each subject's needs. Effective medications and treatments should not be changed merely for the purpose of enabling the subject's participation in the study. If an ineffective treatment is stopped for the purpose of study entry, informed consent should be obtained at the time the ineffective treatment is stopped. For subjects who may need to stop treatment with a biologic, the total screening period may last up to 20 weeks.	

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 Tables, are essential and required for study conduct.

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

Assessments should occur prior to dosing on dosing days and in the following order to the extent possible:

1. Patient-Reported Outcomes in the following order (first to last): Patient Global Impression of Change and Patient Global Impression of Severity
2. Efficacy assessments (IGA, BSA, EASI, Clinician Global Impression of Change)
3. Other safety assessments (such as 12-lead ECG, vital signs, physical examination, height, weight)
4. Laboratory assessments (such as blood draws, urine pregnancy test, parasitic screening, skin biopsy)

Note: Prior to study procedures, subjects will report if emollient was applied within the 2-hour period preceding the study visit.

7.1. Time and Events Tables

Table 2 Time and Events Table: Pre-Screening and Screening

Period:	Pre-Screening and Screening Period		
			Notes
Visits:	**Pre-Screening**	**Screening**	
	Up to 4 wks prior to Screening Visit	**1 to 2 wks prior to Day 1 Baseline Visit**	• Individual Pre-Screening and Screening Visits will be conducted for subjects who have used prohibited medications or non-drug therapies and need to fulfil the prohibited medications period prior to the Screening Visit (See Table 1). For these subjects, the Pre-Screening Visit will be completed up to 4 weeks prior to the Screening Visit. After requirements regarding previous use of prohibited medication and non-drug therapies are met (See Table 1), the Screening Visit will be completed. The Screening visit will be completed up to 2 weeks prior to the Baseline visit. • Assessments for Pre-screening and Screening Periods will be combined into one Screening Visit for subjects who meet prohibited medications or non-drug therapies criteria in Table 1 at entry (total time to complete the combined assessments= 1 to 2 weeks prior to Baseline). • The period between the Screening Visit and Baseline Visit may be extended beyond 2 weeks, if needed, to obtain the results of all screening laboratory assessments. • Perform procedures in the order listed in Section 7
Procedure			
Informed consent	PS		Obtain informed consent prior to study participation. See Section 4.2.1 and Table 1 notes.
Demography	PS		
Fitzpatrick Skin Type Classification	PS		
Inclusion/exclusion criteria	PS	S	
Medical history/Medical conditions	PS	S	Includes drug and alcohol usage, smoking history, cardiovascular medical history, and family history of premature cardiovascular disease.
Safety Assessments			
Vital Signs		S	See Section 7.4.4.
Concomitant medications	PS	S	The subject must apply the same non-prescription, non-medicated emollient twice daily for the 7 consecutive days immediately prior to the Baseline visit. On study visit days,.

Period:	Pre-Screening and Screening Period		
			Notes
Visits:	**Pre-Screening**	**Screening**	
	Up to 4 wks prior to Screening Visit	**1 to 2 wks prior to Day 1 Baseline Visit**	• Individual Pre-Screening and Screening Visits will be conducted for subjects who have used prohibited medications or non-drug therapies and need to fulfil the prohibited medications period prior to the Screening Visit (See Table 1). For these subjects, the Pre-Screening Visit will be completed up to 4 weeks prior to the Screening Visit. After requirements regarding previous use of prohibited medication and non-drug therapies are met (See Table 1), the Screening Visit will be completed. The Screening visit will be completed up to 2 weeks prior to the Baseline visit. • Assessments for Pre-screening and Screening Periods will be combined into one Screening Visit for subjects who meet prohibited medications or non-drug therapies criteria in Table 1 at entry (total time to complete the combined assessments= 1 to 2 weeks prior to Baseline). • The period between the Screening Visit and Baseline Visit may be extended beyond 2 weeks, if needed, to obtain the results of all screening laboratory assessments. Perform procedures in the order listed in Section 7
Procedure			
			emollient must not be applied within the 2-hour period preceding the study visit. If emollient is applied <2 hours prior to the visit, wait ≥2 hours after application to perform study procedures. See Section 6.10.1
Serious Adverse Events (SAEs)	PS	S	Record SAEs related to study participation or to a GSK product 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 (Section 7.4.1.1).
ECG		S	
Laboratory Assessments	**Note: Results of all laboratory assessments must be available prior to randomization**		
HBsAG and hepatitis C antibody	PS		Not required if test otherwise performed within 3 months prior to first dose of study treatment.
Pregnancy test (urine)	PS	S	Females of reproductive potential. If urine pregnancy test is positive, collect serum hCG (central laboratory). See Section 7.4.2 and Appendix 7 for reporting requirements.
FSH and estradiol	PS		Females, if needed to confirm postmenopausal status (See Section 5.1).

Period:	**Pre-Screening and Screening Period**		
			Notes
Visits:	**Pre-Screening**	**Screening**	
	Up to 4 wks prior to Screening Visit	**1 to 2 wks prior to Day 1 Baseline Visit**	• Individual Pre-Screening and Screening Visits will be conducted for subjects who have used prohibited medications or non-drug therapies and need to fulfil the prohibited medications period prior to the Screening Visit (See Table 1). For these subjects, the Pre-Screening Visit will be completed up to 4 weeks prior to the Screening Visit. After requirements regarding previous use of prohibited medication and non-drug therapies are met (See Table 1), the Screening Visit will be completed. The Screening visit will be completed up to 2 weeks prior to the Baseline visit. • Assessments for Pre-screening and Screening Periods will be combined into one Screening Visit for subjects who meet prohibited medications or non-drug therapies criteria in Table 1 at entry (total time to complete the combined assessments= 1 to 2 weeks prior to Baseline). • The period between the Screening Visit and Baseline Visit may be extended beyond 2 weeks, if needed, to obtain the results of all screening laboratory assessments. Perform procedures in the order listed in Section 7
Procedure			
Hematology with differential		S	
Clinical Chemistry		S	
Parasitic screening		S	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. Selection of tests will be at the investigator's judgment.
Efficacy Assessments and Patient-Reported Outcomes			
Investigator's Global Assessment		S	See Section 7.3 and SRM for rater requirements.
% BSA affected		S	Regional assessment. Total % BSA affected will be auto-calculated within the eCRF. The total %BSA score from the eCRF will be utilized to confirm inclusion criteria. See Section 7.3 and SRM for rater requirements.
EASI		S	% BSA affected will be utilized to calculate the EASI score. The EASI score will be auto-calculated within the eCRF. The EASI score from the eCRF will be utilized to confirm inclusion criteria. See Section 7.3 and SRM for rater requirements

Period:	**Pre-Screening and Screening Period**		
			Notes
Visits:	**Pre-Screening**	**Screening**	
	Up to 4 wks prior to Screening Visit	**1 to 2 wks prior to Day 1 Baseline Visit**	• Individual Pre-Screening and Screening Visits will be conducted for subjects who have used prohibited medications or non-drug therapies and need to fulfil the prohibited medications period prior to the Screening Visit (See Table 1). For these subjects, the Pre-Screening Visit will be completed up to 4 weeks prior to the Screening Visit. After requirements regarding previous use of prohibited medication and non-drug therapies are met (See Table 1), the Screening Visit will be completed. The Screening visit will be completed up to 2 weeks prior to the Baseline visit. • Assessments for Pre-screening and Screening Periods will be combined into one Screening Visit for subjects who meet prohibited medications or non-drug therapies criteria in Table 1 at entry (total time to complete the combined assessments= 1 to 2 weeks prior to Baseline). • The period between the Screening Visit and Baseline Visit may be extended beyond 2 weeks, if needed, to obtain the results of all screening laboratory assessments. • Perform procedures in the order listed in Section 7
Procedure			
Daily Sign and Symptom Severity Diary (electronic)		S	To be completed by the subject every evening before 12:00 AM (midnight). If subject fails screening and does not continue in the study, the subject will return the electronic device to the site. (See SRM for guidance).

Abbreviations: AEs= adverse events; BSA= body surface area; EASI= Eczema Area and Severity Index; FSH= follicle stimulating hormone; HBsAG= hepatitis B surface antigen; SAEs= serious adverse events; SRM=Study Reference Manual.

Table 3 Time and Events Table: Baseline through Follow-up Period

Period:	Treatment					Follow-up Period		Notes
					Post-Tx Visit 1 *4 wks after last dose*	Post-Tx Visit 2 *8 wks after last dose*	Early WD	• Perform procedures in the order listed in Section 7. • Early WD visit: same procedures apply both to subjects discontinuing treatment but continuing with Post-Tx visits and to subjects withdrawing from the study.
Day/Week:	**Day 1 Baseline**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16 (No IP dose)**	**Wk 20 (No IP dose)**		
Window (days):		**±3**	**±3**	**±3**	**±3**	**±3**		
Procedure								
Inclusion/exclusion criteria	BL							
Randomization (IVRS)	BL							
Safety Assessments								
Physical examination, height, weight	BL					20	EW	Perform/obtain pre-dose on dosing days. See Section 7.4.3.
Vital signs	BL	4	8	12	16	20	EW	Obtain pre-dose on dosing days. See Section 7.4.4.
ECG		4			16		EW	Obtain pre-dose at Week 4. Unscheduled ECGs may also be performed as clinically indicated during the study.
Concomitant medications	BL	4	8	12	16	20	EW	See Section 6.10.1. Subject must apply the same non-prescription, non-medicated emollient twice daily during Treatment and Follow-up Periods. On study visit days, emollient must not be applied within the 2-hour period preceding the study visit. If emollient is applied <2 hours prior to the visit, wait ≥2 hours after application to perform study procedures.
Adverse events	BL	4	8	12	16	20	EW	Collect AEs from the start of study treatment until the follow-up contact. Record SAEs related to study participation or to a GSK product from the time a subject consents to participate in the study up to and including any follow-up contact (Section 7.4.1.1).

Period:	Treatment					Follow-up Period		Notes
					Post-Tx Visit 1 *4 wks after last dose*	Post-Tx Visit 2 *8 wks after last dose*	Early WD	• Perform procedures in the order listed in Section 7. Early WD visit: same procedures apply both to subjects discontinuing treatment but continuing with Post-Tx visits and to subjects withdrawing from the study.
Day/Week:	**Day 1 Baseline**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16 (No IP dose)**	**Wk 20 (No IP dose)**		
Window (days):		**±3**	**±3**	**±3**	**±3**	**±3**		
Procedure								
Laboratory Assessments	**Note: Labs are collected pre-dose on dosing days (includes blood draws, skin biopsies, and pregnancy testing)**							
Genetic sample- pre-dose	BL							Subject participation is voluntary. Additional informed consent is required.
Hematology with differential	BL	4	8	12	16	20	EW	Total WBC, absolute eosinophil count, and differential (%) will be blinded from the Baseline visit until the end of the study.
Clinical Chemistry	BL	4	8	12	16		EW	
Pregnancy test (urine)	BL	4	8	12	16	20	EW	Females of reproductive potential. If urine pregnancy test is positive, collect serum hCG (central laboratory). See Section 7.4.2 and Appendix 7 for reporting requirements.
Pharmacokinetic blood sample		4	8	12	16	20	EW	Results will be blinded during the study.
Blood sample for immunogenicity	BL	4			16	20	EW	Results will be blinded during the study.
Serum IL-5	BL	4			16	20	EW	Results will be blinded during the study.
Serum sample for biomarkers	BL	4	8	12	16			Results will be blinded during the study.
Skin biopsy sub-study- pre-identified study centers only	BL	4						Subject participation is voluntary. Additional informed consent is required. Results will be blinded during the study. Collect 1 lesional sample (from chronic lesion) and 1 non-lesional sample at each visit.
Efficacy Assessments and Patient-Reported Outcomes								
Patient Global Impression of Change		4	8	12	16		EW	Complete pre-dose prior to other assessments or evaluation by the investigator.

Period:	Treatment				Post-Tx Visit 1 *4 wks after last dose*	Follow-up Period Post-Tx Visit 2 *8 wks after last dose*	Early WD	Notes
								• Perform procedures in the order listed in Section 7. Early WD visit: same procedures apply both to subjects discontinuing treatment but continuing with Post-Tx visits and to subjects withdrawing from the study.
Day/Week:	**Day 1 Baseline**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16 (No IP dose)**	**Wk 20 (No IP dose)**		
Window (days):		**±3**	**±3**	**±3**	**±3**	**±3**		
Procedure								
Patient Global Impression of Severity	BL	4	8	12	16	20	EW	Complete pre-dose prior to other assessments or evaluation by the investigator.
Daily Sign and Symptom Severity Diary (electronic)	←----------					----------→	EW	To be completed by the subject every evening before 12:00 A.M.(midnight) during the Treatment and Follow-up Periods. Site personnel will review subject compliance with the diary at each visit.
Investigator's Global Assessment	BL	4	8	12	16	20	EW	Complete pre-dose. See Section 7.3 and SRM for rater requirements.
% BSA affected	BL	4	8	12	16	20	EW	Complete pre-dose. Regional assessment. Total % BSA affected will be auto-calculated within the eCRF. See Section 7.3 and SRM for rater requirements
EASI	BL	4	8	12	16	20	EW	Complete pre-dose. % BSA affected from each visit will be utilized to calculate the EASI score at each visit. The EASI score will be auto-calculated within the eCRF. See Section 7.3 and SRM for rater requirements
Clinician Global Impression of Change		4	8	12	16		EW	Complete pre-dose. See Section 7.3. and SRM for rater requirements

Period:	**Treatment**					**Follow-up Period**		**Notes**
					Post-Tx Visit 1 *4 wks after last dose*	**Post-Tx Visit 2** *8 wks after last dose*	**Early WD**	• Perform procedures in the order listed in Section 7. Early WD visit: same procedures apply both to subjects discontinuing treatment but continuing with Post-Tx visits and to subjects withdrawing from the study.
Day/Week:	**Day 1 Baseline**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16 (No IP dose)**	**Wk 20 (No IP dose)**		
Window (days):		**±3**	**±3**	**±3**	**±3**	**±3**		
Procedure								
Investigational Product and Other Study Treatment								
Mepolizumab or Placebo Administration	BL	4	8	12	No IP dose	No IP dose		See Section 6.1 and Section 6.1.1 for study treatment administration details. Observation of subject required for 1 hour after administration of study treatment. See Section 6.1.2. Postponement of study treatment and visit assessment is required during course of antibiotic, antiviral or antifungal treatment for acute infection. Postponed doses can be administered no further than 2 weeks after the original scheduled dose (See Section 5.4.3).

Abbreviations: AE= adverse events; BSA= body surface area; EASI= Eczema Area and Severity Index; IL-5= interleukin-5; SAEs= Serious Adverse Events; Tx= Treatment; WBC= white blood cell; WD=withdrawal; Wk=Week; wks=weeks

Table 4 Time and Events Table: Unscheduled Visit for Flare/Relapse

Period:	Treatment and Follow-up	
		Notes
Week:	**Unscheduled**	• This visit is for subjects who experience AD flare/relapse between scheduled study visits. See Section 4.2.4. • In the case of flare/relapse with intolerable AD symptoms where the use of prohibited medication is required (See Table 1), the subject will be permanently withdrawn from treatment • If the subject permanently discontinues study treatment or withdraws from the study, the procedures and visits described in Section 5.4 and Table 3 will apply. • Perform procedures in the order listed in Section 7.
Window (days):	**+5**	Visit window is from the time the subject notifies the site staff of potential AD flare/relapse.
Procedure		
Safety Assessments		
Physical examination, height, weight	U	To be performed only if needed, based on the investigator's judgment.
Vital signs	U	See Section 7.4.4.
Concomitant medications	U	
Adverse events	U	See Appendix 11. The disease under study (AD) or expected progression, signs, or symptoms of AD do not meet the definition of AE unless the worsening is more severe than expected for the subject's condition.
Laboratory Assessments		
Hematology with differential	U	Total WBC, absolute eosinophil count, and differential (%) will remain blinded.
Clinical Chemistry	U	Performed only if needed, based on investigator's judgment.
Efficacy Assessments and Patient-Reported Outcomes		
Daily Sign and Symptom Severity Diary (electronic)	U	To be completed the by subject in the evening.
Investigator's Global Assessment	U	
% BSA affected	U	Regional assessment. Total % BSA affected will be auto-calculated within the eCRF. See Section 7.3 and SRM for rater requirements.
EASI	U	% BSA affected from each visit will be utilized to calculate the EASI score at each visit. The EASI score will be auto-calculated within the eCRF. See Section 7.3 and SRM for rater requirements.

Abbreviations: AD= atopic dermatitis; EASI= Eczema Area and Severity Index; WBC= white blood cell; WD=withdrawal

7.2. Screening and Critical Baseline Assessments

The following demographic parameters will be captured: year of birth, sex, race, and ethnicity. The subject's Fitzpatrick skin type (Table 5) will also be documented.

Table 5 Fitzpatrick Skin Type Classification

Type	Constitutive Skin Color (Unexposed) and Typical Characteristics	Response to Ultraviolet Light Exposure
I	White; very fair; red or blond hair; blue eyes; freckles	Always burns, never tans
II	White; fair; red, blond, or brown hair; blue, hazel, or green eyes	Usually burns, tans with difficulty
III	White; any eye or hair color; very common	Sometimes mild burn, gradually tans
IV	White or light brown; typical Mediterranean Caucasian skin	Rarely burns, tans with ease
V	Brown; mid-eastern skin types	Very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

Source: Based on the characteristics originally described in Fitzpatrick, 1988

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

Medical (including AD history), medication, family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

Results of the blood eosinophil count obtained at the Screening Visit, after requirements regarding previous use of prohibited medication and non-drug therapies (Table 1) are met, will be used to determine eligibility.

7.3. Efficacy

To minimize inter-rater variability, raters will complete required training on each of the required assessments before enrolling subjects at their study center. To the fullest extent possible, the same rater will perform all efficacy assessments for an individual subject throughout the study. A rater must be an investigator, subinvestigator, or qualified healthcare professional. The SRM will specify the required rater qualifications.

Efficacy assessments will be performed at the visits specified in the Time and Events Tables (Section 7.1).

7.3.1. Investigator's Global Assessment (IGA)

The IGA is a clinical tool for assessing the current state/severity of a subject's AD [Rehal, 2011] (Appendix 4). It is a static 5-point morphological assessment of overall disease severity, as determined by the investigator, subinvestigator, or trained healthcare professional with required qualifications (See SRM), using the clinical characteristics of

erythema, infiltration, papulation, oozing, and crusting as guidelines. IGA is made without reference to previous scores.

7.3.2. Pruritus/Itch Severity

Pruritus is the most frequent symptom of AD and potentially has the greatest effect on quality of life. Subject-reported itch severity will be obtained from the Daily Sign and Symptom Severity Diary NRS (Appendix 9).

7.3.3. Body Surface Area (BSA)

The assessment of % body surface area (% BSA) is an estimate of the percentage of total involved skin with AD (Appendix 5). The % BSA assessment will be performed by looking at inflamed areas from within each of the 4 body surface regions separately: the head and neck, the upper extremities, the trunk and the lower extremities, and each of these body regions can potentially have up to 100% involvement. The raters will estimate the percentage of involved skin for each of the regions for a % BSA area score that is then multiplied by the appropriate proportionality multiplier to yield the % BSA regional involved value (for subjects ≥8 years of age, 0.1 for head, 0.2 upper extremities, 0.3 for trunk and 0.4 for lower extremities). The regional % BSA involved values are summed to generate the total involved % BSA. The regional % BSA area score will also be utilized as part of the matrix to calculate the EASI score. The SRM will contain more detailed instructions for this assessment.

The investigator, subinvestigator, or trained healthcare professional with required qualifications (See SRM) will perform this assessment.

7.3.4. Eczema Area and Severity Index (EASI)

The EASI scoring system is a standardized clinical tool for the assessment of AD that takes into account the overall extent of the % body surface area (% BSA) involved and the severity scores for each of the clinical signs: erythema, induration/papulation, excoriation, and lichenification [Hanifin, 2001; Rullo, 2008] (Appendix 6). The % BSA area score from the % BSA assessment is to be used as part of the matrix to calculate the EASI score. Severity scores for each of the clinical signs (erythema, induration/papulation, excoriation, and lichenification) are graded on a 4-point scale (0 to 3) for each of the 4 body regions (head and neck, upper extremities, lower extremities, and trunk). The severity scores for each of the signs are summed for each region and multiplied by the % BSA area score and by the appropriate proportionality multiplier (for subjects ≥8 years of age, 0.1 for head, 0.2 upper extremities, 0.3 for trunk and 0.4 for lower extremities) to generate a regional EASI score. The regional EASI scores are then summed to yield the final EASI score. The EASI score is a static assessment made without reference to previous scores.

The investigator, subinvestigator, or trained healthcare professional with required qualifications (see SRM) will perform this assessment.

7.3.5. Clinician Global Impression of Change Item

This is a single item that asks the investigator to rate the change from baseline in the subject's overall AD symptoms (Appendix 10). Response options range from "1=very improved" to "7=very worse". Results will be used as a clinical anchor in analyses of the minimally-important differences in itch and daily sign and symptom severity. The investigator, subinvestigator, or trained healthcare professional with required qualifications (See SRM) will perform this assessment.

7.4. Safety

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

A GSK study team and/or the GSK Safety Review Team review safety data from ongoing studies on a regular, systematic basis.

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

The definitions of an AE or SAE can be found in Appendix 11.

Additional information (i.e., corresponding symptoms) will be collected on the AE or SAE pages for the following AEs of special interest: systemic reactions and injection site reactions.

In addition, information whether an event met the diagnostic criteria for anaphylaxis as outlined by the Second Symposium on Anaphylaxis [Sampson, 2006] and in Appendix 2 will also be collected on the AE and SAE eCRF pages.

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 (i.e., the Week 20 visit) (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 Appendix 11.

- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 11.

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, non-serious AEs of special interest (as defined in Section 4.6.1) and AEs leading to withdrawal from treatment, 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 Appendix 11.

7.4.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 11 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (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 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, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

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

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

7.4.2. Pregnancy

- Details of all pregnancies in female subjects will be collected after the start of dosing and until 16 weeks after the last dose of study treatment.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 7.

7.4.3. Physical Exams

- A complete physical examination will include, at a minimum, assessment of the skin, cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.4.4. Vital Signs

- Vital signs will be measured in semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse.
- Three readings of blood pressure and pulse rate will be taken.
- First reading should be rejected.
- Second and third readings should be averaged to give the measurement to be recorded in the eCRF.

7.4.5. Electrocardiogram (ECG)

- Triplicate 12-lead ECGs will be obtained at time points indicated in the Time and Events Tables (Section 7.1) and as clinically indicated using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 5.4.5 for QTcF withdrawal criteria and additional QTc readings that may be necessary.
- All sites will use standardized ECG equipment provided by a centralized external vendor. A central ECG reader will be utilized. Details are provided in the SRM.

7.4.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 6, must be conducted in accordance with the laboratory manual and protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

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

Refer to the 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, apart from:

- Parasitic screening (will be performed at a local laboratory)
- Urine hCG pregnancy testing (will be performed at the study site).

Note: If a local laboratory analyzes a hematology sample for a study subject after the Baseline visit, procedures must be in place at the site to ensure that the results of the total WBC, absolute eosinophil count, and differential (%) remain blinded.

Hematology, clinical chemistry, and additional parameters to be tested are listed in Table 6. All laboratory samples are to be obtained pre-dose on dosing days.

Table 6 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count	*RBC Indices*:	*WBC count with Differential:* [1]	
	RBC Count	MCV	Neutrophils	
	Hemoglobin	MCH	Lymphocytes	
	Hematocrit		Monocytes	
			Eosinophils	
			Basophils	
Clinical Chemistry [2]	BUN	Potassium	AST (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Albumin
Other Tests	• Hepatitis B (HBsAg) • Hepatitis C (Hep C antibody) • FSH and estradiol (as needed in women of non-child bearing potential only) • Urine hCG Pregnancy test (as needed for women of child bearing potential) [3] • Parasitic screening [4]			

NOTES :

1. Total WBC, absolute eosinophil count, and differential (%) will be blinded from the Baseline visit until the end of the study.
2. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.4.4 and Appendix 8.
3. Urine pregnancy tests will be completed at each site. If a urine pregnancy test is positive, collect serum hCG sample (central laboratory) to confirm pregnancy. See Section 7.4.2 and Appendix 7 for reporting requirements
4. Local laboratory will be used. Only required for high-risk countries or for subjects who have visited high-risk countries in the 6 months prior to Screening visit. The selection of the tests will be at the investigator's judgment.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; hCG=human chorionic gonadotrophin; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; WBC=white blood cell

7.4.7. Immunogenicity

Pre-dose blood samples will be collected for the determination of anti-mepolizumab antibodies at the visits specified in the Time and Events Table (Table 3). Details for sample collection and processing are provided in the Laboratory Manual. Results will be blinded during the study.

7.5. Pharmacokinetics

7.5.1. Blood Sample Collection

Blood samples for determination of mepolizumab plasma concentration will be collected at the time points indicated in Table 3. The PK samples will be drawn **pre-dose** on days when study treatment is scheduled to be administered. 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 time points to ensure thorough PK monitoring.

Blood samples (approximately 2 mL) for determination of plasma concentrations of mepolizumab will be collected into plastic lithium heparin tubes.

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 Platform Technology and Science (PTS), GlaxoSmithKline, the details of which will be included in the laboratory manual. Concentrations of mepolizumab will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the laboratory manual).

Once the plasma has been analyzed for mepolizumab, any remaining plasma may be analyzed for other compound-related material and the results reported under a separate PTS, GlaxoSmithKline protocol.

The results will be blinded during the study.

7.6. Biomarker(s)/Pharmacodynamic Markers

Blood eosinophil counts will be assessed as part of the standard hematology assessments (Section 7.4.6) performed at the visits specified in the Time and Events Tables (Section 7.1).

Blood samples will be collected for measurement of serum free and total IL-5 levels at the visits specified in the Time and Events Table (Table 3).

Samples will be collected pre-dose on dosing days. The results will be blinded during the study. Collection, processing, and shipping instructions are detailed in the laboratory manual.

7.6.1. Novel Biomarkers- Skin Biopsy Sub-study and Serum Biomarkers

Skin biopsy (3 mm) and blood samples will be collected during this study (Table 3) and may be used for the purposes of measuring novel biomarkers to identify factors that may influence AD as well as the biological and clinical responses to mepolizumab treatment.

If relevant, this approach will be extended to include the identification of biomarkers associated with adverse events.

Skin biopsies from lesional and non-lesional skin will be collected at the Baseline visit and Week 4 from up to 20 subjects. Subject participation in the skin biopsy sub-study is voluntary and will require additional subject informed consent. The sub-study will be conducted only at pre-identified centers.

Blood samples will be collected from all subjects for measurement of serum biomarkers. (See Section 7.6.1.3).

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with AD and/or the action of mepolizumab treatment will be identified by application of:

- RNA transcriptome analysis of skin biopsy samples.
- Measurement of the levels of a subset of RNA species on skin biopsy samples.
- Protein levels of biomarkers in serum samples.

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

Skin biopsies and blood samples will be collected prior to dosing and at the time points indicated in Table 3. Collection, processing, and shipping instructions are detailed in the SRM.

7.6.1.1. RNA Transcriptome Research

Transcriptome studies will be conducted using microarray which facilitates the simultaneous measurement of the relative abundances of thousands of RNA species resulting in a transcriptome profile for each skin biopsy sample. This will enable the evaluation of changes in transcriptome profiles that may correlate with biological response relating to atopic dermatitis or the action of mepolizumab treatment.

The same samples may also be used to confirm findings by application of alternative technologies.

7.6.1.2. RNA Expression Research of a Subset of RNA Species

RNA expression studies may be conducted using quantitative reverse transcription-polymerase chain reaction (RT-PCR) for each skin biopsy sample. The RNAs assayed may be those involved with the pathogenesis of AD or in the subject's response to mepolizumab treatment. In addition, continuing research may identify other proteins or regulatory RNAs that may be involved in response to mepolizumab treatment or the pathogenesis of AD. This will enable the evaluation of changes in RNA expression profiles that may correlate with biological response relating to AD or the action of study treatment.

7.6.1.3. Protein levels of biomarkers in serum

Serum samples will be collected from all subjects at the time points indicated in the Time and Events Table (Table 3) to evaluate the PD effects of mepolizumab on biomarkers, such as total IgE, eosinophil cationic protein (ECP), circulating eosinophils, and chemokines such as TARC (CCL17), Eotaxin-1, Eotaxin-3, macrophage-derived chemokine (MDC), and CCL13.

The same samples may also be used to confirm findings by application of alternative technologies.

7.7. Genetics

Information regarding genetic research is included in Appendix 12.

7.8. Patient-Reported Outcomes

All Patient-Reported Outcomes (PROs) will be completed as specified in the Time and Events Tables (Section 7.1).

All PROs except the Daily Sign and Symptom Severity Diary will be completed:

- at study visits,
- prior to dosing,
- prior to other assessments or evaluation by investigator, and
- in the order recommended in Section 7.

The Daily Sign and Symptom Severity Diary will be completed as described in Section 7.8.1.

7.8.1. Daily Sign and Symptom Severity Diary

The self-administered sign and symptom severity diary (which is based on the content of the Patient-Oriented Eczema Measure) assesses the severity of 11 disease-related signs and symptoms (itching, discoloration, bleeding, oozing, cracking, scaling, flaking, dry/rough, painful, burning, and stinging) (Appendix 9). An additional item assesses the impact of AD on sleep. Response options are on an 11-point NRS and range from 0 (Absent) to 10 (Worst Imaginable). Question 1 of the diary will be used to assess itch.

An electronic diary will be utilized. Subjects will complete the diary every evening before 12:00 AM at approximately the same time, if possible, using a recall period of the past 24 hours.

7.8.2. Patient Global Impression of Severity and Change Items

At the Baseline visit, during the Treatment Period, Early Withdrawal visit, and Follow-up Period, subjects will be asked to rate the overall severity of their AD from “0=absent” to “4=very severe” (Appendix 13).

At all visits in the Treatment Period subsequent to the Baseline visit and at the Early Withdrawal visit, the global impression of change items ask subjects to rate their change from baseline in overall severity of AD symptoms and in overall severity of itch. Response options range from "1=very improved" to "7=very worse" (Appendix 13).

8. DATA MANAGEMENT

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

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

No formal hypothesis testing is planned. The primary objective of this study is to characterize the clinical activity of mepolizumab. A Bayesian approach will be employed to estimate the posterior probability that 1) the IGA response rate for mepolizumab is 40% or greater, and 2) that the improvement over placebo in IGA response rate is at least 15 percentage points.

Descriptive statistics including point estimates and corresponding 90% confidence/ credible intervals will be provided for efficacy endpoints.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

The primary endpoint will be the proportion of subjects who achieve treatment success defined as an IGA score of 0 or 1 and at least a 2-grade improvement at Week 16.

Sample size is based on the objective to characterize the clinical activity of mepolizumab in subjects with moderate-to-severe atopic dermatitis. In order to characterize this, we assume that a 40% IGA response rate in the mepolizumab group and a 10% IGA response in the placebo arm, as well as an at least 15 percentage point improvement over placebo, will constitute a clinically meaningful improvement.

Using Bayesian posterior probability and assuming a flat large variance normal prior for difference in response rate, 25 mepolizumab subjects and 25 placebo subjects (single formal interim at 50% of subjects) will power the study to approximately 80% with predictive probability method based on the success criteria that P (difference in response rate ≥15%|Data) greater than 70% if the true response rate is 40% for mepolizumab group and 10% for placebo group. The 80% credible intervals for the difference in response rate will be presented. No pairwise comparisons are planned.

The primary analysis will be performed on the Intent-to-Treat (ITT) population, with a supporting analysis of the per protocol (PP) population.

9.2.2. Sample Size Sensitivity

If either the actual percentage of patients on placebo that achieve an IGA score of 0 or 1 at Week 16 and at least a 2-grade improvement or the treatment effect of mepolizumab is different from the values assumed in Section 9.2.1, the power to detect a change in the proportion of subjects that achieve an IGA score of 0 or 1 and at least a 2-grade improvement at Week 16 will be affected.

Table 7 Sample Size Effects on the Predictive Probability of Success at the End of the Study

Prior used	Total Sample Size	Probability of Success
Consensus prior	40	0.745
	50	0.799
	60	0.833
	70	0.866

9.2.3. Sample Size Re-estimation or Adjustment

No sample size adjustment is planned.

9.3. Data Analysis Considerations

All pre-specified analyses will be described in a full RAP which will be finalized prior to unblinding. The study will be unblinded once the final subject has completed the Week 20 visit, 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 and who received 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 efficacy measures.

Per Protocol Population:
The Per Protocol (PP) population will consist of all subjects in the Intent-to-Treat 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. The PP population will not be analyzed if this population comprises more than 95% or less than 50% of the ITT population.

Safety Population:
All subjects who received at least one dose of a study treatment will be included in the safety population. Data will be summarized by actual treatment received. This population will be used in the evaluation of safety and tolerability.

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 a 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 serum PD measurement and at least one post-treatment serum PD measurement. This will be the primary population for assessing PD.

Biopsy Population:
The Biopsy population is defined as all subjects in the ITT population who have a baseline measurement and who also have at least one post-treatment PD biomarker measurement derived from skin biopsy samples. This will be the population used for the biopsy sub-study.

9.3.2. Administrative Interim Analyses

- Unblinded in-stream study data summaries will be generated by a GSK study statistician and study programmer. The unblinded summaries will be provided to GSK senior manager(s) for their review of subject efficacy and safety data. These results and randomization assignments will only be shared with members involved in the review and conduct of the analysis.

9.3.3. Formal Interim Analysis

A formal interim analysis may be performed after approximately 50% of subjects have been randomized and have had the opportunity to complete the Week 8 visit for futility and to enable future planning. If the study is anticipated to be fully enrolled at the projected time for this analysis, the interim may not be conducted.

It is expected that GSK's study statistician, programmer, clinical scientist, project physician lead, and/or respective designee(s) will be responsible for presenting the unblinded formal interim analyses. To do so, they will be unblinded to subject level data for the subjects enrolled in the study at the time the database is locked for the purpose of the interim analyses. These persons will not share subject-level randomization assignments with anyone not involved in conducting the analyses. The protection of the study blind and the dissemination plan for summary level results of the interim analyses will be described in the RAP.

The formal interim analyses will include an assessment of the proportion of subjects who have an IGA score of 0 or 1 and a minimum 2-grade improvement from baseline at Week 8 and later time points, and assessments of key secondary endpoints (e.g., change from baseline for EASI score) and key safety data. The interim analysis will not be used to declare success. Futility will be evaluated and may be declared if the predictive probability of meeting the assumptions in Section 9.2.1 is less than 10%.

A full database cleaning is not required for the interim analysis.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

The primary efficacy endpoint is the IGA response rate at week 16. The observed response rate and difference between mepolizumab and placebo and the 80% credible interval for the response rate and the difference in response rate will be presented. The posterior probability that the IGA response rate for mepolizumab is 40% or greater and that the improvement over placebo is at least 15 percentage points will be calculated.

Subjects withdrawing prematurely from the study prior to the Week 16 visit will be assumed to be non-responders.

9.4.2. Secondary Analyses

The secondary efficacy endpoints are defined in Section 3.

IGA: Subjects' change from baseline in IGA score and the proportion of subjects with a 2-point decrease from baseline will be summarized by visit. Point-estimates and 90% confidence intervals for the differences between the experimental and vehicle arm at Week 16 will be presented. No formal hypothesis testing will be performed.

EASI: Subject's change from baseline/percent change from baseline will be summarized by visit. Point-estimates and 90% confidence intervals for the differences between the experimental and vehicle arm at Week 16 will be presented. No formal hypothesis testing will be performed.

Continuous endpoints will be presented as means and 90% confidence intervals.

Safety Analyses

AEs will be coded using the MedDRA coding dictionary and summarized by preferred term and treatment group. SAEs occurring pre-treatment and Aes and SAEs occurring during active treatment and post-treatment will be summarized separately. Separate summaries will be provided for all Aes, investigational product-related Aes, SAEs, Aes of special interest (including systemic reactions [allergic/type I hypersensitivity or Systemic Other] and local injection site reactions) and for Aes leading to permanent discontinuation of investigational product or withdrawal from the study. All laboratory parameters for clinical chemistry and hematology will be summarized and tabulated.

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

Immunogenicity will be summarized using appropriate descriptive statistics.

Full details of planned analyses of safety endpoints will be included in the RAP.

9.4.3. Exploratory Analyses

Pharmacokinetic Analyses

Blood samples will be collected to determine mepolizumab plasma concentrations as per the Time and Events Table (Table 3).

Sparse blood sampling is being implemented in this study and mepolizumab plasma concentrations will be analyzed by population PK methods using the current population PK model in order to determine, for example, the subject's individual systemic exposure, and apparent clearance. In addition to the covariates already included in the current population PK model, the effect on mepolizumab systemic exposure of other covariates of particular interest in subjects with AD may be explored if deemed appropriate. Furthermore, the model will be used to generate predictions against which the model will be validated prospectively using the observed data from the study (sparse sampling) in order to confirm the absence of AD disease impact on mepolizumab exposure. The ability of the model to describe data in AD subjects will be assessed by prospective validation using appropriate goodness of fit tests.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. Full details of the analysis to be performed will be given in the RAP.

Pharmacodynamic (PD) Analyses

PD endpoints are defined in Section 3. Full details of planned analyses of PD endpoints will be included in the RAP.

Patient-Reported Outcomes (PRO) Endpoints

PRO endpoints are defined in Section 3. Full details of planned analyses of PRO

endpoints will be included in the RAP and/or a separate PRO RAP.

Efficacy Endpoints

"Exploratory" efficacy endpoints are defined in Section 3. Full details of the planned analysis of all "Exploratory" efficacy endpoints will be included in the RAP.

EASI: The proportion of subjects with cutpoints (e.g., −50%, −75%) for percent change from baseline will be summarized by visit. Point-estimates and 90% confidence intervals for the differences between the experimental and vehicle arm at Week 16 will be presented. No formal hypothesis testing will be performed.

Itch (Daily Sign and Symptom Severity Diary NRS Question #1): Subject's change from baseline/percent change from baseline in weekly average and the 90% confidence interval for the difference between the experimental and vehicle arm at Week 16 will be presented. No formal hypothesis testing will be performed.

Itch (Daily Sign and Symptom Severity Diary NRS Question #1): Subject's change from baseline/percent change from baseline and the proportion of subjects with cutpoints (e.g., −50%, −75%) for percent change from baseline will be summarized by visit.

Disease Flare/Relapse Endpoints

Disease flare/relapse endpoints are defined in Section 3. Full details of the planned analysis of these endpoints will be included in the RAP.

Relationship between Efficacy and Blood Eosinophils

Endpoints to characterize the relationship between efficacy and blood eosinophil counts are described in Section 3.

If data permits, EASI percent change from baseline will be analyzed using a Mixed Model Repeated Measures (MMRM) analysis, fitting subject as a random effect, and baseline value, treatment group and baseline blood eosinophil count as fixed effects. An unstructured variance-covariance matrix structure will be assumed.

Further exploratory analyses to determine the impact of baseline blood eosinophils may be conducted.

Full details of the planned analysis of these endpoints will be included in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

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

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

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- 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.
- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.
- Definition of what constitutes source data can be found in the Source Document Agreement.

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

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

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

10.4. Quality Assurance

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

10.5. Study and Site Closure

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

10.6. Records Retention

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

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

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

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

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

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12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

AD	atopic dermatitis
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
CI	confidence interval
CRF	case report form
CV	cardiovascular
EASI	Eczema Area and Severity Index
ECGs	electrocardiograms
ECP	eosinophil cationic protein
eCRF	electronic case report form
EGPA	eosinophilic granulomatosis with polyangiitis
FAAN	Food Allergy and Anaphylaxis Network
FRP	females of reproductive potential
FSH	follicle stimulating hormone
GSK	GlaxoSmithKline
HbsAg	hepatitis B surface antigen
hCG	human chorionic gonadotrophin
HIV	human immunodeficiency virus
HPA	hypothalamic-pituitary-adrenal
HRT	hormone replacement therapy
ID_{50}	dose resulting in 50% of the maximum achievable effect
ID_{90}	dose resulting in 90% of the maximum achievable effect
IFN	interferon
IFN-γ	interferon-gamma
IGA	Investigator's Global Assessment
IgE	immunoglobulin E
IgG	immunoglobulin G
IL	interleukin
INR	international normalized ratio
ITT	Intent-to-Treat
IV	intravenous
mAb	monoclonal antibody
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume

MDC	macrophage-derived chemokine
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
NAB	neutralizing antibody
NIAID	National Institute of Allergy and Infectious Diseases (US)
NRS	numeric rating scale
PD	pharmacodynamic
PEF	Peak expiratory flow
PGAI	Physician Global Assessment of Improvement
PK	Pharmacokinetics
PP	Per Protocol
PROs	Patient-Reported Outcomes
PTS	Platform Technology and Science
QTc	QT interval corrected for heart rate
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
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SC	subcutaneous
SCORAD	severity score atopic dermatitis
SRM	Study Reference Manual
TARC	thymus and activation regulated chemokine
Th-2	type 2 helper T-cell
ULN	upper limit of normal
US	United States
UV	ultraviolet
WBC	white blood cell
WHO	World Health Organization

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NUCALA

Trademarks not owned by the GlaxoSmithKline group of companies
Atopiclair
CeraVe
EpiCeram
PruMyx

12.2. Appendix 2 – Anaphylaxis Criteria

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

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

12.3. Appendix 3 – Criteria for Atopic Dermatitis Diagnosis

The diagnosis of atopic dermatitis is based on the Eichenfield revised criteria of Hanifin and Rajka [Eichenfield, 2014].

ESSENTIAL FEATURES- Must be present:

- Pruritus
- Eczema (acute, subacute, chronic)
    - Typical morphology and age-specific patterns*
    - Chronic or relapsing history

Patterns include:

1. *Facial, neck, and extensor involvement in infants and children*
2. *Current or previous flexural lesions in any age group*
3. *Sparing of the groin and axillary regions*

IMPORTANT FEATURES- Seen in most cases, adding support to the diagnosis:

- Early age of onset
- Atopy
    - Personal and/or family history
    - Immunoglobulin E reactivity
- Xerosis

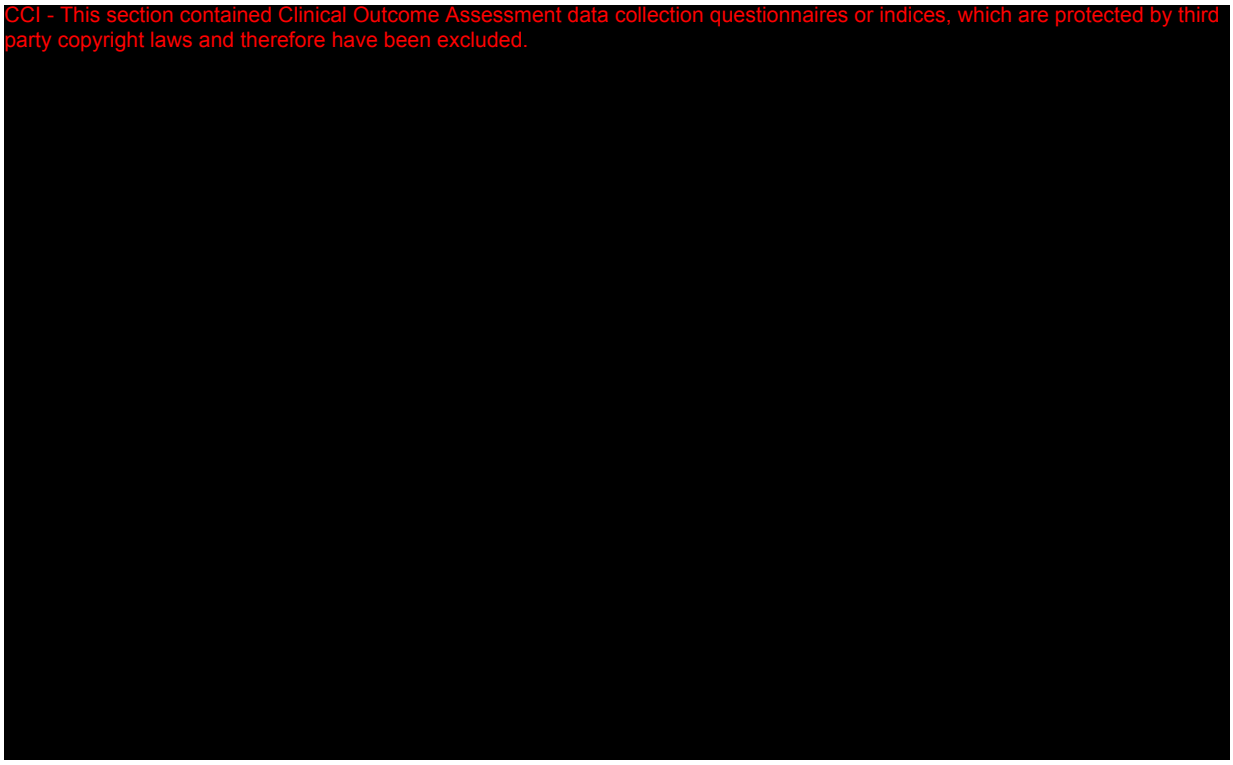
ASSOCIATED FEATURES- These clinical associations help to suggest the diagnosis of atopic dermatitis but are too nonspecific to be used for defining or detecting atopic dermatitis for research and epidemiologic studies:

- Atypical vascular responses (e.g., facial pallor, white dermographism, delayed blanch response)
- Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis
- Ocular/periorbital changes
- Other regional findings (e.g., perioral changes/periauricular lesions)
- Perifollicular accentuation/lichenification/prurigo lesions

EXCLUSIONARY CONDITIONS-It should be noted that a diagnosis of atopic dermatitis depends on excluding conditions, such as:

- Scabies
- Seborrheic dermatitis
- Contact dermatitis (irritant or allergic)
- Ichthyoses
- Cutaneous T-cell lymphoma
- Psoriasis
- Photosensitivity dermatoses
- Immune deficiency diseases
- Erythroderma of other causes

12.4. Appendix 4 – Investigator's Global Assessment (IGA)



12.5. Appendix 5 – Body Surface Area (BSA)

- This study protocol will follow the 3 steps depicted below to calculate total % BSA involvement. However, for purposes of this study, qualified raters will only need to complete Step 1: estimating % BSA involvement in each region. Steps 2 and 3 will be auto calculated within the eCRF after completion of Step 1 (entry of estimated % BSA involvement values).

  Note: This process should be followed to confirm % BSA eligibility at the Screening and Baseline Visit.

- Complete % BSA prior to EASI at each study visit.
- Use visit-specific estimated % BSA involvement (Step 1) to determine the EASI area score at each visit.

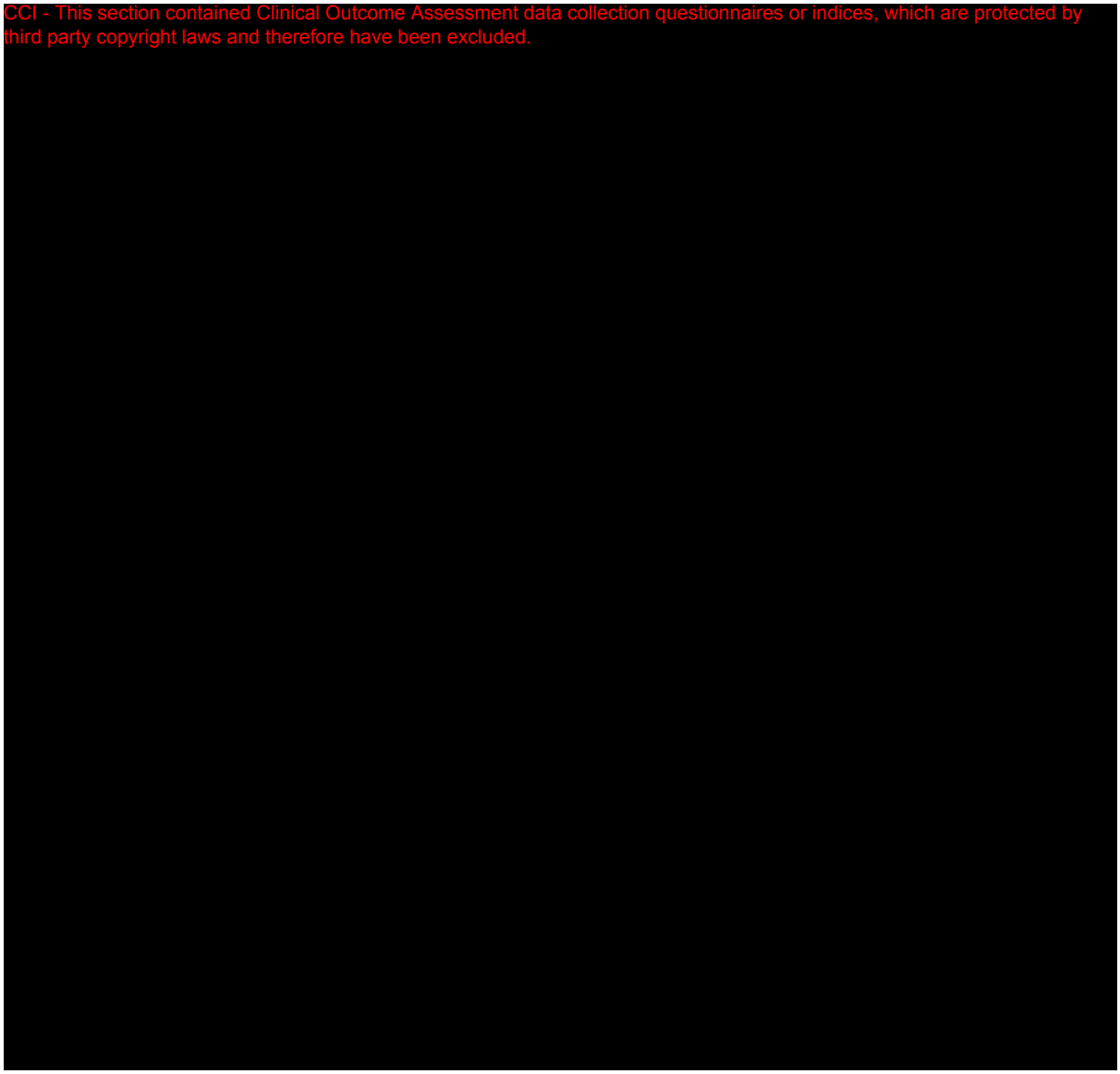
Body Region	% Involvement (0-100% each area)	% Involvement x Proportionality Multiplier	Regional % BSA Involvement
Head and neck		____ x 0.1	
Upper extremities		____ x 0.2	
Trunk		____ x 0.3	
Lower extremities		____ x 0.4	
		Total Involved % BSA (sum of the 4 area values) =	

12.6. Appendix 6 – Eczema Area and Severity Index (EASI)

- For purposes of this study, qualified raters will record the severity of signs (erythema, induration/papulation, excoriation, lichenification) by body region (head/neck, trunk, upper extremities, lower extremities). The severity scores will be entered into the eCRF for each visit. The region score (0-6), score per body region, and final EASI score will be auto calculated within the eCRF.
- The eCRF auto calculated final EASI score will be utilized to confirm eligibility at the Screening Visit and the Baseline Visit.

Once a % BSA involvement for each region is determined, each percentage is translated to an area score based on the following definitions:

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



Reference:
Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The Eczema Area and Severity Index (EASI): an assessment of reliability in atopic dermatitis. Exp Dermatol. 2001;10:11-18.

12.7. Appendix 7: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

12.7.1. 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.

12.7.2. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study (from first dose and until 16 weeks after last dose of study treatment)
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 11. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will discontinue study treatment.

12.7.3. References

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Guideline dated 24 June 1993 (Addendum dated 9 November 2000 incorporated in November 2005. ICH S5 (R2)

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12.8. Appendix 8 – Liver Safety Required Actions and Follow up Assessments

Liver chemistry stopping criteria and required follow up assessments

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

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• Immediately discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (See **MONITORING** below) • **Do not restart/rechallenge.** Permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments (refer to Section 5.4).	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained within 4 weeks after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia. *Note: This blood sample will be sent to the central laboratory to maintain the blind while study is ongoing. Results will be provided only if unblinding of a subject's treatment assignment is required. Also note that the mechanism of action of mepolizumab leads to lowering of eosinophils.*

	• 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
MONITORING: **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	**<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct 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. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Liver chemistry increased monitoring criteria with continued therapy

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

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12.9. Appendix 9 – Daily Sign and Symptom Severity Diary

Individuals with eczema may experience a variety of symptoms.

Please answer each question to the best of your ability. Please indicate how severe each of the following eczema symptoms was in the **past 24 hours**:

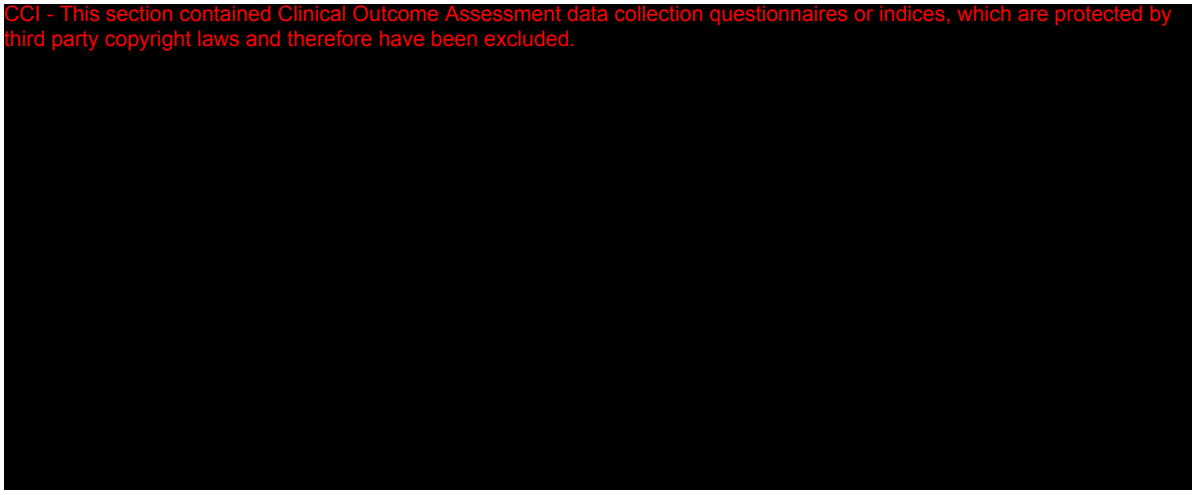
1.	Itchy skin	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
2.	Red or discolored skin	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
3.	Bleeding skin	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
4.	Oozing skin	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
5.	Cracked skin	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
6.	Scaly skin	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
7.	Flaky skin	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
8.	Dry or rough skin	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
9.	Painful skin	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
10.	Burning skin	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable
11.	Stinging skin	0 Absent	1	2	3	4	5	6	7	8	9	10 Worst imaginable

Please respond to the following question about how much your eczema impacted your sleep in the **past 24 hours** by selecting the number to indicate your response.

In the **past 24 hours**, how much was your sleep impacted?

0	1	2	3	4	5	6	7	8	9	10
No impact										Worst sleep imaginable

12.10. Appendix 10 – Clinician Global Impression of Change



12.11. Appendix 11 – Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.11.1. 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.

12.11.2. 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.

- **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
d. Is a congenital anomaly/birth defect
e. 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
f. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.11.3. 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

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

12.11.5. 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.

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

12.12. Appendix 12 – 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;
- Atopic dermatitis susceptibility, severity, and progression and related conditions

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

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

Study Population

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

Study Assessments and Procedures

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

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

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

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

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

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

Informed Consent

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

Subject Withdrawal from Study

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

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

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

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

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

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.

References

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12.13. Appendix 13 – Patient Global Impression of Severity and Change

12.13.1. Patient Global Impression of Severity (PGIS)

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

12.13.2. Patient Global Impression of Change (PGIC)

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

12.14. Appendix 14 – Country Specific Requirements

No country-specific requirements exist.

12.15. Appendix 15: Protocol Changes

Protocol Amendment 02: 22-JUN-2017

Where the amendment applies

This protocol amendment applies to all sites and all countries.

Summary of amendment changes and rationale

Section # and Name	Description of Change	Brief Rationale
Medical Monitor/Sponsor Information Page	Site address for Secondary Medical Monitor was updated	Change in site address
Section 4.1- Overall Design, Figure 1 Study Schematic	A boarder was placed around the Week 16 and Week 20 visits to highlight that no IP dose is administered at the two visits.	Reminder placed within the study schematic noting no IP dose is administered at Weeks 16 and 20.
Synopsis; Section 4.2.1- Pre-screening/Screening Periods; &.Section 7.1- Time and Events Table	Removed requirement for subject data entry into the Daily Sign and Symptom Severity Diary for at least 7 consecutive days immediately prior to the Baseline visit. The process for monitoring subject data entry into the Daily Sign and Symptom Severity Diary has been added.	Under Amendment 1, the itch/pruritus endpoint ('the mean change in weekly average of daily itch/pruritus numeric rating scale [NRS] score [captured within the Daily Sign and Symptom Severity Diary] from baseline to Week 16') was changed from a secondary endpoint to exploratory endpoint. Subject data entry will be monitored throughout the trial. Subjects who do not complete data entry will be re-educated on the importance of diary completion.
Synopsis; Section 4.3- Type and Number of Subjects	Increase in number of subjects screened from approximately 75 to approximately 140.	Increase in screen failure rate requires increase in approximate number of subjects screened. No change was applied to target number of subjects randomized.
Synopsis; Section 6.3- Blinding and Section 9.3.2-Administrative Interim Analyses; Section 9.3.3 Formal Interim Analysis	The 'Interim analysis' section updated to 'Formal interim analysis'. Added separate section on administrative interim analyses'.	Administrative interim analyses will be conducted to enable GSK senior manager(s) review of subject efficacy and safety data summaries. GSK study statistician, study programmer and senior manager(s) will review unblinded data. Administrative and formal interim analyses may be performed.
Section 7- Study Assessments and	Clarification regarding order of assessments. Note added	Clarification regarding recommended order of assessments.

Section # and Name	Description of Change	Brief Rationale
Procedures	regarding subject report of emollient application within the 2-hour period preceding the study visit.	
Section 7.1 Table 2	Clarification added to Pre-Screening column table header- 'prior to the Screening Visit' was added after 'Up to 4 weeks'. Clarification added to Screening column table header- 'prior to the Day 1 Baseline Visit' was added after '1 to 2 weeks'.	Pre-Screening Visit will occur up to 4 weeks prior to the Screening Visit. Screening Visit will occur 1 to 2 weeks prior to the Day 1 Baseline Visit.
Section 7.1 Table 3- Time and Events	'No IP dose' was added to the Week 16 and Week 20 column headers within the Time and Events table.	Reminder that IP dose is not administered at Week 16 and Week 20.
Section 7.4.5- Electrocardiograms	Clarification: Triplicate 12-lead ECGs are required for all ECG time points noted in Section 7 (all Time and Event tables). Original language indicated triplicate ECGs were required for time points noted within Time and Events Table 3 only.	Triplicate 12-lead ECGs are required for all time points.
Section 12.5- Appendix 5: Body Surface Area	Clarification: The process outlined for BSA calculation should be followed at both the Screening and Baseline Visits in order to confirm subject eligibility. Original language describing the process for BSA calculation, only referenced confirmation of subject eligibility at the Screening Visit and not both the Screening and Baseline Visits.	The eCRF auto calculated BSA score will be used for confirmation of BSA eligibility at the Screening and Baseline Visits.
Section 12.6- Appendix 6: EASI	Clarification: Qualified raters will assess the severity of signs by body region. The severity scores will be entered into the eCRF for each visit. The region score (0-6), score per body region, and final EASI score will be auto calculated within the eCRF.	The eCRF auto calculated final EASI score will be used for confirmation of EASI eligibility at the Screening and Baseline visits.

Protocol Amendment 01: 26-December-2016

Where the amendment applies

This protocol amendment applies to all sites and all countries.

Summary of amendment changes and rationale

Protocol amendment 1 includes recommendations from the US Food and Drug Administration (FDA). In addition, some protocol clarifications have been made.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria & throughout document	Enrollment of adult subjects only (ages 18 – 70 years).	US Food and Drug Administration (FDA) recommendation to obtain preliminary safety and efficacy data in adults with moderate to severe atopic dermatitis (AD) prior to initiation of studies in pediatric subjects.[1]
Table 3: Time and Events Table: Baseline through Follow-up Period	Collection of additional pharmacokinetic (PK) samples at Weeks 8 and 12.	FDA recommendation.[1] As this is the first study in subjects with atopic dermatitis (AD) receiving mepolizumab subcutaneous (SC) treatment, additional PK sampling would provide useful data to elucidate the steady state of mepolizumab in subjects with AD.
6.1.2 Observation Period & throughout document	Addition of 1 hour observation period at Week 12 post dose.	FDA recommendation to standardize post-dose safety monitoring.[1] With Amendment 1, the 1 hour observation period will be required for each dosing visit, post dose
5.4.1 Early Withdrawal from Study Treatment & 7.4.1 Aes and SAEs	Addition of stopping criteria for cardiovascular or hematologic Aes consistent with CTCAE grade 2 or higher.	FDA recommendation.[1]
Table 3 Time and Events Table: Baseline through Follow-up Period	Collection of electrocardiograms (ECGs) at Week 4 (pre-dose), Week 16 or Early Withdrawal	FDA recommendation.[1]
6.10.1 Permitted Medications and Non-Drug Therapies; Table 1 Prohibited Medications and Non-Drug Therapies	Prohibit use of oral antihistamines	FDA recommendation.[1] Minimize impact on efficacy evaluation of pruritus.
5.4.3 Postponement of Study Treatment	Require postponement of study medication during treatment with	FDA recommendation.[1]

Section # and Name	Description of Change	Brief Rationale
	oral or IV non-cytotoxic antibiotics, antivirals, anti-protozoals or antifungals.	
5.1 Inclusion Criteria	Revised definition of 'inadequate response to prior treatment' to specify a minimum potency for topical corticosteroid failure. Added inadequate response to optimal use of nonpharmacologic measures such as moisturizers.	FDA recommendation to specify a minimum potency for topical corticosteroid failure and inadequate response to optimal use of nonpharmacologic measures such as moisturizers. [1]
4.2.4 Unscheduled Visit for Flare/Relapse & Table 4 Time and Events Table: Unscheduled Visit for Flare/Relapse	Clarification regarding the management of subjects who experience flare/relapse. In the case of flare/relapse with intolerable AD symptoms where the use of prohibited medication is required (See Table 1), the subject will be permanently withdrawn from treatment.	FDA recommendation to clarify how subjects experiencing flare/relapse will be managed.[1]
3 Objectives and Endpoints & 9.4.3 Exploratory Analyses	Shift in itch/pruritus endpoint ('mean change in weekly average of daily itch/pruritus numeric rating scale [NRS] score from baseline to Week 16') from secondary endpoint to exploratory endpoint.	Insufficient data available to properly design this endpoint as secondary therefore shifted to exploratory.
4.2 Treatment Arms and Duration & Table 2 Prohibited Medications and Non-Drug Therapies	Clarification regarding timing for informed consent. If an ineffective treatment is stopped for the purpose of study entry, informed consent should be obtained at the time the ineffective treatment is stopped.	Clarification.
4.2 Treatment Arms and Duration, Table 2 Prohibited Medications and Non-Drug Therapies	Clarification regarding the total time in the Screening Period for subjects transitioning off a biologic at study entry.	Clarification. For subjects who may need to stop treatment with a biologic, the total Pre-Screening and Screening Period may last up to 20 weeks thus the total approximate time in the study may last for up to 40 weeks.
Table 3 Time and Events Table: Baseline through Follow-up Period; Appendix 12.5 % BSA	Clarification regarding the need to enter %BSA affected and EASI scores in the eCRF in-stream.	Clarification.

Section # and Name	Description of Change	Brief Rationale
Table 2 Time and Events: Pre-Screening through Screening Period; Table 3 Time and Events: Treatment through Follow-up Period and Table 4 Time and Events Table: Unscheduled Visit for Flare/Relapse	Replacement of timepoint markers from 'X' to visit type abbreviation (e.g. 'S' for Screening visit, 'B' for Baseline visit).	To facilitate review.
Table 2 Time and Events: Pre-Screening through Screening Period; Table 3 Time and Events: Treatment through Follow-up Period and Table 6 Protocol Required Safety Lab Assessments	Collection of serum hCG for confirmation of positive urine pregnancy test	Confirmation of urine pregnancy test
4.6 Benefit:Risk Assessment; 5 Selection of Study Population and Withdrawal Criteria; 6.3 Blinding and 11 References	Update to document number of Investigator's Brochure (IB) [GlaxoSmithKline Document Number CM2003/00010/12, 2016 GlaxoSmithKline Document Number CM2003/00010/11, 2016].	An IB update was released on 5-November-2016. This 5-November-2016 IB (version 15) replaces IB version 14 released 3-December-2015 and IB Supplement released 1-August-2016.