Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for Study 200622: A randomised, double-blind, placebo-controlled study to investigate the efficacy and safety of mepolizumab in the treatment of adolescent and adult subjects with severe hypereosinophilic syndrome
Compound Number	:	SB-240563
Effective Date	:	18-JUN-2019

Description:

- The purpose of this RAP is to describe the planned efficacy and safety analyses and output to be included in the Clinical Study Report for Protocol 200622.
- This RAP defines the content of the headline results and SAC deliverables.

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol 200622:

Protocol Revision Chronology:		
2013N171550_00	29-APR-2016	Original

1.1. RAP Amendments

Revision chronology:

RAP Section	Amendment Details
Reporting and Analysis Plan_200622_Final_V1 [12-FEB-2019]	
Reporting and Analysis Plan_200622_Amendment_Final_V1 [18-JUN-2019]	
Section 5.2	• Update to the definition of baseline ECG to include ECG findings
Section 5.4.1.1	• Update to the OCS conversion table to include fluticasone
Section 6.1	• Additional details for the summary of steroid perception questionnaire
Section 7.1.4.1	• Specify an additional sensitivity analysis of the primary estimand excluding subjects from a single site in Mexico.
Section 7.4.4.1	• Update to the sensitivity analysis for missing data for the rate of HES flares endpoint
Section 7.5.4	• Clarification of the implementation of the Wilcoxon rank sum test
Section 7.6.8	• Update to the derivation of MSAS-SF endpoints to include detail of conversion of categorical responses to numeric scores.
Section 14	• New section for exploratory exposure-efficacy response analysis
Section 16.4	• Define treatment phases for HES flare and other efficacy assessments
Section 16.6	• Define derivation of total observed time, time on treatment, time off treatment, missing time (days) • Clarification of QTcB calculation
Section 16.8	• Additional PCI range for Creatine Phosphokinase
Section 16.10	• Updates to relevant display titles in line with changes above • Minor changes to titles of summary tables for AESIs

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To demonstrate the efficacy of mepolizumab compared with placebo based on maintenance of control of HES symptoms during the treatment period.	• Proportion of subjects who experience a HES flare during the 32-week study treatment period
Secondary Objectives	**Secondary Endpoints**
• To demonstrate supportive evidence of the benefit of mepolizumab compared with placebo based on other measures of efficacy.	• Time to first HES flare • Proportion of subjects who experience a HES flare during Week 20 through Week 32 • Rate of HES flares • Change from baseline in fatigue severity based on Brief Fatigue Inventory (BFI) item 3 (worst level of fatigue during past 24 hours) at Week 32
Exploratory Objectives	**Exploratory Endpoints**
• To investigate mepolizumab compared with placebo with respect to additional measures of efficacy.	• Proportion of subjects who have an elevated blood eosinophil level that meets the pre-defined threshold during the 32-week study treatment period[1] • Lung function tests (FEV_1, FVC, and ratio) • Echocardiogram
• To investigate the efficacy of mepolizumab compared with placebo with respect to patient and clinician reported symptoms, health status, and disease impact.	• Change from baseline in HES symptom severity based on HES Daily Symptoms (HES-DS) at Week 32 • Change from baseline in the BFI total score at Week 32[2] • Clinician- and subject-rated overall response to therapy score (RTS) at Week 32[3] • Change from baseline in Subject-rated symptom severity (SSR) at Week 32 • Change from baseline in Modified Memorial Symptom Assessment Scale-Short Form (MSAS-SF) responses at Week 32 • Change from baseline in physical function (Patient Reported Outcome Measurement Information System [PROMIS] physical function items) at Week 32 • Change from baseline in sleep (PROMIS sleep items) at Week 32

Objectives	Endpoints
• To characterize the patient burden of HES.	• SF-36 v2 • Healthcare resource utilization (HCRU) • Work Productivity and Activity Impairment Index – General Health (WPAI-GH) v2 • Steroid perception questionnaire
• To investigate the pharmacokinetics (PK) of mepolizumab.	• Plasma concentration of mepolizumab
• To investigate the pharmacodynamics (PD) of mepolizumab.	• Total IL-5[4] • Blood eosinophil levels
Safety Objectives	**Safety Endpoints**
• To evaluate the safety of mepolizumab compared with placebo in subjects with HES receiving standard of care treatment over a 32-week study treatment period.	• Adverse events including local injection site reactions and systemic reactions (e.g.,hypersensitivity) • Vital signs • 12-lead ECG • Hematological and clinical laboratory tests • Immunogenicity (anti-drug antibody)

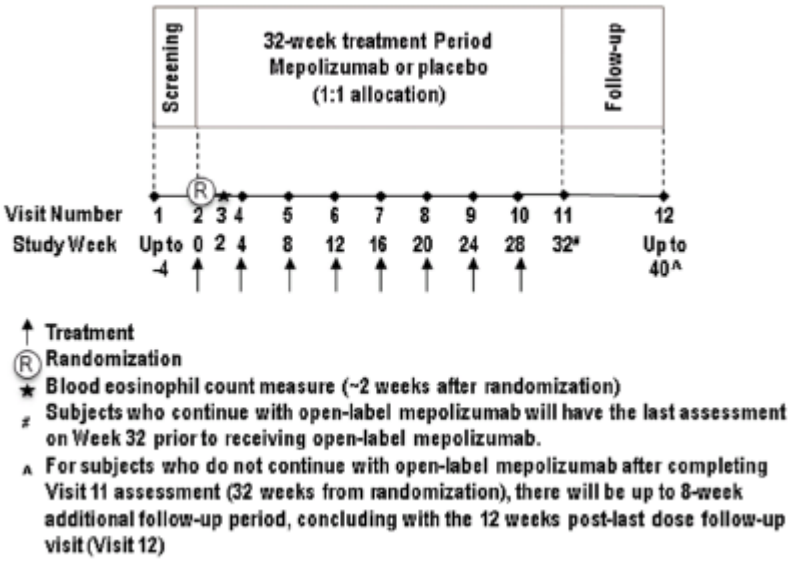
[1]Protocol endpoint was the proportion of subjects who receive blinded active oral corticosteroid (OCS) due to an elevated blood eosinophil level that meets the pre-defined threshold (2 x baseline value or baseline value + 2500 cells/μL) during the 32-week study treatment period. See Section 2.4 for rationale for change.

[2]Protocol endpoint was change from baseline in the BFI total and domain scores at Week 32. See Section 2.4 for rationale for change.

[3]Protocol endpoint was the proportion of subjects with a favourable response as measured by clinician- and subject-rated overall response to therapy score (RTS) at Week 32. See Section 2.4 for rationale for change.

[4]Serum free and total IL-5 were planned in the protocol. See Section 2.4 for rationale for change.

2.2. Study Design

Overview of Study Design and Key Features	
	
Design Features	• 32-week treatment period, randomised, double-blind, placebo-controlled, parallel group, multicentre study of mepolizumab in adolescent and adult subjects with severe HES receiving SoC therapy. • The same regimen of HES therapy will be maintained throughout the 32-week study treatment period unless there is worsening of symptom(s) that requires an increase in therapy. A reduction in dose for safety reasons, with return to the original dosing regimen if possible, is permitted in consultation with the GSK Medical Monitor. • Subjects who withdraw from study treatment prematurely should continue in the study per protocol (including HES flare-related assessments) until 32 weeks from randomization. • Investigators, participating subjects, and GSK study personnel will be blinded to absolute blood eosinophil counts, total white blood cell counts, and white blood count differentials (%) from randomization (Visit 2) until completing the 32-week period from randomization. Blood eosinophil-unblinded GSK personnel/delegates not involved with other aspects of study conduct will monitor the absolute blood eosinophil count results and trigger blinded OCS treatment to treat an eosinophilia when the blood eosinophil count reaches a pre-defined threshold (2 x baseline value or baseline value + 2500 cells/μL). Provided the subject's HES therapy has not been increased due to a symptom flare, the subject will take the blinded active OCS for ~2 weeks. A subject who does not reach the pre-defined blood eosinophilia threshold with a similar blood draw date will be selected to initiate blinded placebo OCS treatment, to maintain study blood eosinophil blinding. Approximately 2 weeks after the scheduled clinic visit, the blood eosinophil count will be assessed again for the subjects who

Overview of Study Design and Key Features	
	started blinded OCS (both active and placebo). The subject who has taken active blinded OCS will be instructed to continue with a new course of blinded OCS until the next scheduled clinic visit if the blood eosinophil count is at or above the threshold unless the subject's HES therapy has been increased due to a symptom flare since the initiation of the current course of blinded OCS, and discontinue if the blood eosinophil count is below the threshold. For subjects taking placebo-blinded OCS, continuation/discontinuation of blinded OCS will be determined depending on the continuation/discontinuation of their matched subject on active-blinded OCS. • An open-label study is also planned (study 205203) for subjects who complete study 200622.
Main subject entry criteria	• Subjects ≥12 years with HES • At least 2 HES flares within the past 12 months; at least one HES flare within the past 12 months must not be related to a decrease in HES therapy during the 4 weeks prior to the flare. • Blood eosinophil count ≥ 1000 cells/μL during screening. Investigators were permitted to use local laboratory results to meet this inclusion criteria.
Dosing	• 300 mg mepolizumab or placebo SC every 4 weeks (8 administrations) while continuing their HES therapy. • The final dose of study treatment will be administered at Visit 10 (Week 28) with completion of the study treatment period achieved at the next 4-weekly visit.
Treatment Assignment	• Subjects will be randomised in a 1:1 ratio to receive either mepolizumab or placebo in addition to SoC therapy. • An initial sample size of N=80 subjects will be randomised. The proportion of subjects that have a HES flare will be monitored, blinded to treatment, and the total number of subjects randomised may be increased up to a maximum of 120 subjects if the blinded overall flare rate is predicted to be <30%. The blinded overall proportion of subjects who have a HES flare will be calculated based on the HES flare data available in the CRF. This will include all HES flares meeting flare endpoint definition 'a)' in Section 7.1.1. In order to maintain the blood eosinophil blinding, HES flares meeting flare end point definition 'b)' in Section 7.1.1 will not be included in the calculation of the blinded overall proportion. • Treatments will be assigned randomly via an interactive response system (IRS). • Randomization schedule will be generated using GSK validated randomisation software RandAll NG. • Randomization stratified by region.
Time and events	• See Appendix 2: Schedule of Activities.
Interim	• An external Independent Data Monitoring Committee (IDMC) will

Overview of Study Design and Key Features	
Analysis	periodically review unblinded safety data from the study, in accordance with the IDMC Charter. The safety data analyses for the IDMC reviews will be performed by an independent statistical analysis data centre (SDAC). There are no circumstances under which IDMC review of the data would lead to a recommendation to stop for efficacy. Therefore, no adjustment to the final alpha level for efficacy will be made based on the safety stopping guidelines.

2.3. Statistical Hypotheses / Statistical Analyses

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

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

- **Alternative hypothesis**: the proportion of subjects who experience a HES flare during the 32-week study treatment period is smaller for mepolizumab compared to placebo.

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

2.4. Changes to the Protocol Defined Statistical Analysis Plan

- The following changes to the exploratory endpoints were made in this RAP:

Protocol Endpoint	RAP Endpoint	Rationale for Change
Proportion of subjects who receive blinded active OCS due to an elevated blood eosinophil level that meets the pre-defined threshold during the 32-week study treatment period	Proportion of subjects who have an elevated blood eosinophil level that meets the pre-defined threshold during the 32-week study treatment period	RAP endpoint considered to be more clinically meaningful as it includes all subjects with blood eosinophil counts meeting the pre-defined threshold during the 32-week study treatment period rather than including only the subset of these subjects who receive blinded active OCS. Subjects did not receive blinded active OCS if their physician had already increased their HES therapy based on symptoms.
Change from baseline in the BFI total and domain scores at Week 32	Change from baseline in the BFI total score at Week 32.	The BFI is a single construct and therefore domain scores are not applicable.
Proportion of subjects with a favourable response as measured by clinician- and subject-	Clinician- and subject-rated overall response to therapy score (RTS) at Week 32	Improvement/worsening is measured on a 7-point scale from significant worsening to significant improvement. The endpoint will be summarised and analysed as a 7-point ordinal endpoint to avoid loss of information and increase the sensitivity of the analysis.

Protocol Endpoint	RAP Endpoint	Rationale for Change
rated overall response to therapy score (RTS) at Week 32		
Serum free and total IL-5	Total IL-5	Free IL-5 levels are generally very low in serum (<BLQ) and are expected to decrease post dosing because most of the free IL-5 becomes complexed with mepolizumab. Hence only total IL-5 will be measured.

- Since some participants were randomised early in error prior to the first dose of mepolizumab, the following changes to the secondary endpoint derivations in the protocol are planned:
  - Time to first HES flare will be calculated from the date of first dose of study treatment and the onset date of the HES flare, rather than the date of randomisation and the onset date of the HES flare.
  - The rate of HES flares will be calculated using the date of the first dose of study treatment and the Week 32 visit/study withdrawal date, rather than the randomisation date and the Week 32 visit/study withdrawal date.
  - For the calculation of the change from baseline in BFI item 3, the mean of the 7 daily assessments of BFI item 3 up to but not including the date of first dose of study treatment will be used as the baseline assessment. Since BFI item 3 is measured daily after 6pm, the date of dosing will not be included in the calculation of the baseline BFI.

3. PLANNED ANALYSES

3.1. Interim Analyses

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

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.
3. A review has taken place by the unblinded global study manager to identify any subjects with a discrepancy between randomised treatment and actual treatment received. This information will be included in the SDTM dataset at DBF. Actual treatment arm will be derived within the ADaM datasets based on the treatment received for more than 50% of treatment administrations. If a subject received an equal number of both treatments then the actual treatment arm will reflect the treatment to which they were randomised.
4. All criteria for unblinding the randomisation codes have been met, and treatment allocations have been unblinded via the RandAll NG system, as described in SOP_54840.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility i.e. for whom record exists in the database.	• Study Population (Pre-screen and screen failures)
Enrolled	• All participants who were successfully screened and entered the study. • Note: screening failures (who never passed screening even if rescreened) and participants who were successfully screened but did not complete any visit 2 assessments are excluded.	• Study Population (EudraCT required displays)
Intent-To-Treat (ITT)	• All randomised subjects • This population will be based on the treatment to which the subject was randomised. • Any subject who receives a treatment randomisation number will be considered to have been randomised.	• Study Population • Efficacy • Listing of Planned and Actual Treatments
Per-Protocol (PP)	• Comprise all subjects in the ITT population not identified as full protocol deviators with respect to criteria that are considered to impact the primary efficacy analysis. • The decision to exclude a subject from the PP population or exclude part of their data from the PP population will be made prior to breaking the blind. • Protocol deviations that would exclude subjects from the PP population are defined in Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population.	• Supplementary analysis of primary endpoint
Safety	• All subjects who are randomised and who receive at least one dose of study treatment. Randomised subjects will be assumed to have received study treatment unless definitive evidence to the contrary exists. • This population will be based on the treatment the subject actually received. • Subjects will be analysed according to treatment received for more than 50% of their treatment administrations. If a subject received an equal number of both treatments then they will be assigned to the treatment to which they were randomised.	• Study Population • Safety
Pharmacokinetic	• All subjects in the ITT population who received	• PK

Population	Definition / Criteria	Analyses Evaluated
	at least one dose of study treatment and for whom at least one PK sample was obtained, analysed and was measurable.	
Pharmacodynamic	• All subjects in the ITT population who received at least one dose of study treatment and who also had a baseline PD measurement and at least one post-treatment PD measurement.	• PD

Refer to Appendix 10: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (PDMP).
- Data will be reviewed prior to Source Data Lock (SDL) to ensure all important deviations and deviations which lead to exclusion from the Per Protocol analysis population are agreed prior to unblinding. Important deviations will be categorised in the SDTM data set. Deviations leading to exclusion from the Per Protocol population will be categorised in the ADaM data set.
- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.
- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.
- Important protocol deviations which result in exclusion from the Per Protocol population will be summarised and listed (see Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
A	Mepolizumab 300mg SC	Mepolizumab 300mg SC	2
P	Placebo	Placebo	1

NOTES:

1. Order represents treatments being presented in Tables, Figures and Listings (TFLs), as appropriate.

5.2. Baseline Definitions

- Baseline will be defined for all subjects in the ITT population.
- For the BFI item 3 which is collected daily from the screening visit (Visit 1) the mean of the 7 daily assessments of BFI item 3 up to but not including the date of first dose of study treatment will be used as the baseline assessment.
- For blood eosinophils, baseline will be defined as the latest central laboratory result prior to the first dose of study treatment. Investigators were permitted to use local laboratory results to meet inclusion criteria, however local laboratory results will not be used in the derivation of the baseline blood eosinophil value.
- For all other endpoints the baseline values for each assessment will be the latest available assessment (including unscheduled visits) prior to first dose of study treatment. For ECG, if multiple assessments are recorded on the same day, the mean of the multiple assessments will be assigned as the baseline value, and the latest ECG interpretation prior to the first dose of study medication will be used as the baseline ECG finding.

5.3. Multicentre Studies

- In this multicentre global study, enrolment will be presented by investigative site and country.
- The randomisation for this study is stratified by region, defined below, with consideration for standard of care medical practice.
  - USA
  - Argentina, Mexico and Brazil
  - Rest of World
- The same definition of region will be used for covariate adjustment in the statistical analysis.
- If there are insufficient subjects in each region for the planned statistical analysis, further combining of regions will be considered.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

- Region and baseline OCS dose, expressed as prednisone equivalent dose, will be covariates in all statistical analysis. These covariates will be included as stratification variables for the Cochran-Mantel-Haenszel test and Wilcoxon Rank Sum test according to the table below. For parametric analysis models, region will be included as a fixed categorical effect and baseline OCS dose will be included as a fixed continuous effect.

Category	Covariates and / or Subgroups
Region	See Section 5.3. • USA • Argentina, Mexico and Brazil • Rest of World
Baseline oral prednisone equivalent dose[1]	See Section 5.4.1.1 • 0-≤20mg prednisone or equivalent • >20mg prednisone or equivalent

[1]For parametric analysis models, baseline OCS dose will be included as a fixed continuous effect.

- If the percentage of subjects is small within a region, then the region categories may be refined prior to unblinding the trial.
- For analyses where a baseline value of the analysis variable is available this will also be included in the statistical analysis. These covariates will be included as stratification variables for the Cochran-Mantel-Haenszel test and Wilcoxon Rank Sum test, and as continuous fixed effects for all parametric analysis models.

5.4.1.1. Derivation of Baseline Oral Prednisone Equivalent Daily Dose

- For each subject, a baseline oral prednisone equivalent daily dose (mg) will be derived prior to unblinding the randomisation codes for the study. Baseline oral prednisone equivalent dose will be identified from the concomitant medications page according to the following criteria:
    - Start date < Date of first dose of study treatment
    - Either "ongoing" or end date ≥ Date of first dose of study treatment
    - Route = "PO"
- Partial start and end dates will be handled as described in Section 16.7.2.1.
- Corticosteroids will be identified from the list of coded concomitant medications for the study, by merging with the GSK respiratory medication class (RMC) reference data set by component code. This reference data is created by dictionary specialists who identify a list of component terms for corticosteroids, which then undergo clinical review to ensure the correct classification is assigned.
- Subjects not receiving OCS therapy, i.e. subjects receiving cytotoxic and/or immunosuppressive HES therapy only at baseline, or subjects not receiving any HES

therapy, will be assigned a prednisone equivalent daily dose of 0 mg and will be categorised in the 0-≤20mg prednisone or equivalent group.

- The corticosteroid conversion factors in the table below will be used to scale each corticosteroid dose to a prednisone equivalent dose.

Medication Name	Scaling Factor
Betamethasone	8.33
Budesonide[1]	0
Cortisone	0.2
Dexamethasone	6.67
Deflazacort	0.83
Fluticasone[1]	0
Hydrocortisone	0.25
Methylprednisone	1.25
Meprednisone	1.25
Prednisone	1
Prednisolone	1
Prednisone acetate	1
Triamcinolone	1.25

[1]Budesonide and fluticasone have negligible systemic exposure and will be classed as "Other HES therapy" rather than oral corticosteroid therapy.

- Where the frequency of the recorded corticosteroid dose is not once daily, the following calculations will be used to determine the daily dose.

Medication Frequency	Daily Dose Equivalent
BID	2 x dose
TID	3 x dose
QID	4 x dose
QOD	dose / 2
2XWK	(2 x dose) / 7
3XWK	(3 x dose) / 7
4XWK	(4 x dose) / 7
5XWK	(5 x dose) / 7

5.4.2. Examination of Subgroups

- The subgroups in the table below are of interest in this study. A separate exploratory analysis of the primary endpoint within each subgroup will be carried out.

- Subgroup categories may be further collapsed if there are a small number of subjects in a treatment arm within a subgroup leading to model convergence issues.

- There is a biological rationale for potentially observing increased efficacy with increasing levels of baseline blood eosinophils. The role of blood eosinophil counts at baseline on the effectiveness of mepolizumab with respect to the primary endpoint will be further assessed based on a statistical model including baseline ($\log_e$) blood eosinophil count as a continuous variable and an interaction with treatment term. Baseline blood eosinophil count is defined in Section 5.2. The analysis will also be adjusted for region and baseline OCS dose, as described in Section 5.4.1. Fractional polynomial models for the baseline blood eosinophil count may also be explored in order to find the best fitting model for the relationship.

- Differential treatment effects are not expected for any of the other subgroups listed below and therefore any differences in efficacy for mepolizumab compared to placebo observed in categories of these subgroups will be viewed as exploratory.

Subgroup	Categories
Age	• 12-<18 years • 18-64 years • ≥65 years
Sex	• Male • Female
Race	• Black or African American • White • Asian • Other
Region	• USA • Argentina, Mexico and Brazil • Rest of World
Baseline OCS	• 0-≤20mg prednisone or equivalent • >20mg prednisone or equivalent
Baseline blood eosinophils	• Quartiles, rounded to 1 decimal place (GI/L); equivalent to rounding to the nearest 100 cells/μL

5.5. Multiple Comparisons and Multiplicity

When strong control of type I error is required for making inferences for the predefined secondary endpoints, multiplicity will be controlled using a hierarchical, closed testing procedure, according to the following hierarchy of endpoints:

1. Proportion of subjects who experience a HES flare during the 32-week study treatment period (primary endpoint)

2. Time to first HES flare

3. Proportion of subjects who experience a HES flare during Week 20 through Week 32

4. Rate of HES flares

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

When strong control of type I error is required, statistical significance for an endpoint in the predefined hierarchy will be dependent on statistical significance for the previous endpoints in the hierarchy.

P-values for secondary endpoints will be provided both unadjusted and adjusted for multiplicity using the hierarchy of endpoints above.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
16.3	Appendix 3: Assessment Windows
16.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
16.5	Appendix 5: Data Display Standards & Handling Conventions
16.6	Appendix 6: Derived and Transformed Data
16.7	Appendix 7: Reporting Standards for Missing Data
16.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the ITT population, unless otherwise specified. If the ITT population and the safety populations differ, study population analyses will also be produced for the safety population.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, exposure and treatment compliance (assessed by number of administrations of study treatment) will be based on GSK Core Data Standards. In addition, summaries of baseline HES therapy, most bothersome HES symptoms and steroid perception questionnaire will be produced; for the summary of the steroid perception questionnaire, only subjects completing the questionnaire who have a baseline oral steroid reported on their concomitant medication form will be summarised.

Details of the planned displays are presented in Appendix 10: List of Data Displays.

7. EFFICACY ANALYSES

The target population for the primary estimand is as defined by the study inclusion/exclusion criteria and therefore the ITT population will be the primary population for all efficacy analyses.

7.1. Primary Efficacy Analyses

7.1.1. Endpoint / Variables

The primary endpoint is the proportion of subjects who experience a HES flare during the 32-week study treatment period.

A HES flare is defined as either:

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

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

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

or

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

HES flares meeting definition a) will be captured on the 'flare details' page in the eCRF.

An increase in blood eosinophils above the pre-defined threshold level (2 x baseline value or baseline value + 2500 cells/μL) without any other clinical manifestations during the study will lead to administration of blinded active OCS treatment (see Section 2.2). If a subject receives a second course of blinded active OCS during the 32-week treatment period, the subject will be considered to be experiencing a flare. The container list for the blinded OCS treatment (indicating which container numbers contained active OCS and which contained placebo OCS) will be used to define HES flares meeting endpoint definition b).

7.1.2. Summary Measure

The difference between mepolizumab and placebo in the proportion of subjects with HES flare during the 32-week study treatment period.

7.1.3. Strategy for Intercurrent (Post-Randomization) Events

7.1.3.1. Primary Estimand

The primary treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications.

The study is designed to continue to collect data on HES flares for subjects who prematurely discontinue from their randomised study treatment. All data on HES flares collected for these subjects will be included in the primary analysis. Subjects who withdraw from the study prior to Week 32 (Visit 11) and therefore have missing data on HES flares will be included in the primary analysis as treatment failures, i.e. for the primary comparison, a subject will be classed as not experiencing a HES flare only if they have no flares reported and complete Week 32 (Visit 11).

Sensitivity analyses will be performed on the ITT population to examine the potential impact of the missing data:

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

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

7.1.3.2. Supplementary Estimand

A supplementary estimand using the 'while on treatment' strategy will be assessed for the intercurrent event of discontinuation of study medication.

Subjects discontinuing from study treatment prematurely will be included as having a HES flare if a flare is recorded with an onset date equal or prior to 28 days after the last dose of study treatment, and not having a flare otherwise.

7.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

A summary of the number and percentage of subjects with HES flares will be produced by treatment group. The total number of HES flares in each treatment group will also be presented. The summary will include all HES flares, as well as a separate breakdown of HES flares meeting definition a) and b) (see Section 7.1.1). A plot of the cumulative number of HES flares over time in each treatment group will be produced.

7.1.4.1. Statistical Methodology Specification

Primary Statistical Analyses
Endpoint
• Proportion of subjects who experience a HES flare during the 32-week study treatment period.
Model Specification
• Cochran-Mantel-Haenszel test stratified by baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region. • Supplemented by a logistic regression analysis adjusting for covariates of baseline OCS dose (continuous scale), region, and treatment.
Model Checking & Diagnostics
• To examine the fit of the logistic regression model, deviance residuals will be calculated and plotted.
Model Results Presentation

• Number of subjects analysed in each treatment group.
• Number of subjects with ≥1 HES flare or who withdraw from the study prior to Week 32 (Visit 11).
  • Number of subjects with ≥1 HES flare.
  • Number of subjects with no HES flare who withdraw from the study prior to Week 32 (Visit 11).
• Number of subjects with no HES flare who complete Week 32 (Visit 11).
• p-value from Cochran-Mantel-Haenszel test.
• Odds ratio and 95% Confidence Interval (CI) from logistic regression model.
• p-value from logistic regression model.

Subgroup Analyses
• A logistic regression analysis will be fitted separately within each subgroup of interest defined in Section 5.4.2. • Odds ratios and 95% confidence intervals from the logistic regression model will be presented. Analysis will be descriptive only; no p-values will be presented for the subgroup analyses. If the number of subjects in each subgroup category are small, confidence intervals may also be omitted.
Sensitivity and Supportive Statistical Analyses
• A supplementary estimand using the 'while on treatment' strategy for intercurrent events will be assessed. • The primary analysis will be repeated using the PP population. • Sensitivity analyses for the primary estimand to assess the impact of missing data will be performed using the ITT population as follows: • Subjects withdrawing from the study prematurely prior to reporting a HES flare, with the primary reason for treatment withdrawal reported as AE or Lack of Efficacy, will be classed as experiencing a HES flare. Subjects withdrawing from the study prematurely with any other reason for treatment withdrawal will be included as having a flare if one is recorded

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prior to study withdrawal, and as not having a flare if no flare is recorded prior to study withdrawal. • Subjects withdrawing from the study prematurely will be included as having a flare if one is recorded prior to study withdrawal, and as not having a flare if no flare is recorded prior to study withdrawal. • The sensitivity of the results of the primary estimand to inclusion of subjects from site PPD in Mexico will be investigated. An Investigation of this site was conducted by GSK following anomalies in pulmonary function test (PFT) data generated by this site for a GSK study with a different investigational product (Study 207597). The report concluded that "there was diminished confidence and trust in the integrity of the data generated at this site and this loss of trust extended to other aspects of study conduct at this site". Therefore, a sensitivity analysis of the primary estimand excluding the two subjects from site PPD will be performed.

7.1.5. Exploratory Modelling of Primary Endpoint

The role of baseline blood eosinophil counts on the effectiveness of mepolizumab with respect to the proportion of subjects who experience a HES flare during the 32-week study treatment period will be investigated. A logistic regression model will be fitted, including baseline blood eosinophils fitted on the $\log_e$ scale as a continuous covariate as well as a treatment-by-baseline blood eosinophils interaction term, in order to predict the odds ratio for mepolizumab vs placebo for each level of the baseline blood eosinophil count. The analysis will also be adjusted for region and baseline OCS dose, as described in Section 5.4.1. Fractional polynomial models may also be explored in order to find the best fitting model for the relationship.

7.2. Secondary Efficacy Analysis – Time to First HES Flare

7.2.1. Endpoint / Variables

The time to first HES flare will be calculated from the date of first dose of study treatment and the onset date of the first HES flare as defined in Section 16.6.4.

7.2.2. Summary Measure

The difference between mepolizumab and placebo in the time to first HES flare.

7.2.3. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. If a subject withdraws prematurely from the study prior to experiencing a HES flare, the event time will be censored at the time point at which the subject withdrew from the study. Sensitivity analyses will be performed to examine the potential impact of the missing data.

7.2.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Time to first HES flare will be graphically represented using a Kaplan-Meier plot of cumulative incidence rates over time for each treatment group.

7.2.4.1. Statistical Methodology Specification

Endpoint
• Time to first HES flare.
Model Specification
• Log-rank test stratified by baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region. • Supplemented by a Cox proportional hazards regression model allowing for covariates of baseline OCS dose (continuous scale) and region.
Model Checking & Diagnostics
• To examine the fit of the Cox proportional hazards model, martingale and deviance residuals will be calculated and plotted.
Model Results Presentation

• In each treatment group
  • Number of subject analysed.
  • Number of subjects with HES flare.

- Number of subjects censored at study withdrawal.
- Number of subjects censored at study completion.

- Stratified Log-Rank test p-value for association between treatment and time to first HES flare.
- Hazard ratio and 95% CI from Cox proportional hazards model.
- Wald chi-square p-value from Cox proportional hazards model.

Subgroup Analyses

- No subgroup analyses will be performed on this endpoint.

Sensitivity and Supportive Analyses

- Sensitivity analyses to assess the impact of missing data will be performed using the ITT population as follows:
  - Subjects withdrawing from the study prematurely prior to reporting a HES flare will be included with a HES flare on the date of study withdrawal.
  - Subjects withdrawing from the study prematurely prior to reporting a HES flare, with primary reason for treatment withdrawal reported as Adverse Event or Lack of Efficacy will be included as a HES flare on the date of study withdrawal. For subjects withdrawing from the study prematurely prior to reporting a HES flare, with any other reason for discontinuation of study treatment, the event time will be censored at the date of study withdrawal.

7.3. Secondary Efficacy Analysis – Proportion of Subject Who Experience a HES Flare During Week 20 Through Week 32

7.3.1. Endpoint / Variables

HES flare during Week 20 through Week 32 will be defined as a HES flare starting or ongoing on or after the date of the Week 20 visit up to and including the date of the Week 32 visit.

7.3.2. Summary Measure

The difference between mepolizumab and placebo in the proportion of subjects with HES flare during Week 20 through Week 32.

7.3.3. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. Subjects who withdraw prematurely from the study prior to Week 32 (Visit 11) and therefore have missing data on HES flares during Week 20 through Week 32 will be included in the analysis as treatment failures i.e., that they experience a flare during Week 20 through Week 32. Sensitivity analyses will be performed to examine the potential impact of the missing data.

7.3.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

A summary of HES flares during Week 20 through Week 32 will be produced as for the primary endpoint (see Section 7.1.4).

7.3.4.1. Statistical Methodology Specification

Endpoint
• Proportion of subjects who experience a HES flare during Week 20 through Week 32.
Model Specification
• Cochran-Mantel-Haenszel test stratified by baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region. • Supplemented by a logistic regression analysis adjusting for covariates of baseline OCS dose (continuous scale), region, and treatment.
Model Checking & Diagnostics
• To examine the fit of the logistic regression model, deviance residuals will be calculated and plotted.
Model Results Presentation
• Number of subjects analysed in each treatment group. • Number of subjects with ≥1 HES flare during Week 20 through Week 32 in each treatment group. • Test statistic and p-value for association between treatment and flare from Cochran-Mantel-Haenszel test. • Odds ratio and 95% CI from logistic regression model. • p-value from logistic regression model.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses

• Sensitivity analyses to assess the impact of missing data will be performed using the ITT population as follows:
  • Subjects withdrawing from the study prematurely prior to reporting a HES flare during Week 20 through Week 32, with the primary reason for treatment withdrawal reported as AE or Lack of Efficacy, will be classed as experiencing a HES flare during Week 20 through Week 32. Subjects withdrawing from the study prematurely with any other reason for treatment withdrawal will be included as having a flare if one is recorded during Week 20 through Week 32 prior to study withdrawal, and as not having a flare if no flare during Week 20 through Week 32 is recorded prior to study withdrawal.
  • Subjects withdrawing from the study prematurely will be included as having a flare if one is recorded during Week 20 through Week 32 prior to study withdrawal, and as not having a flare if no flare during Week 20 through Week 32 is recorded prior to study withdrawal.

7.4. Secondary Efficacy Analysis – Rate of HES Flares

7.4.1. Endpoint / Variables

The rate of HES flares will be calculated for each subject as the number of observed HES flares divided by the time (expressed in years) between the first dose of study treatment and either the Week 32 visit date if available, or otherwise the study withdrawal date (see Section 16.6.4).

The number of observed HES flares will be calculated for each subject as the number of unique starting dates for HES flares. To be considered as a separate episode of HES flare, the onset date of a HES flare must be at least 14 days apart from the resolution date of the preceding HES flare.

For flares meeting endpoint definition b) described in Section 7.1.1, each subsequent course of blinded active OCS beyond 14 days from the resolution date of the preceding flare will be considered as an additional flare (e.g., 3 courses of blinded active OCS are considered as 2 flares, 4 courses of blinded active OCS are considered as 3 flares, etc.).

See Section 16.6.4 for details of the definition of the onset and resolution date of HES flares and full details of the derivation of the rate of HES flares.

7.4.2. Summary Measure

The difference between mepolizumab and placebo in the rate/year of HES flares.

7.4.3. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the ‘treatment policy’ effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. For subjects withdrawing prematurely from the study during the 32-week treatment period, all data up to the time of study withdrawal will be used to calculate the rate of HES flares. Sensitivity analyses will be performed to examine the potential impact of the missing data.

7.4.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

7.4.4.1. Statistical Methodology Specification

Endpoint
• Rate of HES flares.
Model Specification
• Wilcoxon Rank Sum test stratified by baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region. • Supplemented by an analysis using a negative binomial generalised linear model with a log-link function, including terms for baseline OCS dose (continuous scale), region and treatment, and including the log of the observed time as an offset variable. The model estimated mean flare rate per year will be weighted according to the observed proportion of the categorical covariates in the study data by inclusion of the OM (obsmargins) option in the LSMEANS statement of the GENMOD procedure. Missing data will be assumed to be missing at random (MAR) in this analysis.
Model Checking & Diagnostics
• The fit of the negative binomial generalised linear model will be investigated by calculating and plotting standardised deviance residuals.
Model Results Presentation

• In each treatment group:
  • Median rate/year.
  ○ Median rate/year for HES flares meeting definition a) (see Section 7.1.1).
  ○ Median rate/year for HES flares meeting definition b) (see Section 7.1.1).
  • Adjusted mean rate/year from negative binomial model.
• p-value for difference between treatments in rate/year from Wilcoxon Rank Sum test.
• Rate ratio and 95% CI from negative binomial model.
• p-value from negative binomial model.

Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses
• In order to assess the impact of missing data, a sensitivity analysis using a negative binomial generalized linear model will be performed using the ITT population. Missing data for subjects withdrawing from the study prematurely will be imputed for the period between withdrawal from the study and Week 32. For subjects in the mepolizumab treatment group, the missing time period will be imputed assuming that the subject's expected flare rate is shifted to that of the placebo arm (Jump to Reference [J2R]) [Keene, 2014] . For subjects in the placebo group, missing data will be assumed MAR.

7.5. Secondary Efficacy Analysis – Change from Baseline in Fatigue Severity BFI Item 3 (Worst Level of Fatigue in Past 24 Hours) at Week 32

7.5.1. Endpoint / Variables

The BFI has 9 items. The subject rates their fatigue level right now, their usual fatigue level over the last 24 hours and their worst level of fatigue over the last 24 hours using an 11-point rating scale anchored at 0 (no fatigue) and 10 (as bad as you can imagine). The subject also rates how, during the past 24 hours, fatigue has influenced each of the following on an 11-point rating scale anchored at 0 (does not interfere) and 10 (completely interferes): general activity, mood, walking ability, normal work, relations with other people and enjoyment of life. The subject completes item 3 (worst level of fatigue during past 24 hours) of the BFI daily and the full BFI every 7 days at home on the eDiary.

The change from baseline in fatigue severity (worst level of fatigue during past 24 hours) at Week 32 will be calculated using the mean of the 7 daily assessments of BFI item 3 up to and including the date of the Week 32 visit as the Week 32 assessment, and the mean of the 7 daily assessments of BFI item 3 up to but not including the date of first dose of study treatment as the baseline assessment. If any of the 7 daily assessments of BFI item 3 are missing for either the Week 32 time point or the baseline time point, the mean of the available daily assessments over the 7-day period will be used to calculate the change from baseline.

7.5.2. Summary Measure

The difference between mepolizumab and placebo in the change from baseline BFI item 3 at Week 32.

7.5.3. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the ‘treatment policy’ effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. Subjects with missing change from baseline BFI item 3 at Week 32 will be included in the analysis with the largest (i.e. worst) value observed for any subject. Sensitivity analyses to assess the impact of missing data will be performed.

7.5.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Summary statistics for BFI item 3 at each week of treatment will be presented, including change from baseline values. Assessment windows for each week are defined in Section 16.3.1.

The clinical relevance of changes in BFI item 3 at Week 32 will be assessed using a cumulative distribution plot showing the percentage of subjects in each treatment group with a reduction in BFI item 3 greater than equal to each value in the observed range; this will allow assessment of the treatment difference against a range of clinically important differences.

Endpoint
• Change from baseline in fatigue severity (BFI item 3) at Week 32.
Model Specification
• Wilcoxon Rank Sum test stratified by baseline fatigue severity ("severe" defined as BFI item 3 ≥7, and "not severe" defined as BFI item 3<7), baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region. This will be implemented using the FREQ procedure with the SCORES = MODRIDIT option.
Model Checking & Diagnostics
• Not applicable.
Model Results Presentation
• Number analysed in each treatment group. • Median change from baseline BFI item 3 at Week 32 in each treatment group. • p-value for difference between treatments from Wilcoxon Rank Sum test.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses

• Repeated measures analysis including assessments at Week 4, 8, 12, 16, 20, 24, 28 and 32. In this analysis missing data will be assumed to be missing at random and will not be imputed with the largest i.e. worst value. A mixed effects model will be fitted with the following specification:
  • Time point, treatment and region included as fixed categorical effects.
  • Baseline BFI and baseline OCS dose included as continuous fixed covariates.
  • Interaction terms for baseline-by-timepoint and treatment-by-time point interaction.
  • The Kenward and Roger method (DDFM = KR) for approximating the denominator degrees of freedom to correct for bias in the estimated variance-covariance matrix.
  • REPEATED statement with TYPE=UN to specify an unstructured covariance structure for the R matrix.
  • The OBSMARGIN option on the LSMEANS statement in order to compute the adjusted geometric means with weights proportional to the input data set.

7.6. Exploratory Efficacy Analyses

Details of the planned displays for the exploratory endpoints are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

7.6.1. Proportion of Subjects Who Have an Elevated Blood Eosinophil Level That Meets the Pre-Defined Threshold During the 32-Week Study Treatment Period.

7.6.1.1. Endpoint / Variables

Subjects who have an elevated blood eosinophil level (2 x baseline value or baseline value + 2500 cells/μL) during the 32-week study treatment period will be identified from the central laboratory haematology results. Samples taken from the date of first dose of study medication up until the date of Visit 11 (Week 32) will be considered in the derivation. Baseline will be defined as in Section 5.2.

7.6.1.2. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. Subjects withdrawing from the study prematurely leading to missing blood assessments for blood eosinophil count will be included in the analysis as having an elevated blood eosinophil level that meets the pre-defined threshold.

7.6.1.3. Statistical Analyses / Methods

Endpoint
• Proportion of subjects who have an elevated blood eosinophil level during the 32-week study treatment period.
Model Specification
• Cochran-Mantel-Haenszel test stratified by baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region. • A supplementary analysis using a logistic regression analysis adjusting for covariates of baseline OCS dose (continuous scale), region, and treatment will also be performed.
Model Results Presentation
• Number of subjects analysed in each treatment group. • Number of subjects who have an elevated blood eosinophil level during the 32-week study treatment period. • Test statistic and p-value for association between treatment and endpoint from Cochran-Mantel-Haenszel test. • Odds ratio and 95% CI from logistic regression model. • p-value from logistic regression model.

Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses
• No sensitivity/supportive analyses will be performed on this endpoint.

7.6.2. FEV_1, FVC and FEV_1/FVC ratio

7.6.2.1. Endpoint / Variables

- Change from baseline FEV_1 at each visit.
- Change from baseline FVC at each visit.
- FEV_1/FVC at each visit.

7.6.2.2. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. Subjects with missing data will be assumed to be missing at random in the analysis.

7.6.2.3. Statistical Analyses / Methods

Summary statistics for FEV_1, FVC and FEV_1/FVC at each visit will presented by treatment, including change from baseline values. A separate summary and analysis excluding any data from timepoints where the subject did not withhold short-acting bronchodilators for 6 hours or long-acting bronchodilators for 12 hours will be produced. No statistical analysis will be performed on FEV_1/FVC.

Endpoint
• Change from baseline in FEV_1. • Change from baseline in FVC.
Model Specification

• Repeated measures with missing data assumed to be missing at random. A mixed effects model will be fitted with the following specification:
  ◦ Visit, treatment and region included as fixed categorical effects.
  ◦ Baseline FEV_1 (or FVC as appropriate) and baseline OCS dose included as continuous fixed covariates.
  ◦ Interaction terms for baseline-by-visit and treatment-by-visit.
  ◦ The Kenward and Roger method (DDFM = KR) for approximating the denominator degrees of freedom to correct for bias in the estimated variance-covariance matrix.
  ◦ REPEATED statement with TYPE=UN to specify an unstructured covariance structure for the R matrix.

• The OBSMARGIN option on the LSMEANS statement in order to compute the adjusted geometric means with weights proportional to the input data set.
Model Results Presentation
• Number analysed in each treatment group. • LS Mean (SE) and LS Mean Change from baseline (SE) in each treatment group. • Mean difference, 95% CI and p-value for mepolizumab vs placebo.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses
• The analysis will be repeated excluding any data from timepoints where the subject did not withhold short-acting bronchodilators for 6 hours or long-acting bronchodilators for 12 hours.

7.6.3. Echocardiogram

Echocardiogram/MUGA scans at Screening and Week 32 will be summarised by treatment for the ITT population. No statistical analysis of this endpoint will be performed.

7.6.4. Change From Baseline in HES Symptom Severity Based on HES Daily Symptoms (HES-DS) at Week 32

7.6.4.1. Endpoint / Variables

For each of the 6 symptom domains (muscle/joint pain, chills or sweats, abdominal pain or bloating, breathing symptoms, nasal or sinus symptoms and skin symptoms), the change from baseline symptom score at Week 32 will be defined using the mean of the 7 daily symptom scores up to and including the date of the Week 32 visit as the Week 32 assessment, and the mean of the 7 daily symptom scores up to but not including the date of first dose of study treatment as the baseline assessment. For each symptom domain, if any of the 7 daily symptom scores are missing for either the Week 32 time point or the baseline time point, the mean of the available daily symptom scores for the relevant symptom domain over the 7-day period will be used to calculate the change from baseline.

The change from baseline most bothersome symptom score at Week 32 will be derived using the mean domain scores at Week 32 and baseline for the up to 3 symptom domains identified by the subject as most bothersome at Week 0 (Visit 2).

7.6.4.2. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. Subjects with missing change from baseline symptom score or missing most bothersome symptom score at Week 32 will be included in the analysis with the largest (i.e. worst) value observed for any subject.

7.6.4.3. Statistical Analyses / Methods

Summary statistics for the most bothersome symptom score and the symptom score for each symptom domain at each week of treatment will be presented, including change from baseline values. Assessment windows for each week are defined in Section 16.3.1.

Endpoint
• Change from baseline in most bothersome HES symptom severity score (HES-DS) at Week 32. • Change from baseline in HES symptom severity score (HES-DS) for each symptom at Week 32.
Model Specification
• Wilcoxon Rank Sum test stratified by median baseline symptom severity (baseline symptom severity≤median and baseline symptom severity>median), baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region.
Model Results Presentation
• Number analysed in each treatment group. • Median change from baseline at Week 32 in each treatment group. • p-value for difference between treatments from Wilcoxon Rank Sum test.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses

• Repeated measures analysis including assessments at Week 4, 8, 12, 16, 20, 24, 28 and 32. In this analysis missing data will be assumed to be missing at random and will not be imputed with the largest i.e. worst value. A mixed effects model will be fitted with the following specification:
  • Time point, treatment and region included as fixed categorical effects.
  • Baseline symptom severity and baseline OCS included as continuous fixed covariates.
  • Interaction terms for baseline-by-timepoint and treatment-by-time point interaction.
  • The Kenward and Roger method (DDFM = KR) for approximating the denominator degrees of freedom to correct for bias in the estimated variance-covariance matrix.
  • REPEATED statement with TYPE=UN to specify an unstructured covariance structure for the R matrix.
  • The OBSMARGIN option on the LSMEANS statement in order to compute the adjusted geometric means with weights proportional to the input data set.

7.6.5. Change from Baseline in BFI Total Score at Week 32

7.6.5.1. Endpoint / Variables

The full BFI is completed every 7 days at home on the eDiary. The BFI total score will be calculated as the mean of the 9 item scores recorded for the weekly assessment, as long as at least 5 of the 9 item scores are complete. The change from baseline in BFI total

score at Week 32 will be calculated using the weekly assessment windows for Week 32 and baseline defined in Section 16.3.1.

7.6.5.2. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. Subjects with missing change from baseline symptom score at Week 32 will be included in the analysis with the largest (i.e. worst) value observed for any subject.

7.6.5.3. Statistical Analyses / Methods

Summary statistics for BFI total score at each week of treatment will be presented, including change from baseline values. Assessment windows for each week are defined in Section 16.3.1.

Endpoint
• Change from baseline in BFI total score at Week 32.
Model Specification
• Wilcoxon Rank Sum test stratified by median baseline fatigue (baseline fatigue≤median and baseline fatigue>median), baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region.
Model Results Presentation
• Number analysed in each treatment group. • Median change from baseline at Week 32 in each treatment group. • p-value for difference between treatments from Wilcoxon Rank Sum test.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses

• For the change from baseline BFI total score, a repeated measures analysis including assessments at Week 4, 8, 12, 16, 20, 24, 28 and 32. In this analysis missing data will be assumed to be missing at random and will not be imputed with the largest i.e. worst value. A mixed effects model will be fitted with the following specification:
  • Time point, treatment and region included as fixed categorical effects.
  • Baseline BFI total score and baseline OCS included as continuous fixed covariates.
  • Interaction terms for baseline-by-timepoint and treatment-by-time point interaction.
  • The Kenward and Roger method (DDFM = KR) for approximating the denominator degrees of freedom to correct for bias in the estimated variance-covariance matrix.
  • REPEATED statement with TYPE=UN to specify an unstructured covariance structure for the R matrix.
  • The OBSMARGIN option on the LSMEANS statement in order to compute the adjusted geometric means with weights proportional to the input data set.

7.6.6. Clinician- and Subject-Rated Overall Response to Therapy Score (RTS) at Week 32

7.6.6.1. Endpoint / Variables

- Clinician-rated overall response to therapy (significantly improved [1], moderately improved [2], mildly improved [3], no change [4], mildly worse [5], moderately worse [6] and significantly worse [7]) at Week 32.

- Subject-rated overall response to therapy (significantly improved [1], moderately improved [2], mildly improved [3], no change [4], mildly worse [5], moderately worse [6] and significantly worse [7]) at Week 32.

7.6.6.2. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. Subjects with missing response at Week 32 will be included in the analysis with the largest (i.e. worst) value observed for any subject.

7.6.6.3. Statistical Analyses / Methods

Summary statistics for clinician- and subject- rated overall response to therapy at each visit will be presented.

Endpoint
• Clinician-rated overall response to therapy at Week 32. • Subject-rated overall response to therapy at Week 32
Model Specification
• Wilcoxon Rank Sum test stratified by baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region. • Supplemented by an ordinal logistic regression (proportional odds) analysis adjusting for covariates of baseline OCS dose (continuous scale), region and treatment.
Model Results Presentation
• Number analysed in each treatment group. • Median change from baseline at Week 32 in each treatment group. • p-value for difference between treatments from Wilcoxon Rank Sum test. • Odds ratio and 95% CI from ordinal logistic regression model. • p-value from ordinal logistic regression model.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses
• Clinician- and subject-rated overall response to therapy will also be analysed at Week 4, 8, 12, 16, 20, 24 and 28 in the same way as the Week 32 analysis.

7.6.7. Change from Baseline in Subject-Rated Symptom Severity (SSR) at Week 32

7.6.7.1. Endpoint / Variables

At each visit, subjects are asked to rate their symptoms of HES now as none (0), mild (1), moderate (2), severe (3) or very severe (4). The change from baseline at Week 32 will be calculated from the Week 32 assessment and the Week 0 assessment and expressed in terms of number of categories of improvement or worsening of symptoms i.e. 4 point improvement (-4), 3 point improvement (-3), 2 point improvement (-2), 1 point improvement (-1), no change (0), 1 point worsening (1), 2 point worsening (2), 3 point worsening (3) or 4 point worsening (4).

7.6.7.2. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. Subjects with missing SSR score at Week 32 will be included in the analysis with the largest (i.e. worst) value observed for any subject.

7.6.7.3. Statistical Analyses / Methods

Summary statistics for the SSR score at each visit will be presented, as well as the change from baseline.

Endpoint
• Change from baseline in subject-rated symptom severity (SSR) at Week 32.
Model Specification
• Wilcoxon Rank Sum test stratified by baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region. • Supplemented by an ordinal logistic regression (proportional odds) analysis adjusting for covariates of baseline OCS dose (continuous scale), region and treatment.
Model Results Presentation
• Number analysed in each treatment group. • Median change from baseline at Week 32 in each treatment group. • p-value for difference between treatments from Wilcoxon Rank Sum test. • Odds ratio and 95% CI from ordinal logistic regression model. • p-value from ordinal logistic regression model.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses
• No sensitivity analyses will be performed.

7.6.8. Change from Baseline in Modified Memorial Symptom Assessment Scale-Short Form (MSAS-SF) responses at Week 32

7.6.8.1. Endpoint / Variables

The MSAS-SF questionnaire records the distress or bother in the last week caused by each of 28 symptoms on 5-point scale (not at all, a little bit, somewhat, quite a bit, very much) as well as how often during the last week a further 4 symptoms occurred on a 4-point scale (occurs rarely, occasionally, frequently, almost constantly). Conversion of each of the categorical responses to a numeric score will be performed as described in the table below.

Question Type	Categorical Response	Numeric Score
Distress or bother (28 symptoms)	Symptom is absent	0
	Symptom present but causes no distress or bother (i.e. level of distress or bother categorised as "not at all")	0.8
	Symptom present and causes a little bit of distress or bother	1.6
	Symptom present and causes somewhat of distress or bother	2.4
	Symptom present and causes quite a bit of distress or bother	3.2
	Symptom present and causes very much distress or bother	4.0
How often (4 symptoms)	Symptom is absent	0
	Symptom present and occurs rarely	1
	Symptom present and occurs occasionally	2
	Symptom present and occurs frequently	3
	Symptom present and occurs almost constantly	4

Using the numeric conversion above, the following endpoints will be derived:

- Total MSAS-SF score for each visit will be calculated as the mean of the 32 scores recorded for that visit.

- MSAS-SF global distress index (GDI) for each visit will be calculated as the mean of the scores for 10 symptoms (feeling sad, worrying, feeling irritable and feeling nervous, lack of energy, pain, lack of appetite, feeling drowsy, constipation, dry mouth).

- MSAS-SF physical symptom subscale score for each visit will be calculated as the mean of the scores for 12 physical symptoms (lack of energy, pain, lack of appetite, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, feeling bloated, and dizziness).

- MSAS-SF psychological symptom subscale score for each visit will be calculated as the mean of the scores for 6 psychologic symptoms (worrying, feeling sad, feeling nervous, difficulty sleeping, feeling irritable, and difficulty concentrating).

For each score the change from baseline at Week 32 will be calculated from the assessment at Week 0 and Week 32.

7.6.8.2. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. Subjects with missing change from baseline MSAS-SF score at Week 32 will be included in the analysis with the largest (i.e. worst) value observed for any subject.

7.6.8.3. Statistical Analyses / Methods

Summary statistics for MSAS-SF scores at each visit will be presented, including change from baseline values.

Endpoint
• Change from baseline in Total Modified Memorial Symptom Assessment Scale-Short Form (MSAS-SF) score at Week 32. • Change from baseline in Modified Memorial Symptom Assessment Scale-Short Form (MSAS-SF) global distress index at Week 32. • Change from baseline in Modified Memorial Symptom Assessment Scale-Short Form (MSAS-SF) physical symptom subscale score at Week 32. • Change from baseline in Modified Memorial Symptom Assessment Scale-Short Form (MSAS-SF) psychological symptom subscale score at Week 32.
Model Specification
• Wilcoxon Rank Sum test stratified by median baseline score (baseline score≤median and baseline score>median), baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region.
Model Results Presentation
• Number analysed in each treatment group. • Median change from baseline at Week 32 in each treatment group. • p-value for difference between treatments from Wilcoxon Rank Sum test.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses
• A repeated measures analysis including assessments at Week 4, 8, 16, 24 and 32. In this analysis missing data will be assumed to be missing at random and will not be imputed with the largest i.e. worst value. A mixed effects model will be fitted with the following specification:

- Time point, treatment and region included as fixed categorical effects.
- Baseline score and baseline OCS dose included as continuous fixed covariates.
- Interaction terms for baseline-by-timepoint and treatment-by-time point interaction.
- The Kenward and Roger method (DDFM = KR) for approximating the denominator degrees of freedom to correct for bias in the estimated variance-covariance matrix.
- REPEATED statement with TYPE=UN to specify an unstructured covariance structure for the R matrix.
- The OBSMARGIN option on the LSMEANS statement in order to compute the adjusted geometric means with weights proportional to the input data set.

7.6.9. Change from Baseline in Physical Function and Sleep (Patient Reported Outcome Measurement Information System [PROMIS]) at Week 32

7.6.9.1. Endpoint / Variables

- The PROMIS physical function score for each visit will be calculated as the mean of the scores for the 12 physical function items recorded for that visit, as long as at least 6 of the 12 item scores are complete. The change from baseline at Week 32 will be calculated from the Week 32 assessment and the Week 0 assessment.

- The PROMIS sleep score for each visit will be calculated as the mean of the scores for the 2 sleep items recorded for that visit; if either of the items has a missing score, the PROMIS sleep score will be assigned as missing for that visit. The change from baseline at Week 32 will be calculated from the Week 32 assessment and the Week 0 assessment.

7.6.9.2. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. Subjects with missing change from baseline PROMIS score at Week 32 will be included in the analysis with the largest (i.e. worst) value observed for any subject.

7.6.9.3. Statistical Analyses / Methods

Summary statistics for PROMIS physical function and sleep score at each visit will be presented, including change from baseline values.

Endpoint
• Change from baseline in PROMIS physical function score at Week 32. • Change from baseline in PROMIS sleep score at Week 32.
Model Specification
• Wilcoxon Rank Sum test stratified by median baseline score (baseline score≤median and baseline score>median), baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or

equivalent) and region.
Model Results Presentation
• Number analysed in each treatment group. • Median change from baseline at Week 32 in each treatment group. • p-value for difference between treatments from Wilcoxon Rank Sum test.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses

• A repeated measures analysis including assessments at Week 4, 8, 16, 24 and 32. In this analysis missing data will be assumed to be missing at random and will not be imputed with the largest i.e. worst value. A mixed effects model will be fitted with the following specification:
  • Time point, treatment and region included as fixed categorical effects.
  • Baseline score and baseline OCS included as continuous fixed covariates.
  • Interaction terms for baseline-by-timepoint and treatment-by-time point interaction.
  • The Kenward and Roger method (DDFM = KR) for approximating the denominator degrees of freedom to correct for bias in the estimated variance-covariance matrix.
  • REPEATED statement with TYPE=UN to specify an unstructured covariance structure for the R matrix.
  • The OBSMARGIN option on the LSMEANS statement in order to compute the adjusted geometric means with weights proportional to the input data set.

8. HEALTH OUTCOMES ANALYSIS

8.1. SF-36 v2

- Certified scoring of the SF-36 survey will be performed using OPTUM™ software.
- The eight domain scores (bodily pain, general health, mental health, physical functioning, role emotional, role physical, social functioning and vitality) as well as the physical and mental component summary scores provided by the software will be converted to SDTM and ADaM data sets by GSK Biostatistics.
- Domain and component summary scores will be summarised by visit, including change from baseline.
- Summaries will be performed on the ITT population.
- No statistical analysis of the SF-36 scores will be performed.

8.2. Healthcare Resource Utilization (HCRU)

- Healthcare resource utilisation associated with a HES flare will be summarised by treatment group.
- Summaries will be performed on the ITT population.
- For each resource type, the number of flares using resource, total amount of resource and mean (SD) resource per HES flare will be summarised.
- No statistical analysis of this endpoint will be performed.

8.2.1. Work Productivity and Activity Impairment

The following endpoints will be derived and summarised by treatment group and visit for the ITT population. Change from baseline will also be derived and summarised.

Endpoint	Derivation
Percentage work time missed due to health	Q2 / (Q2 + Q4)
Percentage impairment while working due to health	Q5 / 10
Percentage overall work impairment due to health	Q2 / (Q2 + Q4) + [(1- (Q2 / (Q2 + Q4))) x (Q5 / 10)]
Percentage activity impairment due to health	Q6 / 10

No statistical analysis of work productivity and activity impairment will be performed.

9. POPULATION PHARMACOKINETIC ANALYSES

Refer to Data Display Standards & Handling Conventions (Section 16.5.3 Reporting Standards for Pharmacokinetic Data).

In support of the analysis described below, a specific dataset will be generated. Specifications for the generation of the dataset will be provided in a separate document.

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK Data Standards and statistical principles.

9.1. Population of Interest

The population PK analysis will be performed on the PK population.

9.2. Strategy for Intercurrent (Post-Randomization) Events

For subjects withdrawing prematurely from study treatment, all available data will be included in the analysis.

Based on mepolizumab PK knowledge, concentrations below the limit of quantification (BLQ) of the assay is considered unlikely at the 300 mg SC dose investigated, in view of the PK sampling scheme selected in the study. Thus, any such results will be treated as missing.

Outlier data will be assessed for plausibility; however, the aim is to use all available data whenever possible. Any decision to exclude data will be fully documented and specified in the clinical study report.

9.3. Population Pharmacokinetic Methodology

Sparse blood sampling is implemented in this study for determination of mepolizumab plasma concentration and subsequent data analysis by population PK methods using the most recent population pharmacokinetics model (meta-analysis PK model of data across indications described in GlaxoSmithKline Document Number 2015N238436_00). Since mepolizumab PK following intravenous administration in HES subjects has already been evaluated within the population PK meta-analysis (using PK samples collected in previous Phase III study MHE100185), the main objectives of this population PK analysis are:

- To evaluate mepolizumab pharmacokinetics in subjects with HES following the subcutaneous administration of a 300 mg dose every 4 weeks.
- To investigate the impact of covariates of interest in the studied HES population (such as baseline characteristics, co-medication) on specific parameters (e.g. clearance) in order to identify potential sources of inter-individual variability in these parameters.
- To obtain individual plasma concentration predictions for the timepoints at which PD is measured to allow the conduct of population PKPD analyses if deemed appropriate.

Mepolizumab plasma concentration-time data (samples collected at Weeks 4, 16 and 32; at the early Withdrawal and the additional follow-up visits (if applicable)) will be analysed by population methods using nonlinear mixed-effects modelling. The analysis will be carried out using appropriate software (e.g., NONMEM or SAS).

9.3.1. Base Model

In consideration of the sparse sampling (3 samples post-start of treatment over 32 weeks: Week 4, 16 and 32) and the wealth of mepolizumab PK knowledge, the most recent population PK model will be applied directly to the dataset without estimation (e.g. maxevals=0 in NONMEM) and predictions generated, against which the model will be validated prospectively using appropriate goodness of fit tests. For example, the Anderson-Darling and Cramér–von Mises tests are accepted methods of comparing Empirical Distribution Functions for model and data (i.e., PK concentrations) to evaluate whether independent observations (i.e., observed PK concentrations from the study) are adequately described by a model (i.e., most recent population PK model).

The following will be obtained:

- A description of the key models tested during the model development will be provided and tabulated;
- Population mepolizumab plasma PK parameter estimates with 95% CI from the final model will be tabulated. Goodness of fit plots for the final model will be presented;
- Individual post-hoc PK parameter estimates (such as area under the plasma concentration-time curve over the dosing interval [AUC (0-τ)], C_{AV} [AUC (0-τ)/τ]) will be summarised descriptively and listed;
- Individual post-hoc predicted plasma concentrations will be summarised descriptively and listed;
- Accumulation ratio estimate will be assessed at Week 16 and 32.

The most recent model consists of a two-compartment pharmacokinetic model with first-order absorption and elimination. Bodyweight is incorporated into the model using allometry with fixed physiological allometric exponents of 0.75 and unity for clearance and volumes, respectively. Albumin and creatinine clearance are also included as covariates of mepolizumab clearance on physiological grounds, however their effects are small and not of clinical relevance. Details of the model can be found in report GlaxoSmithKline Document Number 2015N238436_00.

9.3.2. Investigation of Covariates

The impact of the following prospectively selected covariates on mepolizumab exposure (e.g. clearance) will be evaluated using the procedures described in Section 9.3.3.

Category	Covariates
Demographics	Weight (included in the structural model), age, race, gender, country
Baseline clinical status	Creatinine clearance, albumin (both already included in the

Category	Covariates
	current model), serum creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, total protein
Baseline disease status	Flare history, blood eosinophils and baseline OCS dose
Concomitant medications	If data permits*, e.g. immunosuppressant therapies (e.g. methotrexate, azathioprine and mycophenolate mofetil), proton pump inhibitors, statins, pain relief (e.g. paracetamol, NSAIDs), interferon alfa and antihypertensive drugs
Others	Presence/absence of anti-drug antibodies and previous biologics use (monoclonal antibodies).

*Attempt to investigate those classes of drug will be made providing data permits.

Covariate selection will be based on physiological plausibility, supported by graphical evaluation (PK parameters vs. covariates), and formally by automated linear model fitting using proc glmselect in SAS 9.2 (or higher). Individual PK parameters and covariates will be log-transformed and standardized before analysis. For forward and backward selections, significance levels of 0.1 and 0.05 will be applied respectively, in line with criteria used in previous analyses. Co-linearity between covariates will be carefully considered.

Identified covariates will then be subjected to traditional covariate analysis (with estimation step) and will follow the procedures described in Section 9.3.3. If deemed appropriate box plots of systemic clearance versus covariates of interest (e.g., immunogenicity status) will be provided.

9.3.3. Covariate Model Selection Procedures

The covariate model building will follow a step-wise process consisting of a forward and backward selection procedure. The likelihood ratio test will be used to evaluate the significance of incorporating or removing covariates into the population model based on alpha levels set *a priori*. For forward and backward selections, a significance level of 0.05 and 0.01 for first order conditional estimation with interaction (FOCE-I) will be used, respectively, in line with criteria used in previous analyses.

- **Step-wise forward addition procedure**

Each covariate will be included individually in the 'base model' to identify covariates resulting in a decrease in the objective function value (OFV) of > 3.84, $\chi 2 < 0.05$ for 1 degree of freedom (*df*) using FOCE-I. The retained covariates will then be added to the base model one by one, starting with the most significant ones until all covariates have been tested. Note, if a covariate exponent estimate is numerically small, the covariate will not be retained; irrespective of objective function. This will also be supported by examination of the goodness of fit. This will constitute the full model.

- **Backward elimination procedure**

From the full model, the significance of each covariate will be tested individually by removing covariates one by one until all non-significant covariates have been excluded. A covariate will be retained if upon removal, the OFV increase by more than 6.64 points ($\chi 2 < 0.01$ for 1 *df)* using FOCE-I. Note, a covariate may be retained in the model despite being found non-statistically significant, if there is a strong rationale for its inclusion. This will constitute the final model.

Note: centering of continuous covariates may be considered, as appropriate. The mean or median value of the subjects included in the analysis may be used for example.

The impact of the presence of anti-mepolizumab antibodies may not be formally tested as a covariate in the model, considering the low incidence observed in the mepolizumab programme to date. Instead a graphical approach will be used, if deemed appropriate.

9.3.4. Model Evaluation

The uncertainty in the parameter estimates will be assessed (e.g. from the standard error estimates provided by NONMEM or from the 95% CI estimates provided by other appropriate analysis conducted using other software). Furthermore, the model performance will be investigated using a set of goodness of fit plots as well as Visual Predictive Check (VPC) method. Other evaluation methods may be used (e.g., bootstrapping) if deemed appropriate.

10. PHARMACODYNAMIC ANALYSES

10.1. Blood Eosinophils

10.1.1. Population of Interest

Blood eosinophil analyses will be based on the Pharmacodynamic population.

10.1.2. Endpoint / Variables

Absolute and ratio to baseline blood eosinophil counts at each visit. For blood eosinophils, baseline will be defined as the latest blood eosinophil value measured by the central laboratory prior to the first dose of study treatment.

10.1.3. Summary Measure

The difference between mepolizumab and placebo in the ratio to baseline of blood eosinophils.

10.1.4. Strategy for Intercurrent (Post-Randomization) Events

For subjects withdrawing prematurely from study treatment, only the endpoint values up to and including 28 days after the last dose of study treatment will be included in the analysis ('while on treatment' estimand).

10.1.5. Statistical Analyses / Methods

- Blood eosinophil counts will be $\log_e$-transformed prior to analysis. Non-detectable blood eosinophil values of 0 GI/L, or results below the limit of quantification will be replaced by half of the lowest observed detectable (non-zero) value in the study data set, prior to log transformation.

- Absolute and ratio to baseline blood eosinophil counts will be summarised by treatment group and visit. Only results from the central laboratory will be included in the summary, however all data will be listed.

- Full details of data displays to be presented are given in Appendix 10: List of Data Displays.

10.1.5.1. Statistical Methodology Specification

Endpoint
• Ratio to baseline blood eosinophil count
Model Specification
• A mixed effects repeated measures model will be fitted to the $\log_e$ transformed blood eosinophil data with the following specification: • Visit, treatment and region included as fixed categorical effects.

• Baseline blood eosinophil count (log_e scale) and baseline OCS dose included as continuous fixed covariates. • Interaction terms for baseline (screening) blood eosinophil count-by-visit and treatment-by-visit. • The Kenward and Roger method (DDFM = KR) for approximating the denominator degrees of freedom to correct for bias in the estimated variance-covariance matrix. • REPEATED statement with TYPE=UN to specify an unstructured covariance structure for the R matrix. • The OBSMARGIN option on the LSMEANS statement in order to compute the adjusted geometric means with weights proportional to the input data set.
Model Results Presentation
• Number analysed in each treatment group. • LS Mean (SE) and LS Mean ratio to screening (SE) in each treatment group. • Mean treatment ratio, 95% CI and p-value for mepolizumab vs placebo.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses
• The MMRM model specified above will also be fitted to the log transformed absolute blood eosinophil counts and adjusted mean absolute blood eosinophil counts and 95% CI from this model will be plotted.

10.2. Serum Total IL-5

10.2.1. Population of Interest

Total IL-5 analyses will be based on the Pharmacodynamic population.

10.2.2. Endpoint / Variables

Absolute and ratio to baseline total IL-5 at Week 32

10.2.3. Summary Measure

The difference between mepolizumab and placebo in the ratio to baseline of serum total IL-5 at Week 32.

10.2.4. Strategy for Intercurrent (Post-Randomization) Events

For subjects withdrawing prematurely from study treatment, only the endpoint values up to and including 28 days after the last dose of study treatment will be included in the analysis ('while on treatment' estimand).

10.2.5. Statistical Analyses / Methods

- Total IL-5 values will be log_e-transformed prior to analysis. Values below the limit of quantification will be replaced by half the limit of quantification, prior to log

transformation. Summary statistics will include the number and percentage of BLQ values.

- Absolute and ratio to baseline total IL-5 values will be summarised by treatment group and visit (Baseline and Week 32).

- Full details of data displays to be presented are given in Appendix 10: List of Data Displays.

10.2.5.1. Statistical Methodology Specification

Endpoint
• Ratio to baseline total IL-5 at Week 32
Model Specification
• Wilcoxon Rank Sum test stratified by baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region.
Model Results Presentation
• Number analysed in each treatment group. • Median change from baseline at Week 32 in each treatment group. • p-value for difference between treatments from Wilcoxon Rank Sum test.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses
• No sensitivity analyses will be performed.

11. SAFETY ANALYSES

The safety analyses will be based on the Safety population, unless otherwise specified.

11.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. Common AEs will be defined as AEs with frequency ≥3% (prior to rounding to nearest percent) in either treatment group.

The details of the planned displays are provided in Appendix 10: List of Data Displays.

11.1.1. Adverse Events of Special Interest

Adverse events of special interest (AESIs) reported by the investigator as systemic reactions (further categorised by the investigator as either allergic [type I hypersensitivity] or other systemic reactions and assessed against Sampson criteria for anaphylaxis) are collected via targeted eCRF within the study. Local injection site reactions are also collected via targeted eCRF within the study.

AESIs of potential opportunistic infections, malignancies, serious cardiac, vascular and thromboembolic (CVT) events and serious ischemic events will be identified from a list of relevant preferred terms maintained within a project level reference dataset created based on the MedDRA dictionary available at the time of DBF for this study. Further details of how relevant preferred terms are identified are given in the Program Safety Analysis Plan (PSAP).

Separate summary tables showing the number and percent of subjects with each type of AESI, broken down by preferred term will be created.

For each type of AESI a profile summary table will be produced containing information including, but not limited to, the number of occurrences of the event, event characteristics, time to onset, intensity, outcome and action taken.

The relative risk of each AESI between mepolizumab and placebo with 95% confidence intervals will also be presented.

Separate listings of AESIs identified by the investigator as anaphylaxis, allergic (type I hypersensitivity), other systemic reactions and local injection site reactions will be produced, as well as listings of potential opportunistic infections, malignancies, serious CVT events and serious ischemic events.

11.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Haematology laboratory tests and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 10: List of Data Displays.

A scatter plot of maximum ALT vs baseline ALT, and maximum ALT vs total bilirubin will be produced. In addition, if any liver stopping or liver monitoring events occur during the study, summaries of liver monitoring/stopping event reporting and hepatobiliary laboratory abnormalities will be produced.

11.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 10: List of Data Displays.

12. IMMUNOGENICITY ANALYSES

12.1. Overview of Immunogenicity Analyses

For the immunogenicity assessment, two types of anti-drug antibody (ADA) assays will be performed, a binding anti-drug antibody assay and a neutralizing antibody assay.

For the binding assay, there will be a three tiered analysis: screening, confirmation and titration. The screening assay produces a result of positive or negative relative to a screening cut point. Positive samples continue with the confirmation assay, which also produces a result of positive or negative relative to a confirmation cut point. For positive confirmation samples, a titre value will also be obtained to quantify the degree of binding in a titration assay and the sample will be tested with the neutralizing assay, which also reports results as positive or negative.

The binding ADA results at each visit will be categorised as negative, transient positive (defined as a single confirmatory positive immunogenic response that does not occur at the final study assessment) or persistent positive (defined as a confirmatory positive immunogenic response for at least 2 consecutive assessments excluding the screening visit, or a single result at the final study assessment). In addition, the highest post-baseline binding ADA confirmatory result obtained for a subject will be summarised. Subjects with both positive and negative results will be identified in the positive category. Summary statistics for the titre result by visit will also be presented.

A summary of adverse events by highest post-baseline binding ADA confirmatory result (as defined above) will be produced.

A summary of treatment emergent positive confirmatory binding ADA results in the subset of subjects who did not have a positive confirmatory binding ADA result prior to the dosing of study treatment will also be presented.

Neutralizing antibody assay results will be summarised by visit. In addition, the highest post-baseline neutralising antibody assay result during the treatment period of the study will be summarised, with subjects with both positive and negative results identified in the positive category.

Immunogenicity data will be listed for subjects with at least one positive screening binding assay.

13. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

In support of the analysis described below, a specific dataset will be generated. Specifications for the generation of the dataset will be provided in a separate document.

The details of the planned displays are presented in Appendix 10: List of Data Displays.

13.1. Population of Interest

The population PKPD analysis will be performed on the PK and PD populations.

13.2. Strategy for Intercurrent (Post-Randomization) Events

For subjects withdrawing prematurely from study treatment, all available data will be included in the analysis.

Zero values for the baseline blood eosinophil count as well as for blood eosinophil count will be replaced by half of the lowest observed detectable (non-zero) value in the study data set (consistent with approaches used in other analyses).

Outlier data will be assessed for plausibility, however the aim is to use all available data whenever possible. Any decision to exclude data will be fully documented and specified in the clinical study report.

13.3. Population Pharmacokinetic/Pharmacodynamic Methodology

If deemed appropriate, a population pharmacokinetic/pharmacodynamic analysis will be conducted.

Blood eosinophil count were measured during the course of the study over the 32 weeks treatment period and will be analysed by population methods using the most recent population PKPD model (meta-analysis PKPD model of data across indications described in GlaxoSmithKline Document Number 2015N238436_00).

The objectives of the population PKPD analysis are:

- To evaluate mepolizumab pharmacodynamics in subjects with HES following subcutaneous administration of a 300 mg dose every 4 weeks;
- To investigate the impact of covariates of interest in the studied HES population (such as baseline characteristics, co-medication) on specific parameters (e.g. maximum blood eosinophil reduction) in order to identify potential sources of inter-individual variability in these parameters.

Mepolizumab blood eosinophil count-time data (samples collected at screening, Week 2, Week 4 and every 4 weeks for the remainder of the 32-week treatment period) will be analysed by population methods using nonlinear mixed-effects modelling. The analysis will be carried out using appropriate software (e.g., NONMEM or SAS).

13.3.1. Base Model

The most recent population PKPD model will be applied directly to the dataset without estimation (e.g. maxevals=0 in NONMEM) and predictions generated against which the model will be validated prospectively using appropriate goodness of fit tests as described in Section 9.3.1 (using the observed data from the study).

The following will be obtained:

- A description of the key models tested during the model development will be provided and tabulated.
- The population PD parameter estimates with 95% CI from the final model will be tabulated. Goodness of fit plots for the final model will be presented.

The most recent population PKPD model consists of an indirect response model parameterised in term of baseline blood eosinophil count (KRO), rate of elimination of eosinophils in the blood (Kout), concentration resulting in 50% of maximum drug effect (IC_{50}) and maximum effect (Imax). Observed baseline blood eosinophil count is included as covariates of both predicted baseline and mepolizumab inhibitory response; and disease for predicted baseline blood eosinophil count. Details of the model can be found in GlaxoSmithKline Document Number 2015N238436_00 and GlaxoSmithKline Document Number 2015N255079_00 (extension of the former report).

13.3.2. Investigation of Covariates

The impact of the following prospectively selected plausible covariates on relevant parameters (i.e., baseline blood eosinophil count and maximum effect) will be evaluated.

Category	Covariates
Demographics	Age, race, gender
Baseline disease status	Flare history, blood eosinophils (already included in the current model)
Others	Baseline OCS absolute dose, presence/absence of anti-drug antibodies*, immunosuppressant therapies* (e.g. methotrexate, azathioprine and mycophenolate mofetil), interferon alfa*

*Attempt to investigate those covariates will be made providing data permits.

Covariate selection will be based on physiological plausibility, supported by graphical evaluation (PD parameters vs. covariates), and formally by automated linear model fitting using proc glmselect in SAS 9.2 (or higher). Individual PD parameters and covariates will be log-transformed and standardized before analysis. For forward and backward selections, significance levels of 0.1 and 0.05 will be applied respectively, in line with criteria used in previous analyses. Co-linearity between covariates will be carefully considered.

Identified covariates will then be subjected to traditional covariate analysis (with estimation step) and will follow the same procedures as described in Section 9.3.3 for the population PK model.

Model evaluation will be as described in Section 9.3.4 for the population PK model.

14. EXPLORATORY EXPOSURE-EFFICACY RESPONSE ANALYSIS

If deemed appropriate an exposure response analysis for the proportion of subjects who experience a HES flare during the 32-week study treatment period will be conducted.

14.1. Population of Interest

The exploratory exposure-efficacy response analysis will be performed on the ITT population.

14.2. Endpoints

Two separate measures of exposure will be considered for this analysis:

i) Dose/bodyweight

ii) C_{av} = Dose/(Tau*CL/F),

where CL/F is the PK model-estimated apparent systemic clearance for each individual, and Tau the (fixed) inter-dosing interval (28 days).

The efficacy endpoint analysed will be the primary endpoint of the proportion of subjects who experience a HES flare during the 32-week study treatment period. Subjects who withdraw from the study prior to Week 32 (Visit 11) and therefore have missing data on HES flares will be included in this analysis as treatment failures, i.e. a subject will be classed as not experiencing a HES flare only if they have no flares reported and complete Week 32 (Visit 11).

14.3. Methodology

A logistic regression model (linear, and if necessary, non-linear) will be fitted with exposure (dose/bodyweight or C_{av}) fitted on the $\log_e$ scale as a continuous covariate. The analysis will also be adjusted for region, baseline blood eosinophil count and baseline OCS dose. The odds ratio for each level of mepolizumab exposure versus placebo will be presented. Fractional polynomial models may also be explored in order to find the best fitting model for any relationship.

15. REFERENCES

GlaxoSmithKline Document Number 2013N171550_00 Study ID 200622. A randomised, double-blind, placebo-controlled study to investigate the efficacy and safety of mepolizumab in the treatment of adolescent and adult subjects with severe hypereosinophilic syndrome. Report Date 29-APR-2016.

GlaxoSmithKline Document Number 2015N238436_00 Study ID N/A. A population PK and PKPD meta-analysis of combined intravenous and subcutaneous mepolizumab data. Report Date 27-MAY-2015.

GlaxoSmithKline Document Number 2015N255079_00 Study ID N/A. Supplementary outputs from a population PK and PKPD meta-analysis of combined intravenous and subcutaneous mepolizumab data. Report Date 04-OCT-2015.

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16. APPENDICES

16.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

Subjects with important protocol deviations considered to potentially have an effect on the primary efficacy analysis will be excluded from the Per Protocol (PP) population. The decision to exclude a subject from the PP population or exclude part of their data from the PP population will be made prior to breaking the blind.

16.1.1. Exclusions from Per Protocol Population

A subject meeting any of the following criteria will be excluded from the Per Protocol population:

Number	Exclusion Description
01	Inclusion #3 – Insufficient evidence that subject has been diagnosed with HES for at least 6 months at randomization (Visit 2).
02	Inclusion #4 – Subject did not have a history of two or more flares within the past 12 months prior to screening (Visit 1), with at least one HES flare not related to a decrease in HES therapy during the 4 weeks prior to the flare.
03	Inclusion #5 – Subject did not have a blood eosinophil count ≥1000 cells/μL collected during screening (within 4 weeks prior to randomization). Investigators were permitted to use local laboratory results to meet this inclusion criteria, therefore if the screening central laboratory blood eosinophil count is <1000 cells/μL but a local laboratory blood eosinophil count ≥1000 cells/μL is available during screening the subject will not be considered a protocol deviation or excluded from the Per Protocol population.
04	Inclusion #6 – Subject was not on a stable dose of HES therapy for the 4 weeks prior to randomization (Visit 2).
05	Incorrect study treatment administered at any point during the study i.e. subject received placebo instead of mepolizumab or vice versa.
06	Subject received a medication or herbal remedy which may alter the course of HES or interact with the study treatment with the exception of HES therapy to treat a HES flare.

16.2. Appendix 2: Schedule of Activities

16.2.1. Protocol Defined Schedule of Events

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

Procedures	Pre-screen	Screen	Randomi-zation	Double-blinded treatment period												Additional follow-up
assessment) /Flare detail																
Clinician-RTS					X	X	X	X	X	X	X	X			X	

Procedures	Pre-screen	Screen	Randomi-zation	Double-blinded treatment period												Additional follow-up
Study visit	0	1	2	3	4	5	6	7	8	9	10	11 End-of-treatment	Flare[19]	3-11 for subjects who prematurely discontinue study treatment[20]	EW	12
Study week		Up to ~4 weeks (wks)	0	2 (± 5 days)	4 ±1 wks	8 ±1 wks	12 ±1 wks	16 ±1 wks	20 ±1 wks	24 ±1 wks	28 ±1 wks	32 ±1 wks				~12 wks after last dose ±1 wks
HCRU			X		X	X	X	X	X	X	X	X			X	
Spirometry			X			X		X		X		X	X			
Echocardiogram[4]		X										X	X			
Safety assessments																
Physical examination[5]		X	X		X	X	X	X	X	X	X	X	X			
Height and weight[6]		X	X					X				X			X	
Concomitant meds including maintenance OCS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[7]		X	X		X	X	X	X	X	X	X	X	X		X	
ECG		X										X	X			
AEs			X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAEs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory assessments[8]																
Hematology[9]		X	X	X	X	X	X	X	X	X	X	X	X	X	X[21]	

Procedures	Pre-screen	Screen	Randomi-zation	Double-blinded treatment period											Additional follow-up
Chemistry[10]		X			X	X	X	X	X	X	X	X	X	X[21]	X[21]	
Troponin		X			X	X	X	X	X	X	X	X	X	X[21]	X[21]	
Pregnancy test[11]		X	X		X	X	X	X	X	X	X	X		X[21]	X[21]	
Aldolase		X			X	X	X	X	X	X	X	X	X			
Lipoproteins (fasting)[12]		X														
Urinalysis[13]		X										X		X[21]	X[21]	
Hep B & C serology[14]		X														
F/P status[15]		X														
T-cell profile		X										X		X[21]	X[21]	
Total IgE			X													

Procedures	Pre-screen	Screen	Randomi-zation	Double-blinded treatment period											Additional follow-up
Study visit	0	1	2	3	4	5	6	7	8	9	10	11 End-of-treatment	Flare[19]	3-11 for subjects who prematurely discontinue study treatment[20]	EW	12
Study week		Up to ~4 weeks (wks)	0	2 (± 5 days)	4 ±1 wks	8 ±1 wks	12 ±1 wks	16 ±1 wks	20 ±1 wks	24 ±1 wks	28 ±1 wks	32 ±1 wks				~12 wks after last dose ±1 wks
PK					X			X				X		X[21]	X[21]	X[21]
PD (IL-5)			X									X	X			
Immunogenicity (Anti-drug antibody)			X					X				X		X[21]	X[21]	X[21]
Genetics[16]			X													
Sample collection for biomarker sub-study[17]			X									X	X	X[21]	X[21]	
Investigational product & other study treatment																

Procedures	**Pre-screen**	**Screen**	**Randomi-zation**	**Double-blinded treatment period**											**Additional follow-up**
Study treatment administration[18]			X		X	X	X	X	X	X	X					
Dispense/collect blinded OCS			X	X	X	X	X	X	X	X	X	X		X	X	
Interactive Response Technology (IRT)/electronic CRF (eCRF)/electronic Diary (eDiary)																
Register visit on IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete eCRF		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense (D) /collect (C) eDiary[22]		D										C		C for Visit 11	C	
Review eDiary			X	X	X	X	X	X	X	X	X	X		X	X	

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

16.3. Appendix 3: Assessment Windows

16.3.1. Definition of Weekly Assessment Windows

Daily assessments of BFI item 3 and HES daily symptoms as well as weekly assessments of the full BFI will be assigned a single weekly analysis time point according to the table below.

Analysis Timepoint	Analysis Window		
	Beginning Timepoint	Ending Timepoint	Special Rules for Handling Overlapping Timepoints
Week 32	Week 32 (Visit 11) visit date – 6 days	Week 32 (Visit 11) visit date	
Week 31	Week 32 (Visit 11) visit date – 13 days	Week 32 (Visit 11) visit date – 7 days	If assessment falls into Week 31/Week 30/Week 29 and Week 28, assign assessment as Week 28. If assessment date is less than Week 28 (Visit 10) visit date, assign a relevant timepoint less than Week 28.
Week 30	Week 32 (Visit 11) visit date – 20 days	Week 32 (Visit 11) visit date – 14 days	
Week 29	Week 32 (Visit 11) visit date – 27 days	Week 32 (Visit 11) visit date – 21 days	
Week 28	Week 28 (Visit 10) visit date – 6 days	Week 28 (Visit 10) visit date	
Week 27	Week 28 (Visit 10) visit date – 13 days	Week 28 (Visit 10) visit date – 7 days	If assessment falls into Week 27/Week 26/Week 25 and Week 24, assign assessment as Week 24. If assessment date is less than Week 24 (Visit 9) visit date, assign a relevant timepoint less than Week 24.
Week 26	Week 28 (Visit 10) visit date – 20 days	Week 28 (Visit 10) visit date – 14 days	
Week 25	Week 28 (Visit 10) visit date – 27 days	Week 28 (Visit 10) visit date – 21 days	
Week 24	Week 24 (Visit 9) visit date – 6 days	Week 24 (Visit 9) visit date	
Week 23	Week 24 (Visit 9) visit date – 13 days	Week 24 (Visit 9) visit date – 7 days	If assessment falls into Week 23/Week 22/Week 21 and Week 20, assign assessment as Week 20. If assessment date is less than Week 20 (Visit 8) visit date, assign a relevant timepoint less than Week 20.
Week 22	Week 24 (Visit 9) visit date – 20 days	Week 24 (Visit 9) visit date – 14 days	
Week 21	Week 24 (Visit 9) visit date – 27 days	Week 24 (Visit 9) visit date – 21 days	
Week 20	Week 20 (Visit 8) visit date – 6 days	Week 20 (Visit 8) visit date	
Week 19	Week 20 (Visit 8) visit date – 13 days	Week 20 (Visit 8) visit date – 7 days	If assessment falls into Week 19/Week 18/Week 17 and Week 16, assign assessment as Week 16. If assessment date is less than Week 16 (Visit 7) visit date, assign a relevant timepoint less than
Week 18	Week 20 (Visit 8) visit date – 20 days	Week 20 (Visit 8) visit date – 14 days	
Week 17	Week 20 (Visit 8) visit date – 27 days	Week 20 (Visit 8) visit date – 21 days	

Analysis Timepoint	Analysis Window		
	Beginning Timepoint	Ending Timepoint	Special Rules for Handling Overlapping Timepoints
			Week 16.
Week 16	Week 16 (Visit 7) visit date – 6 days	Week 16 (Visit 7) visit date	
Week 15	Week 16 (Visit 7) visit date – 13 days	Week 16 (Visit 7) visit date – 7 days	If assessment falls into Week 15/Week 14/Week 13 and Week 12, assign assessment as Week 12. If assessment date is less than Week 12 (Visit 6) visit date, assign a relevant timepoint less than Week 12.
Week 14	Week 16 (Visit 7) visit date – 20 days	Week 16 (Visit 7) visit date – 14 days	
Week 13	Week 16 (Visit 7) visit date – 27 days	Week 16 (Visit 7) visit date – 21 days	
Week 12	Week 12 (Visit 6) visit date – 6 days	Week 12 (Visit 6) visit date	
Week 11	Week 12 (Visit 6) visit date – 13 days	Week 12 (Visit 6) visit date – 7 days	If assessment falls into Week 11/Week 10/Week 9 and Week 8, assign assessment as Week 8. If assessment date is less than Week 8 (Visit 5) visit date, assign a relevant timepoint less than Week 8.
Week 10	Week 12 (Visit 6) visit date – 20 days	Week 12 (Visit 6) visit date – 14 days	
Week 9	Week 12 (Visit 6) visit date – 27 days	Week 12 (Visit 6) visit date – 21 days	
Week 8	Week 8 (Visit 5) visit date – 6 days	Week 8 (Visit 5) visit date	
Week 7	Week 8 (Visit 5) visit date – 13 days	Week 8 (Visit 5) visit date – 7 days	If assessment falls into Week 7/Week 6/Week 5 and Week 4, assign assessment as Week 4. If assessment date is less than Week 4 (Visit 4) visit date, assign a relevant timepoint less than Week 4.
Week 6	Week 8 (Visit 5) visit date – 20 days	Week 8 (Visit 5) visit date – 14 days	
Week 5	Week 8 (Visit 5) visit date – 27 days	Week 8 (Visit 5) visit date – 21 days	
Week 4	Week 4 (Visit 4) visit date – 6 days	Week 4 (Visit 4) visit date	
Week 3	Week 4 (Visit 4) visit date – 13 days	Week 4 (Visit 4) visit date – 7 days	If assessment falls into Week 3/Week 2/Week 1 and Baseline (Week 0) or Screening, assign assessment as Baseline (Week 0) or Screening.
Week 2	Week 4 (Visit 4) visit date – 20 days	Week 4 (Visit 4) visit date – 14 days	
Week 1	Week 4 (Visit 4) visit date – 27 days	Week 4 (Visit 4) visit date – 21 days	
Baseline (Week 0)	Date of first dose of study treatment – 7 days	Date of first dose of study treatment - 1	
Screening	N/A	Date of first dose of study treatment – 8 days	

16.4. Appendix 4: Study Phases

Assessments and events will be classified according to the time of occurrence relative to the first dose of study treatment.

16.4.1. Treatment Phases for HES Flare

Study Phase	Definition
Pre-Treatment	Flare onset date < Date of first dose of study treatment
On-Treatment	Date of first dose of study treatment ≤ Flare onset date ≤ Date of last dose of study treatment + 28 days
Off-Treatment	Date of last dose of study treatment + 28 days < Flare onset date ≤ Date of Week 32 visit /Study withdrawal date
Post-Treatment	Flare onset date > Date of Week 32 visit

16.4.2. Treatment Phases for BFI and HES-DS

Since the electronic diary is completed daily in the evening, BFI and HES-DS assessments will be classified as follows:

Study Phase	Definition
Pre-Treatment	Assessment date < Date of first dose of study treatment
On-Treatment	Date of first dose of study treatment ≤ Assessment date ≤ Date of last dose of study treatment + 28 days
Off-Treatment	Date of last dose of study treatment + 28 days < Assessment date ≤ Date of Week 32 visit /Study withdrawal date
Post-Treatment	Assessment date > Date of Week 32 visit

16.4.3. Treatment Phases for Other Efficacy Assessments

Study Phase	Definition
Pre-Treatment	Assessment date ≤ Date of first dose of study treatment
On-Treatment	Date of first dose of study treatment < Assessment date ≤ Date of last dose of study treatment + 28 days
Off-Treatment	Date of last dose of study treatment + 28 days < Assessment date ≤ Date of Week 32 visit /Study withdrawal date
Post-Treatment	Assessment date > Date of Week 32 visit

16.4.4. Treatment Phases for Adverse Events

Study Phase	Definition
Pre-Treatment	AE onset date/time < Date/time of first dose of study treatment
On-Treatment	Date/time of first dose of study treatment ≤ AE onset date/time ≤ Date of last dose of study treatment + 28 days
Post-Treatment	AE onset date > Date of last dose of study treatment + 28 days

NOTES:

- Please refer to Section 16.7.2.1 for handling of missing and partial dates for adverse events.

16.4.5. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before the date of first dose of study treatment
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Section 16.7.2.1 for handling of missing and partial dates for concomitant medications.

16.5. Appendix 5: Data Display Standards & Handling Conventions

16.5.1. Reporting Process

Software	
• The currently supported version of SAS software (SAS 9.4 or later) will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Area	: sb240563/mid200622
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards. • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files will be generated for the final reporting effort.	

16.5.2. Reporting Standards

General

• All data displays (Tables, Figures & Listings) will use the term “Subject” rather than “Participant” which reflects CDISC and GSK Data Display Standards terminology.
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include subject level listings in the main body of the GSK Clinical Study Report. All subject level listings should be located in the modular appendices as ICH or non-ICH listings

Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DPs) will be adopted for reporting of data based on the raw data collected but may be adjusted to a clinically interpretable number of DPs. • For FEV_1 and FVC, the mean and median (L) will be reported to 3 decimal places (i.e. to the nearest mL), SD to 4 decimal places, minimum and maximum to 2 decimal places.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.

• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.
• Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings, summaries and statistical analyses.

Unscheduled Visits
• HES flare data collected at unscheduled visits will be included in the derivation of all flare related endpoints for summary and analysis. • For summaries by visit, data recorded at an unscheduled visit will be re-assigned in the ADaM data sets to the closest nominal visit at which collection of data was scheduled, unless information already exists at that visit. Unscheduled data re-assigned to a scheduled visit will be included in analyses, summary tables and figures by scheduled visit. Unscheduled data that is not re-assigned to a scheduled visit will not be included in analyses, summary tables or figures by scheduled visit. Unscheduled data that is not re-assigned to a scheduled visit will be considered in the derivation of baseline and highest/worst case post baseline result for relevant summary tables. • Data recorded at unscheduled visits will be included in the assessment of maximum or worst case post-baseline for relevant endpoints. • All unscheduled visits will be included in listings.
Early Withdrawal Visits
• Data recorded at the early withdrawal visit will be re-assigned in the ADaM data sets to the next scheduled visit, unless information already exists at that visit. Early withdrawal data re-assigned to a scheduled visit will be included in analyses, summary tables and figures by scheduled visit. Early withdrawal visit data that is not re-assigned to a scheduled visit will not be included in analyses, summary tables or figures by scheduled visit. • Data recorded at early withdrawal visits will be included in the assessment of maximum or worst case post-baseline for relevant endpoints. • Data from all early withdrawal visits will be included in listings.

Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %

Graphical Displays
• Refer to IDSL Statistical Principals 7.01 to 7.13.

16.5.3. Reporting Standards for Pharmacokinetic Data

Pharmacokinetic Concentration Data	
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: BLQ concentration values will be imputed as per GUI_51487 for descriptive summary statistics only.
NONMEM/Pop PK	Pop-PK file (CSV and SAS format) for the POP-PK and POP-PKPD

File	analyses performed by the Clinical Pharmacology Modelling and Simulation function will be created according to the POP-PKPD Dataset Specification document.
Pharmacokinetic Parameter Data	
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1.

16.6. Appendix 6: Derived and Transformed Data

16.6.1. General

Multiple Measurements at One Analysis Time Point
• If there are two results identified at a single visit the latter of the two measurements will be flagged and used in any derivation of summary statistics. All values will be presented on listings. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from the date of the first dose of study treatment:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

Total observed time, time on treatment, time off treatment, missing time

• For subjects completing the Week 32 visit
  • Total observed time (days) = Week 32 visit date – Date of first dose + 1 day
  • Time on treatment (days) = Minimum(Week 32 visit date, Date of last dose + 28 days) – Date of first dose + 1 day
  • Time off treatment (days) = Week 32 visit date – Minimum(Week 32 visit date, Date of last dose + 28 days)
  • Missing time (days) = 0
• For subjects not completing the Week 32 visit
  • Total observed time (days) = Study withdrawal date – Date of first dose + 1 day
  • Time on treatment (days) = Minimum(Study withdrawal date, Date of last dose + 28 days) - Date of first dose + 1 day
  • Time off treatment (days) = Study withdrawal date – Minimum(Study withdrawal date, Date of last dose + 28 days)
  • Missing time (days) = Predicted Week 32 visit date – Study withdrawal date, where predicted Week 32 visit date = Date of first dose + 224 days.

•

16.6.2. Change from Baseline Definitions

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]
Ratio to Baseline	= Visit Value / Baseline

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 5.2 will be used for derivations for endpoints / parameters.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and result will be set to missing.

16.6.3. Study Population

Age
• GSK standard IDSL algorithms will be used for calculating age where birth day and month will be imputed 'PPD • Birth date will be presented in listings as 'YYYY'. • Age will be calculated relative to the date of the screening visit (Visit 1).
Body Mass Index (BMI)
Calculated as **Weight (kg) / [Height (m)^2]**
Baseline HES Therapy
• Baseline oral corticosteroid use and baseline oral prednisone equivalent daily dose will be derived as detailed in Section 5.4.1.1. • Cytotoxic therapy/immunosuppressive therapy and other HES therapy will be identified by clinical review of the concomitant medications page according to the following criteria: ○ Medication type = "Hypereosinophilic syndrome" ○ Start date < Date of first dose of study treatment ○ Either "ongoing" or End date ≥ Date of first dose of study treatment • Oral budesonide has negligible systemic exposure and will be counted as "Other HES therapy" rather than oral corticosteroid therapy.
Duration of HES
• Duration of HES in years will be calculated from the date of the screening visit (Visit 1) and the date of HES diagnosis as follows: Duration (years) = (Date of visit 1 – date of HES diagnosis)/365.25 • If the date of HES diagnosis is a partial date, a '01' will be used for a missing day and 'Jan' will be used for a missing month.
Exposure (therapeutic coverage)
• The number of days of exposure (therapeutic coverage) to study drug will be calculated based on the formula: Duration of exposure in days = Date of last dose of study treatment – date of first dose of study treatment + 29. • Exposure in months will be calculated using the formula: Exposure (months) = (Exposure in days / 365.25) * 12 • Total subject years exposure will be calculated using the formula: Total subject-years exposure = (Sum across subjects of exposure in days)/365.25

16.6.4. Efficacy

HES Flare

Definition of HES Flare

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

- An increase in the maintenance OCS dose by at least 10mg/day for 5 days
- An increase in or addition of any cytotoxic and/or immunosuppressive HES therapy

or

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

- The maintenance OCS dose is the dose received during the 4 weeks prior to randomisation i.e. baseline OCS therapy, which should be maintained for the duration of the treatment period. If a subject has their OCS dose reduced during the treatment period, the maintenance dose will be redefined as the new dose they have received for at least 4 weeks. If the OCS dose is increased during the treatment period, the maintenance OCS dose will not be redefined and will remain as therapy taken during the 4 weeks prior to randomisation.
- Flares meeting endpoint definition a) will be captured on the 'flare details' form in the eCRF.
- An increase in blood eosinophils above the pre-defined threshold level (2 x baseline value or baseline value + 2500 cells/μL) without any other clinical manifestations during the study will lead to administration of blinded active OCS treatment (see Section 2.2). If a subject receives a second course of blinded active OCS during the 32-week treatment period, the subject will be considered to be experiencing a flare. The container list for the blinded OCS treatment (indicating which container numbers contained active OCS and which contained placebo OCS) will be used to define HES flares meeting endpoint definition b). This container list will be incorporated into the final SDTM data sets at the end of the study, at the same time as the randomised treatment information.

HES flare onset and resolution dates

- The onset and resolution dates of HES flares meeting endpoint definition a) will be recorded on the 'Flare details' form in the eCRF.
- The start date of HES flares meeting endpoint definition b) is defined as the date of the blood draw at which the second course of blinded active OCS was triggered via schedule blood sampling for eosinophil monitoring. The resolution date for a flare meeting endpoint definition b) is the date of the first blood draw at which blood eosinophil count is below the threshold to trigger blinded active OCS (see protocol Section 6.4 for full details of blood eosinophil monitoring).

HES flare during Week 20 through Week 32

- Defined as a HES flare starting or ongoing on or after the date of the Week 20 visit (Visit 8) up to and including the date of the Week 32 visit (Visit 11).

Time to First HES Flare

- Calculated for each subject as

(Onset date of first HES flare – Date of first dose of study treatment) + 1

HES Flare

Rate of HES Flares

- For subjects completing the study, the rate of HES flares will be calculated as

$$\frac{365.25 \times Number\ of\ observed\ HES\ flares}{Date\ of\ Week\ 32\ (Visit\ 11) - Date\ of\ first\ dose\ of\ mepolizumab + 1}$$

- For subjects withdrawing prematurely from the study, the rate of HES flares will be calculated as

$$\frac{365.25 \times Number\ of\ observed\ HES\ flares}{Date\ of\ study\ withdrawal - Date\ of\ first\ dose\ of\ mepolizumab + 1}$$

The number of HES flares is the number of unique starting dates for HES flares. To be considered as a separate episode of HES flare, the start date of a HES flare must be at least 14 days apart from the resolution date of the preceding HES flare.

- For flares meeting endpoint definition b), each subsequent course of blinded active OCS beyond 14 days from the resolution date of the preceding flare will be considered as an additional flare (e.g., 3 courses of blinded active OCS are considered as 2 flares, 4 courses of blinded active OCS are considered as 3 flares, etc.).

Subjects who have an elevated blood eosinophil level (2 x baseline value or baseline value + 2500 cells/μL) during the 32-week study treatment period

- Subjects with elevated blood eosinophils either 2 x baseline value or baseline value + 2500 cells/μL during the 32-week study treatment period will be identified from the central laboratory haematology results. Samples taken from the date of first dose of study medication up until the date of Visit 11 (Week 32) will be considered in the derivation. Baseline will be defined as in Section 5.2.

Worst Level of Fatigue in Past 24 Hours (BFI Item 3)

- A BFI item 3 score for baseline and each week of treatment will be derived by taking the mean of up to 7 available daily assessments in each week of treatment.
- Assessment windows defining each week will be based on the date recorded for each BFI assessment and are defined in Section 16.3.1.

HES Symptom Severity Based on HES Daily Symptoms (HES-DS)

- For each of the 6 symptom domains (muscle/joint pain, chills or sweats, abdominal pain or bloating, breathing symptoms, nasal or sinus symptoms and skin symptoms, a symptom score for baseline and each week of treatment will be derived by taking the mean of up to 7 available daily assessments in each weekly assessment window.
- Assessment windows defining each week will be based on the date recorded for each HES-DS assessment and are defined in Section 16.3.1.
- A symptom score for most bothersome symptoms will be derived by taking the mean of the symptom scores for the up to 3 symptom domains identified by the subject as most bothersome at visit 2 (Week 0).

BFI Total Score
• The BFI total score (range 0 – 10) will be calculated as the mean of the 9 domain scores (range 0 – 10) recorded for the weekly assessment. If less than 4 domain scores are complete, the BFI total score will be set to missing.

16.6.5. Safety

Adverse Events
Drug Related AEs
AEs with relationship marked 'YES' or relationship missing.
AEs Leading to Permanent Discontinuation from Study Treatment or Withdrawal from the Study
AEs with action marked "Study treatment withdrawn" or withdrawn from study status marked "YES", or a response to either of these questions is missing.
AEs on Day of Dosing
AEs with an onset date equal to a study treatment dosing date and an onset time on or after the study treatment dosing time.
AE Time Since First Dose
• If AE onset time is missing, calculate in days as follows:- o If AE start date < Date of first dose of study treatment then Time since first dose = AE start date - Date of first dose of study treatment o If AE start date ≥ Date of first dose of study treatment then Time since first dose = AE start date – Date of first dose of study treatment +1 o Missing if AE start date or date of first dose of study treatment is missing. • If AE onset time is present, calculate in days, hours, minutes as Time since first dose = AE start date/time – Date/time of first dose of study treatment
AE Duration (Days)
• If AE onset time is missing, calculate in days as AE end date – AE start date + 1 • If AE onset time is present, calculate in days, hours and minutes as AE end date/time – AE start date/time • Missing if AE start date or end date is missing.
AEs of Special Interest
• See Section 11.1.1.
ECG
• QTc(B) (msec) will be derived from QT (uncorrected in msec) and RR interval (msec) as $QTc(B) = \frac{QT}{\sqrt{\frac{RR}{1000}}}$

16.7. Appendix 7: Reporting Standards for Missing Data

16.7.1. Premature Withdrawals

Element	Reporting Detail
General	• A subject will be considered to have **completed study treatment** if they receive study treatment at week 28 (Visit 10). • For the purpose of the primary endpoint, a subject will be considered to have **completed the study** if they continue to participate in the study until Week 32 (Visit 11). If a subject's last dose of study treatment is on Week 24 (Visit 9) or Week 28 (Visit 10) *and* the subject does not continue into the open-label extension study 205203 after completing Visit 11 assessments (32 weeks from randomization), then the protocol requires an up to 8-week additional follow-up period, concluding with the 12-weeks post last dose follow-up visit (Visit 12). Subjects who continue to participate in the study until Week 32 (Visit 11) but withdraw from the study prior to the final follow-up visit (Visit 12) will be documented separately in the study disposition table. • Subjects who discontinue study treatment or withdraw early will not be replaced in the study.
Pre-Screen and Run-in Failures	• A subject will be assigned a subject number at the time when the informed consent form (ICF) is signed. A subject who is assigned a subject number but does not complete any Visit 1 procedures will be considered a **pre-screen failure.** • **Screen failures** are defined as subjects who consent to participate in the clinical trial but are never subsequently randomised.

16.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument. These data will be indicated by the use of a "blank" in subject listing displays, unless all data for a specific visit are missing in which case the data is excluded from the listing. • BLQ is not missing data and must be displayed as such and included in all listings and summaries. For blood eosinophil and IL-5 data, see Section 10.1.5 and Section 10.2.5 respectively. For PK data, refer to Section 16.5.3.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

16.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
HES Flare and Adverse Events	• Any partial dates for HES flare and adverse events will be raised to data management. If the full date cannot be ascertained, the following assumptions will be made:

Element	Reporting Detail
	○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month. ○ However, if this imputation results in a date prior to the first dose of study treatment and the event could possibly have occurred during treatment from the partial information, then the date of the first dose of study treatment will be assumed to be the start date. ○ The event will then be considered to start on-treatment (worst case). ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • The recorded partial date will be displayed in listings.
Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

16.8. Appendix 8: Values of Potential Clinical Importance

16.8.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Age Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	12+	0.201	0.599
Haemoglobin	G/L	12+	71	199
Platelet Count	GI/L	1+	31	1499
White Blood Cell Count (WBC)	GI/L	12+	1.1	

Clinical Chemistry				
Laboratory Parameter	**Units**	**Age Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
ALT	U/L	3-12		>143 (and Total Bilirubin >43)
	U/L	13+		>239 (and Total Bilirubin >43)
Calcium	mmol/L	3+	1.50	3.24
Glucose	mmol/L	1+	2.2	27.8
Phosphorus, Inorg	mmol/L	3+	0.32	
Potassium	mmol/L	3+	2.8	6.5
Sodium	mmol/L	0+	120	160
Creatine Phosphokinase	IU/L	12+		>5 x ULN

Possible Hy's Law Cases			
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**
ALT, Bilirubin			ALT ≥ 3xULN and Bilirubin ≥ 2xULN (>35% direct)
ALT, INR			ALT ≥ 3xULN and INR > 1.5

NOTES:

- ULN = Upper Limit of Normal.

16.8.2. Urinalysis

As per GSK IDSL display standards, a subject is considered to have urinalysis results of PCI if there is an increase in Protein or an increase in Occult Blood results during the study, or if microscopy is performed.

16.9. Appendix 9: Abbreviations & Trade Marks

16.9.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
A&R	Analysis and Reporting
BFI	Brief Fatigue Index
BLQ	Below limit of quantification
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GSK	GlaxoSmithKline
HCRU	Healthcare Resource Utilisation
HES-DS	HES Daily Symptoms
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
ITT	Intent-To-Treat
J2R	Jump to Reference
MAR	Missing at Random
MMRM	Mixed Model Repeated Measures
MSAS-SF	Modified Memorial Symptom Assessment Scale – Short Form
MUGA	Multigated Aquisition
OCS	Oral Corticosteroid
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
Pop-PK	Population PK
Pop-PKPD	Population PKPD
PROMIS	Patient Reported Outcome Measurement Information System
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate

Abbreviation	Description
RAP	Reporting & Analysis Plan
RMC	Respiratory Medication Class
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SDTM	Study Data Tabulation Model
SoC	Standard of Care
SSR	Subject-Rated Symptom Severity
TFL	Tables, Figures & Listings

16.9.2. Trademarks

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16.10. Appendix 10: List of Data Displays

16.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.n	1.1 to 1.n
Efficacy	2.1 to 2.n	2.1 to 2.n
Health Outcome Tables	3.1 to 3.n	3.1 to 3.n
Safety	4.1 to 4.n	4.1 to 4.n
Pharmacokinetic	5.1 to 5.n	5.1 to 5.n
Pharmacodynamic and / or Biomarker	6.1 to 6.n	6.1 to 6.n
Pharmacokinetic / Pharmacodynamic	7.1 to 7.n	7.1 to 7.n
Section	**Listings**	
ICH Listings	1 to x	

16.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 11: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Population Pharmacokinetic (PopPK)	POPPK_Fn	POPPK_Tn	POPPK_Ln
Pharmacodynamic and / or Biomarker	PD_Fn	PD_Tn	PD_Ln
Pharmacokinetic / Pharmacodynamic	PKPD_Fn	PKPD_Tn	PK/PD_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

16.10.3. Deliverables

Deliverable	Description
Headline	Headline results
SAC	Final Statistical Analysis Complete

16.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	ITT	ES1	Summary of Subject Disposition	Include Completed, Withdrawn and subsets of completed/withdrawn as follows:- Completed, Completed Week 32 and entered 205203, Completed Week 32 and Follow-up Withdrawn, Withdrawn prior to Week 32, Completed Week 32 and withdrawn prior to Follow up	SAC
1.2.	ITT	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		SAC
1.3.	ITT	*POP_T1*	Summary of Subject Accountability During 32-Week Treatment Period		SAC
1.4.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	As a subset of "Enrolled" subjects, also include the number of subjects for whom inclusion criteria #5 is based on local rather than central laboratory result. Use text "Inclusion criteria #5 based on local laboratory result [1]", and add footnote: "[1] The number of subjects for whom the screening central laboratory blood eosinophil count is <1000 cells/uL but a local laboratory blood eosinophil count ≥1000 cells/uL was used to meet study inclusion criteria."	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.5.	Enrolled	NS1	Summary of Number of Subjects by Country and Site ID		SAC
Protocol Deviation					
1.6.	ITT	DV1	Summary of Important Protocol Deviations		SAC
Population Analysed					
1.7.	Screened	SP1	Summary of Study Populations		Headline
1.8.	ITT	SP2	Summary of Exclusions from the Per Protocol Population		SAC
Demographic and Baseline Characteristics					
1.9.	ITT	DM1	Summary of Demographic Characteristics		SAC
1.10.	Enrolled	DM11	Summary of Age Ranges		SAC
1.11.	ITT	DM5	Summary of Race and Racial Combinations		SAC
1.12.	ITT	*POP_T8*	Summary of Duration of HES		SAC
Prior and Concomitant Medications/Conditions					
1.13.	ITT	*POP_T2*	Summary of Baseline HES Therapy		SAC
1.14.	ITT	*POP_T3*	Summary of Baseline Prednisone Equivalent Daily Dose		Headline
1.15.	ITT	CM1	Summary of Concomitant Medications		SAC
1.16.	ITT	MH4	Summary of Current Medical Conditions		SAC
1.17.	ITT	MH4	Summary of Past Medical Conditions		SAC
Exposure and Treatment Compliance					
1.18.	ITT	*POP_T4*	Summary of Exposure (Therapeutic Coverage) to Study Treatment		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.19.	ITT	*POP_T5*	Summary of Number of Treatments Administered		SAC
Most Bothersome HES Symptoms					
1.20.	ITT	*POP_T6*	Summary of Most Bothersome HES Related Symptoms		SAC
Steroid Perception Questionnaire					
1.21.	ITT	*POP_T7*	Summary of Steroid Perception Questionnaire		SAC

16.10.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
HES Flare					
2.1.	ITT	*EFF_T1*	Overview of HES Flares		SAC
2.2.	ITT	*EFF_T2*	Summary of Frequency of All HES Flares		SAC
2.3.	ITT	*EFF_T3*	Primary Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period (Treatment Policy Estimand)		Headline
2.4.	ITT	*EFF_T3a*	Supportive Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period (While on Treatment Estimand)		Headline
2.5.	PP	*EFF_T3*	Supportive Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period (Treatment Policy Estimand, PP Population)		Headline
2.6.	ITT	*EFF_T3b*	Sensitivity Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period (Treatment Policy Estimand, Alternative Missing Data Imputation Strategy #1)		Headline
2.7.	ITT	*EFF_T3c*	Sensitivity Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period (Treatment Policy Estimand, Alternative Missing Data Imputation Strategy #2)		Headline
2.8.	ITT	*EFF_T3*	Sensitivity Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period (Treatment Policy Estimand, Excluding Subjects From Site PPD		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.9.	ITT	*EFF_T3*	Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period by Age (Treatment Policy Estimand)	Descriptive summary only; do not present p-values.	SAC
2.10.	ITT	*EFF_T3*	Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period by Sex (Treatment Policy Estimand)	Descriptive summary only; do not present p-values.	SAC
2.11.	ITT	*EFF_T3*	Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period by Race (Treatment Policy Estimand)	Descriptive summary only; do not present p-values.	SAC
2.12.	ITT	*EFF_T3*	Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period by Region (Treatment Policy Estimand)	Descriptive summary only; do not present p-values.	SAC
2.13.	ITT	*EFF_T3*	Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period by Baseline OCS (Treatment Policy Estimand)	Descriptive summary only; do not present p-values.	SAC
2.14.	ITT	*EFF_T3*	Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period by Baseline Blood Eosinophils (Treatment Policy Estimand)	Descriptive summary only; do not present p-values.	SAC
2.15.	ITT	*EFF_T4*	Analysis of Time to First HES Flare (Treatment Policy Estimand)	Add footnote: “Note: Subjects withdrawing from the study prematurely are censored at the date of study withdrawal.”	Headline
2.16.	ITT	*EFF_T4a*	Sensitivity Analysis of Time to First HES Flare (Treatment Policy Estimand, Alternative Missing Data Imputation Strategy #1)	Add footnote: “Note: Subjects withdrawing from the study prematurely prior to reporting a HES flare are included with a HES flare on the date of study withdrawal.”	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.17.	ITT	*EFF_T4b*	Sensitivity Analysis of Time to First HES Flare (Treatment Policy Estimand, Alternative Missing Data Imputation Strategy #2)	Add footnote: "Note: Subjects withdrawing from the study prematurely prior to reporting a HES flare, with primary reason for treatment withdrawal reported as Adverse Event or Lack of Efficacy are included with a HES flare on the date of study withdrawal. For subjects withdrawing from the study prematurely prior to reporting a HES flare, with any other reason for discontinuation of study treatment, the event time will be censored at the date of study withdrawal."	SAC
2.18.	ITT	*EFF_T3*	Analysis of Proportion of Subjects Who Experience a HES Flare During Week 20 Through Week 32 (Treatment Policy Estimand)		SAC
2.19.	ITT	*EFF_T3*	Sensitivity Analysis of Proportion of Subjects Who Experience a HES Flare During Week 20 Through Week 32 (Treatment Policy Estimand, Alternative Missing Data Imputation Strategy #1)		SAC
2.20.	ITT	*EFF_T3*	Sensitivity Analysis of Proportion of Subjects Who Experience a HES Flare During Week 20 Through Week 32 (Treatment Policy Estimand, Alternative Missing Data Imputation Strategy #2)		SAC
2.21.	ITT	*EFF_T5*	Analysis of Rate of HES Flares (Treatment Policy Estimand)	Add footnote: "Note: For subjects withdrawing prematurely from the study during the 32-week treatment period, all data up to the time of study withdrawal is used to calculate the rate of HES flares."	Headline
2.22.	ITT	*EFF_T5a*	Sensitivity Analysis of Rate of HES Flares (Treatment Policy Estimand, Jump to Reference Negative Binomial Model)		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Daily Fatigue Severity - Worst Level of Fatigue in Past 24 Hours (BFI Item 3)					
2.23.	ITT	*EFF_T6*	Summary of Mean Daily Fatigue Severity - Worst Level of Fatigue in Past 24 Hours (BFI Item 3) (Treatment Policy Estimand)	Present Baseline (week 0) up Week 32.	SAC
2.24.	ITT	*EFF_T7*	Analysis of Change from Baseline in Mean Daily Fatigue Severity - Worst Level of Fatigue in Past 24 Hours (BFI Item 3) – at Week 32 (Treatment Policy Estimand)		SAC
2.25.	ITT	*EFF_T8*	Analysis of Change from Baseline in Mean Daily Fatigue Severity - Worst Level of Fatigue in Past 24 Hours (BFI Item 3) (Treatment Policy Estimand, Mixed Model Repeated Measures)		SAC
2.26.	ITT	*EFF_T9*	Summary of P-values for Primary and Secondary Endpoints (Treatment Policy Estimand)		SAC
Elevated Blood Eosinophil Level					
2.27.	ITT	*EFF_T10*	Analysis of Proportion of Subjects Who Have an Elevated Blood Eosinophil Count (2 x Baseline Value or Baseline Value + 2500 cells/μL) During the 32-Week Treatment Period (Treatment Policy Estimand)		SAC
FEV_1, FVC, FEV_1/FVC Ratio					
2.28.	ITT	*EFF_T6*	Summary of FEV1, FVC and FEV1/FVC	Add a by-line for parameter. Column header “Visit” rather than “Analysis Time Point”.	SAC
2.29.	ITT	*EFF_T8*	Analysis of Change from Baseline in FEV1 (Treatment Policy Estimand, Mixed Model Repeated Measures)		SAC
2.30.	ITT	*EFF_T8*	Analysis of Change from Baseline in FVC (Treatment Policy Estimand, Mixed Model Repeated Measures)		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.31.	ITT	*EFF_T6*	Summary of FEV1, FVC and FEV1/FVC - Excluding Data where SABA/LABA was Taken Within 6/12 Hours Respectively	Add a by-line for parameter. Column header "Visit" rather than "Analysis Time Point".	SAC
2.32.	ITT	*EFF_T8*	Analysis of Change from Baseline in FEV1 - Excluding Data where SABA/LABA was Taken Within 6/12 Hours Respectively (Treatment Policy Estimand, Mixed Model Repeated Measures)		SAC
2.33.	ITT	*EFF_T8*	Analysis of Change from Baseline in FVC - Excluding Data where SABA/LABA was Taken Within 6/12 Hours Respectively (Treatment Policy Estimand, Mixed Model Repeated Measures)		SAC
ECHO/MUGA					
2.34.	ITT	*EFF_T16*	Summary of ECHO/MUGA		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
HES Symptom Severity (HES-DS)					
2.35.	ITT	*EFF_T6a*	Summary of Most Bothersome HES Symptom Severity Score (HES-DS)	Includes number (%) of subjects with no reported symptoms.	SAC
2.36.	ITT	*EFF_T7*	Analysis of Change from Baseline in Most Bothersome HES Symptom Severity Score (HES-DS) at Week 32 (Treatment Policy Estimand)	Scale 0 = None to 10 = As bad as you can imagine.	SAC
2.37.	ITT	*EFF_T8*	Analysis of Change from Baseline in Most Bothersome HES Symptom Severity Score (HES-DS) (Treatment Policy Estimand, Mixed Model Repeated Measures)	Scale 0 = None to 10 = As bad as you can imagine.	SAC
2.38.	ITT	*EFF_T6a*	Summary of HES Symptom Severity Score (HES-DS) by Symptom	Includes number (%) of subjects with no reported symptoms. Use T_EFF6a with Endpoint = Symptom Severity Score and by line for symptom domain. Add footnote "Note: 1. The mean of the available assessments on the 7 days up to and including the date of each study visit is used as the value for that visit. For time points between visits i.e week 1, 2, 3, 5, 6, 7, 9, 10, 11, 13, 14, 15, 17, 18, 19, 21, 22, 23, 25, 26, 27, 29, 30, 31, the number of available assessments depends on the elapsed time between visits. 2. Scale 0 = None to 10 = As bad as you can imagine."	SAC
2.39.	ITT	*EFF_T7*	Analysis of Change from Baseline HES Symptom Severity Score (HES-DS) by Symptom at Week 32 (Treatment Policy Estimand)	Use T_EFF7 with by line for symptom domain. Scale 0 = None to 10 = As bad as you can imagine	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.40.	ITT	*EFF_T8*	Analysis of Change from Baseline in HES Symptom Severity Score (HES-DS) by Symptom (Treatment Policy Estimand, Mixed Model Repeated Measures)	Use T_EFF8 with by line for symptom domain. Scale 0 = None to 10 = As bad as you can imagine.	SAC
Weekly Fatigue Severity – BFI Total Scores					
2.41.	ITT	*EFF_T6*	Summary of Total BFI Score	Present Baseline (week 0) up Week 32. Scale: 0 = No fatigue/Does not interfere to 10 = As bad as you can imagine/Completely interferes.	SAC
2.42.	ITT	*EFF_T7*	Analysis of Change from Baseline in Total BFI Score at Week 32 (Treatment Policy Estimand)	Scale: 0 = No fatigue/Does not interfere to 10 = As bad as you can imagine/Completely interferes.	SAC
2.43.	ITT	*EFF_T8*	Analysis of Change from Baseline in Total BFI Score (Treatment Policy Estimand, Mixed Model Repeated Measures)	Scale: 0 = No fatigue/Does not interfere to 10 = As bad as you can imagine/Completely interferes.	SAC
Clinical- and Subject- Rated Overall Response to Therapy					
2.44.	ITT	*EFF_T11*	Summary of Clinician-Rated Overall Response to Therapy		SAC
2.45.	ITT	*EFF_T12*	Analysis of Clinician-Rated Overall Response to Therapy (Treatment Policy Estimand)		SAC
2.46.	ITT	*EFF_T11*	Summary of Subject-Rated Overall Response to Therapy		SAC
2.47.	ITT	*EFF_T12*	Analysis of Subject-Rated Overall Response to Therapy (Treatment Policy Estimand)		SAC
Subject-Rated Symptom Severity (SSR)					
2.48.	ITT	*EFF_T13*	Summary of Subject-Rated Symptom Severity		SAC
2.49.	ITT	*EFF_T12*	Analysis of Subject-Rated Symptom Severity at Week 32 (Treatment Policy Estimand)		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Modified Memorial Symptom Assessment Scale-Short Form (MSAS-SF)					
2.50.	ITT	*EFF_T6*	Summary of MSAS-SF Total and Subscale Scores	Include by line: Total MSAS-SF Score, MSAS-SF Global Distress Index, MSAS-SF Physical Subscale Score, MSAS-SF Psychological Subscale Score. Present Baseline (week 0) up Week 32. Column header "Visit" rather than "Analysis Time Point". Add footnote: "Scale 0 = Not at all distressed or bothered/No symptoms to 4 = Very much distressed or bothered/Almost constant symptoms."	SAC
2.51.	ITT	*EFF_T7*	Analysis of Change from Baseline in MSAS-SF Total and Subscale Scores at Week 32 (Treatment Policy Estimand)	Include by line: Total MSAS-SF Score, MSAS-SF Global Distress Index, MSAS-SF Physical Subscale Score, MSAS-SF Psychological Subscale Score. Scale 0 = Not at all distressed or bothered/No symptoms to 4 = Very much distressed or bothered/Almost constant symptoms.	SAC
2.52.	ITT	*EFF_T8*	Analysis of Change from Baseline in MSAS-SF Total and Subscale Scores (Treatment Policy Estimand, Mixed Model Repeated Measures)	Include by line: Total MSAS-SF Score, MSAS-SF Global Distress Index, MSAS-SF Physical Subscale Score, MSAS-SF Psychological Subscale Score. Scale 0 = Not at all distressed or bothered/No symptoms to 4 = Very much distressed or bothered/Almost constant symptoms.	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PROMIS Physical Function and Sleep					
2.53.	ITT	*EFF_T6*	Summary of PROMIS Physical Function Score	Present Baseline (week 0) up Week 32. Column header "Visit" rather than "Analysis Time Point". Add footnote: "Scale 1 = Cannot do/unable to do to 5 = Not at all/Without any difficulty."	SAC
2.54.	ITT	*EFF_T7*	Analysis of Change from Baseline in PROMIS Physical Function Score at Week 32 (Treatment Policy Estimand)	Scale 1 = Cannot do/unable to do to 5 = Not at all/Without any difficulty.	SAC
2.55.	ITT	*EFF_T8*	Analysis of Change from Baseline in PROMIS Physical Function Score (Treatment Policy Estimand, Mixed Model Repeated Measures)	Scale 1 = Cannot do/unable to do to 5 = Not at all/Without any difficulty.	SAC
2.56.	ITT	*EFF_T6*	Summary of PROMIS Sleep Score	Present Baseline (week 0) up Week 32. Column header "Visit" rather than "Analysis Time Point". Add footnote: "Scale 1 = Not at all difficulty in falling asleep /Never trouble staying asleep to 5 = Very much difficulty in falling asleep /Always trouble staying asleep."	SAC
2.57.	ITT	*EFF_T7*	Analysis of Change from Baseline in PROMIS Sleep Score at Week 32 (Treatment Policy Estimand)	Scale 1 = Not at all difficulty in falling asleep /Never trouble staying asleep to 5 = Very much difficulty in falling asleep /Always trouble staying asleep.	SAC
2.58.	ITT	*EFF_T8*	Analysis of Change from Baseline in PROMIS Sleep Score (Treatment Policy Estimand, Mixed Model Repeated Measures)	Scale 1 = Not at all difficulty in falling asleep /Never trouble staying asleep to 5 = Very much difficulty in falling asleep /Always trouble staying asleep.	SAC

16.10.6. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
HES Flare					
2.1.	ITT	*EFF_F1*	Cumulative Number of HES Flares		Headline
2.2.	ITT	*EFF_F2*	Analysis of Proportion of Subjects with HES Flare During the 32-Week Treatment Period	Present odds ratios and 95% CI from 5 analyses of the primary endpoint on one figure: Primary estimand, While on treatment estimand, Per protocol population, Alternative missing data imputation strategy #1, Alternative missing data imputation strategy #2.	Headline
2.3.	ITT	*EFF_F3*	Kaplan-Meier Cumulative Incidence Curve for Time to First HES Flare		SAC
2.4.	ITT	*EFF_F2*	Analysis of Time to First HES Flare (Treatment Policy Estimand)	Present relative risk and 95% CI from 3 analyses corresponding to 3 missing data imputation strategies: Primary estimand, Alternative missing data imputation strategy #1, Alternative missing data imputation strategy #2	SAC
2.5.	ITT	-	Exploratory Modelling of Proportion of Subjects with HES Flare During the 32-Week Treatment Period vs Baseline Blood Eosinophils		SAC
2.6.	ITT	*EFF_F2*	Analysis of Proportion of Subjects with HES Flare During Week 20 Through Week 32 (Treatment Policy Estimand)	Present odds ratio and 95% CI from 3 analyses corresponding to 3 missing data imputation strategies: Primary estimand, Alternative missing data imputation strategy #1, Alternative missing data imputation strategy #2	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.7.	ITT	*EFF_F2*	Analysis of Rate of HES Flare (Treatment Policy Estimand)	Present rate ratio and 95% CI from two analyses: Primary estimand, Jump to reference	SAC
Worst Level of Fatigue in Past 24 Hours (BFI Item 3)					
2.8.	ITT	*EFF_F6*	Cumulative Distribution Plot for the Change from Baseline in Mean Daily Fatigue Severity - Worst Level of Fatigue in Past 24 Hours (BFI Item 3) – at Week 32		SAC
2.9.	ITT	*EFF_F4*	Change from Baseline in Fatigue Severity - Worst Level of Fatigue in Past 24 Hours (BFI Item 3) (Treatment Policy Estimand, Mixed Model Repeated Measures)	Present adjusted mean (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 12, 16, 20, 24, 28, 32. Add footnote: "Note: Adjusted for baseline (week 0) BFI item 3 score and region".	SAC
2.10.	ITT	*EFF_F5*	Change from Baseline in Fatigue Severity - Worst Level of Fatigue in Past 24 Hours (BFI Item 3) - Treatment Difference vs Placebo (Treatment Policy Estimand, Mixed Model Repeated Measures)	Present adjusted mean treatment difference (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 12, 16, 20, 24, 28, 32. Add footnote: "Note: Adjusted for baseline (week 0) BFI item 3 score and region".	SAC
FEV_1 and FVC					
2.11.	ITT	*EFF_F4*	Change from Baseline in FEV_1 (Treatment Policy Estimand, Mixed Model Repeated Measures)		SAC
2.12.	ITT	*EFF_F5*	Change from Baseline in FEV_1 - Treatment Difference vs Placebo (Treatment Policy Estimand, Mixed Model Repeated Measures)		SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.13.	ITT	*EFF_F4*	Change from Baseline in FVC (Treatment Policy Estimand, Mixed Model Repeated Measures)		SAC
2.14.	ITT	*EFF_F5*	Change from Baseline in FVC - Treatment Difference vs Placebo (Treatment Policy Estimand, Mixed Model Repeated Measures)		SAC
HES Symptom Severity (HES-DS)					
2.15.	ITT	*EFF_F4*	Change from Baseline in Most Bothersome HES Symptom Severity Score (HES-DS) (Treatment Policy Estimand, Mixed Model Repeated Measures)	Present adjusted mean (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 12, 16, 20, 24, 28, 32. Add footnote: "Note: Adjusted for baseline (week 0) most bothersome symptom score and region".	SAC
2.16.	ITT	*EFF_F5*	Change from Baseline in Most Bothersome HES Symptom Severity Score (HES-DS) - Treatment Difference vs Placebo (Treatment Policy Estimand, Mixed Model Repeated Measures)	Present adjusted mean treatment difference (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 12, 16, 20, 24, 28, 32. Add footnote: "Note: Adjusted for baseline (week 0) most bothersome symptom score and region".	SAC
2.17.	ITT	*EFF_F4*	Change from Baseline in HES Symptom Severity Score (HES-DS) by Symptom (Treatment Policy Estimand, Mixed Model Repeated Measures)	One page per domain with byline. Present adjusted mean (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 12, 16, 20, 24, 28, 32. Add footnote: "Note: Adjusted for baseline (week 0) symptom score and region".	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.18.	ITT	*EFF_F5*	Change from Baseline in HES Symptom Severity Score (HES-DS) by Symptom - Treatment Difference vs Placebo (Treatment Policy Estimand, Mixed Model Repeated Measures)	One page per domain with byline. Present adjusted mean treatment difference (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 12, 16, 20, 24, 28, 32. Add footnote: "Note: Adjusted for baseline (week 0) symptom score and region".	SAC
Weekly Fatigue Severity – BFI Total Scores					
2.19.	ITT	*EFF_F4*	Change from Baseline in Total BFI Score (Treatment Policy Estimand, Mixed Model Repeated Measures)	Present adjusted mean (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 12, 16, 20, 24, 28, 32. Add footnote: "Note: Adjusted for baseline (week 0) total BFI score and region".	SAC
2.20.	ITT	*EFF_F5*	Change from Baseline in Total BFI Score - Treatment Difference vs Placebo (Treatment Policy Estimand, Mixed Model Repeated Measures)	Present adjusted mean treatment difference (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 12, 16, 20, 24, 28, 32. Add footnote: "Note: Adjusted for baseline (week 0) total BFI score and region".	SAC
Modified Memorial Symptom Assessment Scale-Short Form (MSAS-SF)					

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.21.	ITT	*EFF_F4*	Change from Baseline in MSAS-SF Total and Subscale Scores (Treatment Policy Estimand, Mixed Model Repeated Measures)	One plot per page, 4 pages with by line: Total MSAS-SF Score, MSAS-SF Global Distress Index, MSAS-SF Physical Subscale Score, MSAS-SF Psychological Subscale Score. Present adjusted mean (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 16, 24, 32. Add footnote: "Note: Adjusted for baseline (week 0) score and region. Scale: 0 = Not at all distressed or bothered/No symptoms to 4 = Very much distressed or bothered/Almost constant symptoms."	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.22.	ITT	*EFF_F5*	Change from Baseline in MSAS-SF Total and Subscale Scores - Treatment Difference vs Placebo (Treatment Policy Estimand, Mixed Model Repeated Measures)	Either one plot per page, 4 pages with by line, or 4 lines on one plot, as data permit: Total MSAS-SF Score, MSAS-SF Global Distress Index, MSAS-SF Physical Subscale Score, MSAS-SF Psychological Subscale Score. Present adjusted mean treatment difference (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 12, 16, 20, 24, 28, 32. Add footnote: "Note: Adjusted for baseline (week 0) score and region. Scale: 0 = Not at all distressed or bothered/No symptoms to 4 = Very much distressed or bothered/Almost constant symptoms."	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PROMIS Physical Function and Sleep					
2.23.	ITT	*EFF_F4*	Change from Baseline in PROMIS Physical Function and Sleep Score (Treatment Policy Estimand, Mixed Model Repeated Measures)	One plot per page, 2 pages with by line: PROMIS Physical Function Score, PROMIS Sleep Score. Present adjusted mean (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 16, 24, 32. Add footnote: "Note: 1. Adjusted for baseline (week 0) score and region. 2. Sleep score scale 1 = Not at all difficulty in falling asleep /Never trouble staying asleep to 5 = Very much difficulty in falling asleep /Always trouble staying asleep. 3. Physical function scale 0 = Not at all distressed or bothered/No symptoms to 4 = Very much distressed or bothered/Almost constant symptoms."	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.24.	ITT	*EFF_F5*	Change from Baseline in PROMIS Physical Function and Sleep Score - Treatment Difference vs Placebo (Treatment Policy Estimand, Mixed Model Repeated Measures)	Either one plot per page, 2 pages with by line, or 2 lines on one plot, as data permit: PROMIS Physical Function Score, PROMIS Sleep Score. Present adjusted mean treatment difference (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 16, 24, 32. Add footnote: "Note: 1. Adjusted for baseline (week 0) score and region. 2. Sleep score scale 1 = Not at all difficulty in falling asleep /Never trouble staying asleep to 5 = Very much difficulty in falling asleep /Always trouble staying asleep. 3. Physical function scale 0 = Not at all distressed or bothered/No symptoms to 4 = Very much distressed or bothered/Almost constant symptoms."	SAC

16.10.7. Health Outcomes Tables

Health Outcomes: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
SF-36					
3.1.	ITT	*EFF_T6*	Summary of SF-36 Health Survey Domain Scores	Include change from baseline values. Include 95% CIs for the mean.	SAC
3.2.	ITT	*EFF_T6*	Summary of SF-36 Health Survey Component Summary Scores	Include change from baseline values Include 95% CIs for the mean.	SAC
Healthcare Resource Utilisation					
3.3.	ITT	*EFF_T14*	Summary of Healthcare Resource Utilisation Associated with HES Flare		SAC
Work Productivity and Activity Impairment Questionnaire					
3.4.	ITT	*EFF_T15*	Summary of Work Productivity and Activity Impairment		SAC

16.10.8. Safety Tables

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Adverse Event Overview					
4.1.	Safety	*SAFE_T1*	Adverse Event Overview		SAC
Adverse Events					
4.2.	Safety	AE1	Summary of All On-Treatment Adverse Events by System Organ Class and Preferred Term		SAC
4.3.	Safety	AE1	Summary of All Post-Treatment Adverse Events by System Organ Class and Preferred Term		SAC
4.4.	Safety	AE3	Summary of Common (>=3% Incidence) On-Treatment Adverse Events by Overall Frequency		SAC
4.5.	Safety	AE15	Summary of Common (>=3% Incidence) On-Treatment Non-Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
4.6.	Safety	AE5A	Summary of All On-Treatment Adverse Events by Maximum Intensity by System Organ Class and Preferred Term		SAC
4.7.	Safety	AE1	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term		SAC
4.8.	Safety	AE5A	Summary of All Drug-Related Adverse Events by Maximum Intensity by System Organ Class and Preferred Term		SAC
4.9.	Safety	AE1	Summary of Non-Serious Drug-Related Adverse Events by System Organ Class and Preferred Term		SAC
4.10.	Safety	AE1	Summary of On-Treatment Adverse Events by Highest Post-Baseline Binding Antibody Result	Add in row with n in each binding antibody result category.	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
4.11.	Safety	AE3	Summary of All Adverse Events Leading to Permanent Discontinuation from Study Treatment by Overall Frequency		SAC
4.12.	Safety	AE3	Summary of All Adverse Events Leading to Withdrawal from the Study by Overall Frequency		SAC
4.13.	Safety	AE1	Summary of Adverse Events Reported on the Day of Dosing by System Organ Class and Preferred Term		SAC
4.14.	Safety	AE7	Listing of Subject Numbers for Individual On-Treatment Adverse Events		SAC
4.15.	Safety	AE7	Listing of Subject Numbers for Individual Post-Treatment Adverse Events		SAC
4.16.	Safety	AE2	Listing of Relationship of Adverse Event, System Organ Classes, Preferred Terms and Verbatim Text		SAC
Serious Adverse Events					
4.17.	Safety	AE3	Summary of Fatal Serious Adverse Events by Overall Frequency		Headline
4.18.	Safety	AE3	Summary of Drug-Related Fatal Serious Adverse Events by Overall Frequency		SAC
4.19.	Safety	AE3	Summary of Non-Fatal Serious Adverse Events by Overall Frequency		SAC
4.20.	Safety	AE3	Summary of All Serious Adverse Events by Overall Frequency		Headline
4.21.	Safety	AE1	Summary of All On-Treatment Serious Adverse Events by System Organ Class and Preferred Term		SAC
4.22.	Safety	AE1	Summary of All Post-Treatment Serious Adverse Events by System Organ Class and Preferred Term		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
4.23.	Safety	AE1	Summary of All Pre-Treatment Serious Adverse Events by System Organ Class and Preferred Term		SAC
4.24.	Safety	AE16	Summary of All Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
4.25.	Safety	AE1	Summary of All Drug-Related Serious Adverse Events by System Organ Class and Preferred Term		SAC
Adverse Events of Special Interest					
4.26.	Safety	*SAFE_T5*	Summary of On-Treatment Serious AEs and AEs of Special Interest Incidence, Relative Risk and Risk Difference – Mepolizumab 300mg SC vs Placebo		SAC
4.27.	Safety	AE1	Summary of On-Treatment Adverse Events Reported by the Investigator as Systemic Reactions Meeting the Criteria for Anaphylaxis		SAC
4.28.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Reported by the Investigator as Systemic Reactions Meeting the Criteria for Anaphylaxis		SAC
4.29.	Safety	AE1	Summary of On-Treatment Adverse Events Reported by the Investigator as Systemic Reactions - Allergic (Type I Hypersensitivity) and Other Systemic		SAC
4.30.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Reported by the Investigator as Systemic Reactions - Allergic (Type I Hypersensitivity) and Other Systemic		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
4.31.	Safety	AE1	Summary of On-Treatment Adverse Events Reported by the Investigator as Systemic Reactions - Allergic (Type I Hypersensitivity)		SAC
4.32.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Reported by the Investigator as Systemic Reactions - Allergic (Type I Hypersensitivity)		SAC
4.33.	Safety	AE1	Summary of On-Treatment Adverse Events Reported by the Investigator as Systemic Reactions – Other Systemic		SAC
4.34.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Reported by the Investigator as Systemic Reactions - Other Systemic		SAC
4.35.	Safety	AE1	Summary of On-Treatment Adverse Events Reported by the Investigator as Local Injection Site Reactions		SAC
4.36.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Reported by the Investigator as Local Injection Site Reactions		SAC
4.37.	Safety	AE1	Summary of On-Treatment Adverse Events Categorised as Serious Cardiac, Vascular and Thromboembolic Events		SAC
4.38.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Categorised as Serious Cardiac, Vascular and Thromboembolic Events		SAC
4.39.	Safety	AE1	Summary of On-Treatment Adverse Events Categorised as Serious Ischemic Events		SAC
4.40.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Categorised as Serious Ischemic Events		SAC
4.41.	Safety	AE1	Summary of On-Treatment Adverse Events Categorised as Malignancies		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
4.42.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Categorised as Malignancies		SAC
4.43.	Safety	AE1	Summary of On-Treatment Adverse Events Categorised as Potential Opportunistic Infections		SAC
4.44.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Categorised as Potential Opportunistic Infections		SAC
Laboratory – Haematology					
4.45.	Safety	LB1	Summary of Haematology Changes from Baseline by Visit	Include baseline values	SAC
4.46.	Safety	LB3	Summary of Haematology Shifts from Baseline Relative to Normal Range by Visit	Include worst case post-baseline. If there are unscheduled assessments add footnote: "Note: Worst case post baseline Includes scheduled and unscheduled assessments."	SAC
4.47.	Safety	LB3	Summary of Haematology Shifts from Baseline Relative to PCI Criteria by Visit	Include worst case post-baseline. If there are unscheduled assessments add footnote: "Note: Worst case post baseline Includes scheduled and unscheduled assessments."	SAC
Laboratory – Clinical Chemistry					
4.48.	Safety	LB1	Summary of Clinical Chemistry Changes from Baseline by Visit	Include baseline values	SAC
4.49.	Safety	LB3	Summary of Clinical Chemistry Shifts from Baseline Relative to Normal Range by Visit	Include worst case post-baseline. If there are unscheduled assessments add footnote: "Note: Worst case post baseline Includes scheduled and unscheduled assessments."	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
4.50.	Safety	LB3	Summary of Clinical Chemistry Shifts from Baseline Relative to PCI Criteria by Visit	Include worst case post-baseline. If there are unscheduled assessments add footnote: "Note: Worst case post baseline Includes scheduled and unscheduled assessments."	SAC
Laboratory – Urinalysis					
4.51.	Safety	UR1	Summary of Worst Case Urinalysis Results Post-Baseline Relative to Baseline		SAC
Laboratory: Hepatobiliary (Liver)					
4.52.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting		SAC
4.53.	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities		SAC
ECG					
4.54.	Safety	EG1	Summary of ECG Findings by Visit	Include worst case post-baseline. If there are unscheduled assessments add footnote: "Note: Worst case post baseline Includes scheduled and unscheduled assessments."	SAC
4.55.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit	Include baseline values	SAC
4.56.	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category	QTc(B) and QTc(F) If there are unscheduled assessments add footnote: "Note: Includes scheduled and unscheduled assessments."	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
4.57.	Safety	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category	QTc(B) and QTc(F) If there are unscheduled assessments add footnote: "Note: Includes scheduled and unscheduled assessments."	SAC
Vital Signs					
4.58.	Safety	VS1	Summary of Vital Signs by Visit		SAC
4.59.	Safety	VS1	Summary of Change from Baseline in Vital Signs by Visit	Include baseline values	SAC
Immunogenicity					
4.60.	Safety	*SAFE_T3*	Summary of Binding Antibody by Visit	Include highest post baseline result.	SAC
4.61.	Safety	*SAFE_T3*	Summary of Binding Antibody By Visit – Subjects Without Positive Result Prior to Dosing	Post-Week 0 visits only, plus highest post baseline result.	SAC
4.62.	Safety	*SAFE_T4*	Summary of Neutralising Antibody by Visit	Include highest post baseline result.	SAC

16.10.9. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events					
4.1.	Safety	AE10	Common (>=3% Incidence) On-Treatment Adverse Events and Relative Risk		SAC
4.2.	Safety	SAFE_F1	Relative Risk of On-Treatment Serious Adverse Events and AEs of Special Interest Mepolizumab 300mg SC vs Placebo		SAC
Laboratory					
4.3.	Safety	LIVER14	Scatter Plot of Maximum vs Baseline for ALT	If there are unscheduled assessments add footnote: “Note: Maximum Value includes scheduled and unscheduled assessments.”	SAC
4.4.	Safety	LIVER9	Scatter Plot of Maximum Total Bilirubin vs Maximum ALT	If there are unscheduled assessments add footnote: “Note: Maximum Value includes scheduled and unscheduled assessments.”	SAC

16.10.10. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
5.1.	PK	PK01	Summary of Plasma Mepolizumab Concentration-Time Data (Observed and Predicted)		SAC
5.2.	PK	PK06	Summary Statistics of Individual Model Predicted Plasma Mepolizumab Pharmacokinetic Parameters (Non-transformed and Log-transformed)		SAC
5.3.	PK	-	Description and Evaluation of Key PK Models Tested	Provided by CPMS	SAC
5.4.	PK	-	Population PK Parameter Estimates with 95% CI of Final PK Model	Provided by CPMS	SAC
5.5.	PK	-	Demographics Summary	Provided by CPMS	SAC
5.6.	PK	-	Samples Summary	Provided by CPMS	SAC
5.7.	PK	-	Accumulation Ratio Estimate at Week 16 and 32	Provided by CPMS	SAC

16.10.11. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
5.1.	PK	-	Plasma Mepolizumab Concentration-Time Profiles (by Treatment)	Provided by CPMS	SAC
5.2.	PK	-	Model Goodness of Fit Plots	Provided by CPMS	SAC
5.3.	PK	-	Continuous Covariate Correlation Plot	Provided by CPMS	SAC
5.4.	PK	-	Categorical Covariate Correlation Plot	Provided by CPMS	SAC
5.5.	PK	-	Automated Covariate Selection	Provided by CPMS	SAC
5.6.	PK	-	Visual Predictive Check	Provided by CPMS	SAC
5.7.	PK	-	Observed Plasma Mepolizumab Concentration-Time Profiles by Anti-Drug Antibody Status	Provided by CPMS	SAC
5.8.	PK	-	Plasma Mepolizumab Observed/Predicted Concentration-Time Profiles (by Subject)	Provided by CPMS	SAC
5.9.	PK	-	Box Plot of Systemic Clearance versus Covariates of Interest	Provided by CPMS	SAC

16.10.12. Pharmacodynamic Tables

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Blood Eosinophils					
6.1.	PD	*PD_T1*	Summary of Blood Eosinophil Count	Include absolute blood eosinophils at Screening, Baseline and Week 2 through Week 32, and ratio to baseline values for Week 2 through Week 32. Number of decimal places as follows: geometric mean (2), SD logs (3), median (2), min (2), max (2).	SAC
6.2.	PD	*PD_T2*	Analysis of On-Treatment Ratio to Baseline Blood Eosinophils (While on Treatment Estimand, Mixed Model Repeated Measures)	Include Week 2 through Week 32.	SAC
IL-5					
6.3.	PD	*PD_T1*	Summary of Serum Total IL-5	Include absolute and ratio to baseline values. Include summary statistics for the number and % of BLQ values.	SAC
6.4.	PD	*PD_T3*	Analysis of On-Treatment Ratio to Baseline Serum Total IL-5 at Week 32 (While on Treatment Estimand)		SAC

16.10.13. Pharmacodynamic Figures

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Blood Eosinophils					
6.1.	PD	*EFF_F4*	On-Treatment Absolute Blood Eosinophils (While on Treatment Estimand, Mixed Model Repeated Measures)	No reference line. Include screening and baseline unadjusted geometric mean values without 95% CI. Week 2 onwards adjusted estimates from MMRM model with 95% CI.	SAC
6.2.	PD	*EFF_F4*	On-Treatment Ratio to Baseline Blood Eosinophils (While on Treatment Estimand, Mixed Model Repeated Measures)	Reference line at 1.	SAC
6.3.	PD	*EFF_F5*	On-Treatment Ratio to Baseline Blood Eosinophils – Treatment Difference vs Placebo (While on Treatment Estimand, Mixed Model Repeated Measures)	Reference line at 1.	SAC

16.10.14. Pharmacokinetic / Pharmacodynamic Tables

Pharmacokinetic / Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
7.1.	PK and PD	-	Description and Evaluation of Key PKPD Models Tested	Provided by CPMS	SAC
7.2.	PK and PD	-	Population PD Parameter Estimates with 95% CI of Final PKPD Model	Provided by CPMS	SAC
7.3.	PK and PD	-	Demographics Summary	Provided by CPMS	SAC
7.4.	PK and PD	-	Samples Summary	Provided by CPMS	SAC
7.5.	ITT	-	Exploratory Exposure-Efficacy Response Modelling of Proportion of Subjects with HES Flare During the 32-Week Treatment Period vs Dose/Body weight		Post-SAC
7.6.	ITT	-	Exploratory Exposure-Efficacy Response Modelling of Proportion of Subjects with HES Flare During the 32-Week Treatment Period vs Cav		Post-SAC

16.10.15. Pharmacokinetic / Pharmacodynamic Figures

Pharmacokinetic / Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
7.1.	PK and PD	-	Blood Eosinophil Count-Time Profiles	Provided by CPMS	SAC
7.2.	PK and PD	-	Model Goodness of Fit Plots	Provided by CPMS	SAC
7.3.	PK and PD	-	Continuous Covariate Correlation Plot	Provided by CPMS	SAC
7.4.	PK and PD	-	Categorical Covariate Correlation Plot	Provided by CPMS	SAC
7.5.	PK and PD	-	Automated Covariate Selection	Provided by CPMS	SAC
7.6.	PK and PD	-	Visual Predictive Check	Provided by CPMS	SAC
7.7.	PK and PD	-	Observed Blood Eosinophil Count -Time Profiles by Anti-Drug Antibody Status	Provided by CPMS	SAC
7.8.	PK and PD	-	Observed/Predicted Blood Eosinophil Count-Time Profiles (by Subject)	Provided by CPMS	SAC
7.9.	ITT	-	Exploratory Exposure-Efficacy Response Modelling of Proportion of Subjects with HES Flare During the 32-Week Treatment Period vs Dose/Body weight		Post-SAC
7.10.	ITT	-	Exploratory Exposure-Efficacy Response Modelling of Proportion of Subjects with HES Flare During the 32-Week Treatment Period vs Cav		Post-SAC

16.10.16. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure		SAC
2.	ITT	ES2	Listing of Reasons for Study Withdrawal		SAC
3.	ITT	SD2	Listing of Reasons for Study Treatment Discontinuation		SAC
4.	ITT	BL1	Listing of Subjects for Whom the Treatment Blind was Broken		SAC
5.	ITT	TA1	Listing of Planned and Actual Treatments		SAC
Protocol Deviations					
6.	ITT	DV2	Listing of Important Protocol Deviations		SAC
7.	ITT	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
Populations Analysed					
8.	ITT	SP3	Listing of Subjects Excluded from Any Population	Include Per Protocol, Safety, PK, PD	SAC
Demographic and Baseline Characteristics					
9.	ITT	DM2	Listing of Demographic Characteristics		SAC
10.	ITT	DM9	Listing of Race		SAC
11.	ITT	MH2	Listing of Medical Conditions		SAC
Prior and Concomitant Medications					
12.	ITT	CP_CM3	Listing of Concomitant Medications	Flag baseline HES therapy on listing.	SAC
Exposure and Treatment Compliance					
13.	ITT	EX3	Listing of Exposure Data	Exposure to Mepolizumab/Placebo only.	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Burden of HES					
14.	ITT	*POP_L1*	Listing of Most Bothersome HES Related Symptoms		SAC
15.	ITT	*POP_L2*	Listing of Steroid Perception Questionnaire		SAC
Efficacy					
16.	ITT	*EFF_L1*	Listing of Investigator Reported HES Flare		SAC
17.	ITT	*EFF_L2*	Listing of Blinded OCS Therapy		SAC
18.	ITT	*EFF_L3*	Listing of Mean Daily Fatigue Severity – Worst Level of Fatigue in the Past 24 Hours (BFI Item 3) and Weekly Fatigue Severity (Total BFI Score)		SAC
19.	ITT	*EFF_L4*	Listing of FEV_{1}, FVC and FEV1/FVC		SAC
20.	ITT	*EFF_L5*	Listing of Echocardiogram/MUGA		SAC
21.	ITT	*EFF_L6*	Listing of Symptom Severity (HES-DS)		SAC
22.	ITT	*EFF_L7*	Listing of Subject- and Clinician-Rated Overall Response to Therapy		SAC
23.	ITT	*EFF_L8*	Listing of Subject-Rated Symptom Severity		SAC
24.	ITT	*EFF_L9*	Listing of MSAS-SF Total and Subscale Scores		SAC
25.	ITT	*EFF_L10*	Listing of PROMIS Physical Function and Sleep Score		SAC
Healthcare Resource Utilisation					
26.	ITT	*EFF_L11*	Listing of SF-36 Health Survey		SAC
27.	ITT	*EFF_L12*	Listing of Healthcare Resource Utilisation Associated with HES Flare		SAC
28.	ITT	*EFF_L13*	Listing of Work Productivity and Activity Impairment		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events					
29.	Safety	AE8	Listing of All Adverse Events	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC
Serious and Other Significant Adverse Events[1]					
30.	Safety	AE8	Listing of Fatal Serious Adverse Events	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC
31.	Safety	AE8	Listing of Non-Fatal Serious Adverse Events	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC
32.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC
33.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC
34.	Safety	AE8	Listing of Adverse Events Reported on the Day of Dosing	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC
35.	Safety	AE8	Listing of Adverse Events Reported by the Investigator as Systemic Reactions Meeting the Criteria for Anaphylaxis	Add phase: Pre-treatment, on-treatment, post-treatment. Add injection reaction symptoms and number of doses prior to event. Include treatment in by-line.	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
36.	Safety	AE8	Listing of Adverse Events Reported by the Investigator as Systemic Reactions - Allergic (Type I Hypersensitivity)	Add phase: Pre-treatment, on-treatment, post-treatment. Add injection reaction symptoms and number of doses prior to event. Include treatment in by-line.	SAC
37.	Safety	AE8	Listing of Adverse Events Reported by the Investigator as Systemic Reactions – Other Systemic	Add phase: Pre-treatment, on-treatment, post-treatment. Add injection reaction symptoms and number of doses prior to event. Include treatment in by-line.	SAC
38.	Safety	AE8	Listing of Adverse Events Reported by the Investigator as Local Injection Site Reactions	Add phase: Pre-treatment, on-treatment, post-treatment. Add injection reaction symptoms and number of doses prior to event. Include treatment in by-line.	SAC
39.	Safety	AE8	Listing of Adverse Events Categorised as Serious Cardiac, Vascular and Thromboembolic Events	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC
40.	Safety	AE8	Listing of Adverse Events Categorised as Serious Ischemic Events	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC
41.	Safety	AE8	Listing of Adverse Events Categorised as Malignancies	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
42.	Safety	AE8	Listing of Adverse Events Categorised as Potential Opportunistic Infections	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC
Hepatobiliary (Liver)					
43.	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events	Programming note: Include all subjects meeting protocol defined liver stopping criteria even if liver pages were not completed by the site.	SAC
44.	Safety	SU2	Listing of Substance Use for Subjects with Liver Stopping Events	Programming note: Include all subjects meeting protocol defined liver stopping criteria even if liver pages were not completed by the site.	SAC
All Laboratory					
45.	Safety	LB5	Listing of Haematology Data for Subjects with Any Value of Potential Clinical Importance		SAC
46.	Safety	LB5	Listing of Clinical Chemistry Data for Subjects with Any Value of Potential Clinical Importance		SAC
47.	Safety	LB14	Listing of Laboratory Data with Character Results		SAC
48.	Safety	UR2A	Listing of Urinalysis Data for Subjects with Any Value of Potential Clinical Importance		SAC
ECG					
49.	Safety	EG3	Listing of All ECG Values for Subjects Meeting Protocol Defined QTc Stopping Criteria		SAC
Immunogenicity					
50.	Safety	*SAFE_L1*	Listing of Immunogenicity Data for Subjects with at Least One Positive Screening Binding Assay		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Pharmacokinetic					
51.	PK	-	Listing of Data and Subjects Excluded from Analysis	Provided by CPMS	SAC
52.	PK	-	Final PK Model Listings	Provided by CPMS	SAC
Pharmacodynamic					
53.	Safety	*PD_L1*	Listing of Blood Eosinophils *(unit)*		SAC
54.	Safety	*PD_L2*	Listing of Serum Total IL-5 *(unit)*		SAC
Pharmacokinetic / Pharmacodynamic					
55.	PK and PD	-	Listing of Data and Subjects Excluded from Analysis	Provided by CPMS	SAC
56.	PK and PD	-	Final PKPD Model Listings	Provided by CPMS	SAC

[1] For deaths and any cardiovascular events, subject profiles will be produced as per GSK IDSL standard template.

16.11. Appendix 11: Example Mock Shells for Data Displays

Available upon request

Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for Study 200622: A randomised, double-blind, placebo-controlled study to investigate the efficacy and safety of mepolizumab in the treatment of adolescent and adult subjects with severe hypereosinophilic syndrome
Compound Number	:	SB-240563
Effective Date	:	12-FEB-2019

Description:

- The purpose of this RAP is to describe the planned efficacy and safety analyses and output to be included in the Clinical Study Report for Protocol 200622.
- This RAP defines the content of the headline results and SAC deliverables.

RAP Author(s):

Author	Date
PPD Project Statistician	05-FEB-2019
PPD Clinical Pharmacology, Modelling and Simulation	

RAP Team Review Confirmations
(Method: E-mail):

Approver	Date
PPD Clinical Pharmacology, Modelling and Simulation	07-FEB-2019
PPD Lead Programmer	06-FEB-2019
PPD Project Physician Lead	06-FEB-2019
PPD Safety Evaluation and Risk Management	07-FEB-2019
PPD Patient Centred Outcomes	06-FEB-2019

Clinical Statistics and Clinical Programming Line Approvals
(Method: Pharma TMF eSignature):

Approver	Date
PPD Senior Statistics Director	12-FEB-2019
PPD Director Programming	11-FEB-2019

TABLE OF CONTENTS

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol 200622:

Protocol Revision Chronology:		
2013N171550_00	29-APR-2016	Original

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Study Objective(s) and Endpoint(s)

Objectives	**Endpoints**
Primary Objectives	**Primary Endpoints**
• To demonstrate the efficacy of mepolizumab compared with placebo based on maintenance of control of HES symptoms during the treatment period.	• Proportion of subjects who experience an HES flare during the 32-week study treatment period
Secondary Objectives	**Secondary Endpoints**
• To demonstrate supportive evidence of the benefit of mepolizumab compared with placebo based on other measures of efficacy.	• Time to first HES flare • Proportion of subjects who experience an HES flare during Week 20 through Week 32 • Rate of HES flares • Change from baseline in fatigue severity based on Brief Fatigue Inventory (BFI) item 3 (worst level of fatigue during past 24 hours) at Week 32
Exploratory Objectives	**Exploratory Endpoints**
• To investigate mepolizumab compared with placebo with respect to additional measures of efficacy.	• Proportion of subjects who have an elevated blood eosinophil level that meets the pre-defined threshold during the 32-week study treatment period[1] • Lung function tests (FEV_1, FVC, and ratio) • Echocardiogram
• To investigate the efficacy of mepolizumab compared with placebo with respect to patient and clinician reported symptoms, health status, and disease impact.	• Change from baseline in HES symptom severity based on HES Daily Symptoms (HES-DS) at Week 32 • Change from baseline in the BFI total score at Week 32[2] • Clinician- and subject-rated overall response to therapy score (RTS) at Week 32[3] • Change from baseline in Subject-rated symptom severity (SSR) at Week 32 • Change from baseline in Modified Memorial Symptom Assessment Scale-Short Form (MSAS-SF)

Objectives	Endpoints
	responses at Week 32 • Change from baseline in physical function (Patient Reported Outcome Measurement Information System [PROMIS] physical function items) at Week 32 • Change from baseline in sleep (PROMIS sleep items) at Week 32
• To characterize the patient burden of HES.	• SF-36 v2 • Healthcare resource utilization (HCRU) • Work Productivity and Activity Impairment Index – General Health (WPAI-GH) v2 • Steroid perception questionnaire
• To investigate the pharmacokinetics (PK) of mepolizumab.	• Plasma concentration of mepolizumab
• To investigate the pharmacodynamics (PD) of mepolizumab.	• Total IL-5[4] • Blood eosinophil levels
Safety Objectives	**Safety Endpoints**
• To evaluate the safety of mepolizumab compared with placebo in subjects with HES receiving standard of care treatment over a 32-week study treatment period.	• Adverse events including local injection site reactions and systemic reactions (e.g.,hypersensitivity) • Vital signs • 12-lead ECG • Hematological and clinical laboratory tests • Immunogenicity (anti-drug antibody)

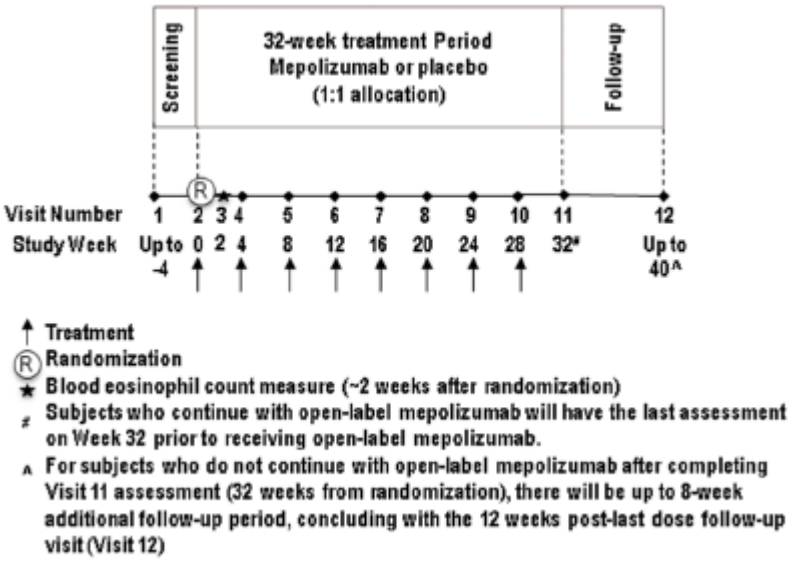
[1]Protocol endpoint was the proportion of subjects who receive blinded active oral corticosteroid (OCS) due to an elevated blood eosinophil level that meets the pre-defined threshold (2 x baseline value or baseline value + 2500 cells/μL) during the 32-week study treatment period. See Section 2.4 for rationale for change.

[2]Protocol endpoint was change from baseline in the BFI total and domain scores at Week 32. See Section 2.4 for rationale for change.

[3]Protocol endpoint was the proportion of subjects with a favourable response as measured by clinician- and subject-rated overall response to therapy score (RTS) at Week 32. See Section 2.4 for rationale for change.

[4]Serum free and total IL-5 were planned in the protocol. See Section 2.4 for rationale for change.

2.2. Study Design

Overview of Study Design and Key Features	
	
Design Features	• 32-week treatment period, randomised, double-blind, placebo-controlled, parallel group, multicentre study of mepolizumab in adolescent and adult subjects with severe HES receiving SoC therapy. • The same regimen of HES therapy will be maintained throughout the 32-week study treatment period unless there is worsening of symptom(s) that requires an increase in therapy. A reduction in dose for safety reasons, with return to the original dosing regimen if possible, is permitted in consultation with the GSK Medical Monitor. • Subjects who withdraw from study treatment prematurely should continue in the study per protocol (including HES flare-related assessments) until 32 weeks from randomization. • Investigators, participating subjects, and GSK study personnel will be blinded to absolute blood eosinophil counts, total white blood cell counts, and white blood count differentials (%) from randomization (Visit 2) until completing the 32-week period from randomization. Blood eosinophil-unblinded GSK personnel/delegates not involved with other aspects of study conduct will monitor the absolute blood eosinophil count results and trigger blinded OCS treatment to treat an eosinophilia when the blood eosinophil count reaches a pre-defined threshold (2 x baseline value or baseline value + 2500 cells/μL). Provided the subject's HES therapy has not been increased due to a symptom flare, the subject will take the blinded active OCS for ~2 weeks. A subject who does not reach the pre-defined blood eosinophilia threshold with a similar blood draw date will be selected to initiate blinded placebo OCS treatment, to maintain study blood eosinophil blinding. Approximately 2 weeks after the scheduled clinic visit, the blood eosinophil count will be assessed again for the subjects who

Overview of Study Design and Key Features	
	started blinded OCS (both active and placebo). The subject who has taken active blinded OCS will be instructed to continue with a new course of blinded OCS until the next scheduled clinic visit if the blood eosinophil count is at or above the threshold unless the subject's HES therapy has been increased due to a symptom flare since the initiation of the current course of blinded OCS, and discontinue if the blood eosinophil count is below the threshold. For subjects taking placebo-blinded OCS, continuation/discontinuation of blinded OCS will be determined depending on the continuation/discontinuation of their matched subject on active-blinded OCS. • An open-label study is also planned (study 205203) for subjects who complete study 200622.
Main subject entry criteria	• Subjects ≥12 years with HES • At least 2 HES flares within the past 12 months; at least one HES flare within the past 12 months must not be related to a decrease in HES therapy during the 4 weeks prior to the flare. • Blood eosinophil count ≥ 1000 cells/μL during screening. Investigators were permitted to use local laboratory results to meet this inclusion criteria.
Dosing	• 300 mg mepolizumab or placebo SC every 4 weeks (8 administrations) while continuing their HES therapy. • The final dose of study treatment will be administered at Visit 10 (Week 28) with completion of the study treatment period achieved at the next 4-weekly visit.
Treatment Assignment	• Subjects will be randomised in a 1:1 ratio to receive either mepolizumab or placebo in addition to SoC therapy. • An initial sample size of N=80 subjects will be randomised. The proportion of subjects that have an HES flare will be monitored, blinded to treatment, and the total number of subjects randomised may be increased up to a maximum of 120 subjects if the blinded overall flare rate is predicted to be <30%. The blinded overall proportion of subjects who have an HES flare will be calculated based on the HES flare data available in the CRF. This will include all HES flares meeting flare endpoint definition 'a)' in Section 7.1.1. In order to maintain the blood eosinophil blinding, HES flares meeting flare end point definition 'b)' in Section 7.1.1 will not be included in the calculation of the blinded overall proportion. • Treatments will be assigned randomly via an interactive response system (IRS). • Randomization schedule will be generated using GSK validated randomisation software RandAll NG. • Randomization stratified by region.
Time and events	• See Appendix 2: Schedule of Activities.
Interim	• An external Independent Data Monitoring Committee (IDMC) will

Overview of Study Design and Key Features	
Analysis	periodically review unblinded safety data from the study, in accordance with the IDMC Charter. The safety data analyses for the IDMC reviews will be performed by an independent statistical analysis data centre (SDAC). There are no circumstances under which IDMC review of the data would lead to a recommendation to stop for efficacy. Therefore, no adjustment to the final alpha level for efficacy will be made based on the safety stopping guidelines.

2.3. Statistical Hypotheses / Statistical Analyses

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

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

- **Alternative hypothesis**: the proportion of subjects who experience an HES flare during the 32-week study treatment period is smaller for mepolizumab compared to placebo.

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

2.4. Changes to the Protocol Defined Statistical Analysis Plan

- The following changes to the exploratory endpoints were made in this RAP:

Protocol Endpoint	RAP Endpoint	Rationale for Change
Proportion of subjects who receive blinded active OCS due to an elevated blood eosinophil level that meets the pre-defined threshold during the 32-week study treatment period	Proportion of subjects who have an elevated blood eosinophil level that meets the pre-defined threshold during the 32-week study treatment period	RAP endpoint considered to be more clinically meaningful as it includes all subjects with blood eosinophil counts meeting the pre-defined threshold during the 32-week study treatment period rather than including only the subset of these subjects who receive blinded active OCS. Subjects did not receive blinded active OCS if their physician had already increased their HES therapy based on symptoms.
Change from baseline in the BFI total and domain scores at Week 32	Change from baseline in the BFI total score at Week 32.	The BFI is a single construct and therefore domain scores are not applicable.
Proportion of subjects with a favourable response as measured by clinician- and subject-	Clinician- and subject-rated overall response to therapy score (RTS) at Week 32	Improvement/worsening is measured on a 7-point scale from significant worsening to significant improvement. The endpoint will be summarised and analysed as a 7-point ordinal endpoint to avoid loss of information and increase the sensitivity of the analysis.

Protocol Endpoint	RAP Endpoint	Rationale for Change
rated overall response to therapy score (RTS) at Week 32		
Serum free and total IL-5	Total IL-5	Free IL-5 levels are generally very low in serum (<BLQ) and are expected to decrease post dosing because most of the free IL-5 becomes complexed with mepolizumab. Hence only total IL-5 will be measured.

- Since some participants were randomised early in error prior to the first dose of mepolizumab, the following changes to the secondary endpoint derivations in the protocol are planned:
  - Time to first HES flare will be calculated from the date of first dose of study treatment and the onset date of the HES flare, rather than the date of randomisation and the onset date of the HES flare.
  - The rate of HES flares will be calculated using the date of the first dose of study treatment and the Week 32 visit/study withdrawal date, rather than the randomisation date and the Week 32 visit/study withdrawal date.
  - For the calculation of the change from baseline in BFI item 3, the mean of the 7 daily assessments of BFI item 3 up to but not including the date of first dose of study treatment will be used as the baseline assessment. Since BFI item 3 is measured daily after 6pm, the date of dosing will not be included in the calculation of the baseline BFI.

3. PLANNED ANALYSES

3.1. Interim Analyses

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

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.
3. A review has taken place by the unblinded global study manager to identify any subjects with a discrepancy between randomised treatment and actual treatment received. This information will be included in the SDTM dataset at DBF. Actual treatment arm will be derived within the ADaM datasets based on the treatment received for more than 50% of treatment administrations. If a subject received an equal number of both treatments then the actual treatment arm will reflect the treatment to which they were randomised.
4. All criteria for unblinding the randomisation codes have been met, and treatment allocations have been unblinded via the RandAll NG system, as described in SOP_54840.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility i.e. for whom record exists in the database.	• Study Population (Pre-screen and screen failures)
Enrolled	• All participants who were successfully screened and entered the study. • Note: screening failures (who never passed screening even if rescreened) and participants who were successfully screened but did not complete any visit 2 assessments are excluded.	• Study Population (EudraCT required displays)
Intent-To-Treat (ITT)	• All randomised subjects • This population will be based on the treatment to which the subject was randomised. • Any subject who receives a treatment randomisation number will be considered to have been randomised.	• Study Population • Efficacy • Listing of Planned and Actual Treatments
Per-Protocol (PP)	• Comprise all subjects in the ITT population not identified as full protocol deviators with respect to criteria that are considered to impact the primary efficacy analysis. • The decision to exclude a subject from the PP population or exclude part of their data from the PP population will be made prior to breaking the blind. • Protocol deviations that would exclude subjects from the PP population are defined in Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population.	• Supplementary analysis of primary endpoint
Safety	• All subjects who are randomised and who receive at least one dose of study treatment. Randomised subjects will be assumed to have received study treatment unless definitive evidence to the contrary exists. • This population will be based on the treatment the subject actually received. • Subjects will be analysed according to treatment received for more than 50% of their treatment administrations. If a subject received an equal number of both treatments then they will be assigned to the treatment to which they were randomised.	• Study Population • Safety
Pharmacokinetic	• All subjects in the ITT population who received	• PK

Population	Definition / Criteria	Analyses Evaluated
	at least one dose of study treatment and for whom at least one PK sample was obtained, analysed and was measurable.	
Pharmacodynamic	• All subjects in the ITT population who received at least one dose of study treatment and who also had a baseline PD measurement and at least one post-treatment PD measurement.	• PD

Refer to Appendix 10: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (PDMP).
- Data will be reviewed prior to Source Data Lock (SDL) to ensure all important deviations and deviations which lead to exclusion from the Per Protocol analysis population are agreed prior to unblinding. Important deviations will be categorised in the SDTM data set. Deviations leading to exclusion from the Per Protocol population will be categorised in the ADaM data set.
- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.
- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.
- Important protocol deviations which result in exclusion from the Per Protocol population will be summarised and listed (see Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
A	Mepolizumab 300mg SC	Mepolizumab 300mg SC	2
P	Placebo	Placebo	1

NOTES:

1. Order represents treatments being presented in Tables, Figures and Listings (TFLs), as appropriate.

5.2. Baseline Definitions

- Baseline will be defined for all subjects in the ITT population.
- For the BFI item 3 which is collected daily from the screening visit (Visit 1) the mean of the 7 daily assessments of BFI item 3 up to but not including the date of first dose of study treatment will be used as the baseline assessment.
- For blood eosinophils, baseline will be defined as the latest central laboratory result prior to the first dose of study treatment. Investigators were permitted to use local laboratory results to meet inclusion criteria, however local laboratory results will not be used in the derivation of the baseline blood eosinophil value.
- For all other endpoints the baseline values for each assessment will be the latest available assessment (including unscheduled visits) prior to first dose of study treatment. For ECG, if multiple assessments are recorded on the same day, the mean of the multiple assessments will be assigned as the baseline value.

5.3. Multicentre Studies

- In this multicentre global study, enrolment will be presented by investigative site and country.
- The randomisation for this study is stratified by region, defined below, with consideration for standard of care medical practice.
  - USA
  - Argentina, Mexico and Brazil
  - Rest of World
- The same definition of region will be used for covariate adjustment in the statistical analysis.
- If there are insufficient subjects in each region for the planned statistical analysis, further combining of regions will be considered.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

- Region and baseline OCS dose, expressed as prednisone equivalent dose, will be covariates in all statistical analysis. These covariates will be included as stratification variables for the Cochran-Mantel-Haenszel test and Wilcoxon Rank Sum test according to the table below. For parametric analysis models, region will be included as a fixed categorical effect and baseline OCS dose will be included as a fixed continuous effect.

Category	Covariates and / or Subgroups
Region	See Section 5.3. • USA • Argentina, Mexico and Brazil • Rest of World
Baseline oral prednisone equivalent dose[1]	See Section 5.4.1.1 • 0-≤20mg prednisone or equivalent • >20mg prednisone or equivalent

[1]For parametric analysis models, baseline OCS dose will be included as a fixed continuous effect.

- If the percentage of subjects is small within a region, then the region categories may be refined prior to unblinding the trial.
- For analyses where a baseline value of the analysis variable is available this will also be included in the statistical analysis. These covariates will be included as stratification variables for the Cochran-Mantel-Haenszel test and Wilcoxon Rank Sum test, and as continuous fixed effects for all parametric analysis models.

5.4.1.1. Derivation of Baseline Oral Prednisone Equivalent Daily Dose

- For each subject, a baseline oral prednisone equivalent daily dose (mg) will be derived prior to unblinding the randomisation codes for the study. Baseline oral prednisone equivalent dose will be identified from the concomitant medications page according to the following criteria:
    - Start date < Date of first dose of study treatment
    - Either "ongoing" or end date ≥ Date of first dose of study treatment
    - Route = "PO"
- Partial start and end dates will be handled as described in Section 15.7.2.1.
- Corticosteroids will be identified from the list of coded concomitant medications for the study, by merging with the GSK respiratory medication class (RMC) reference data set by component code. This reference data is created by dictionary specialists who identify a list of component terms for corticosteroids, which then undergo clinical review to ensure the correct classification is assigned.
- Subjects not receiving OCS therapy, i.e. subjects receiving cytotoxic and/or immunosuppressive HES therapy only at baseline, or subjects not receiving any HES

therapy, will be assigned a prednisone equivalent daily dose of 0 mg and will be categorised in the 0-≤20mg prednisone or equivalent group.

- The corticosteroid conversion factors in the table below will be used to scale each corticosteroid dose to a prednisone equivalent dose.

Medication Name	Scaling Factor
Betamethasone	8.33
Budesonide[1]	0
Cortisone	0.2
Dexamethasone	6.67
Deflazacort	0.83
Hydrocortisone	0.25
Methylprednisone	1.25
Meprednisone	1.25
Prednisone	1
Prednisolone	1
Prednisone acetate	1
Triamcinolone	1.25

[1]Budesonide has negligible systemic exposure and will be classed as "Other HES therapy" rather than oral corticosteroid therapy.

- Where the frequency of the recorded corticosteroid dose is not once daily, the following calculations will be used to determine the daily dose.

Medication Frequency	Daily Dose Equivalent
BID	2 x dose
TID	3 x dose
QID	4 x dose
QOD	dose / 2
2XWK	(2 x dose) / 7
3XWK	(3 x dose) / 7
4XWK	(4 x dose) / 7
5XWK	(5 x dose) / 7

5.4.2. Examination of Subgroups

- The subgroups in the table below are of interest in this study. A separate exploratory analysis of the primary endpoint within each subgroup will be carried out.

- Subgroup categories may be further collapsed if there are a small number of subjects in a treatment arm within a subgroup leading to model convergence issues.

- There is a biological rationale for potentially observing increased efficacy with increasing levels of baseline blood eosinophils. The role of blood eosinophil counts at baseline on the effectiveness of mepolizumab with respect to the primary endpoint will be further assessed based on a statistical model including baseline ($\log_e$) blood eosinophil count as a continuous variable and an interaction with treatment term. Baseline blood eosinophil count is defined in Section 5.2. The analysis will also be adjusted for region and baseline OCS dose, as described in Section 5.4.1. Fractional polynomial models for the baseline blood eosinophil count may also be explored in order to find the best fitting model for the relationship.

- Differential treatment effects are not expected for any of the other subgroups listed below and therefore any differences in efficacy for mepolizumab compared to placebo observed in categories of these subgroups will be viewed as exploratory.

Subgroup	Categories
Age	• 12-<18 years • 18-64 years • ≥65 years
Sex	• Male • Female
Race	• Black or African American • White • Asian • Other
Region	• USA • Argentina, Mexico and Brazil • Rest of World
Baseline OCS	• 0-≤20mg prednisone or equivalent • >20mg prednisone or equivalent
Baseline blood eosinophils	• Quartiles, rounded to 1 decimal place (GI/L); equivalent to rounding to the nearest 100 cells/μL

5.5. Multiple Comparisons and Multiplicity

When strong control of type I error is required for making inferences for the predefined secondary endpoints, multiplicity will be controlled using a hierarchical, closed testing procedure, according to the following hierarchy of endpoints:

1. Proportion of subjects who experience an HES flare during the 32-week study treatment period (primary endpoint)

2. Time to first HES flare

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

4. Rate of HES flares

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

When strong control of type I error is required, statistical significance for an endpoint in the predefined hierarchy will be dependent on statistical significance for the previous endpoints in the hierarchy.

P-values for secondary endpoints will be provided both unadjusted and adjusted for multiplicity using the hierarchy of endpoints above.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
15.3	Appendix 3: Assessment Windows
15.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
15.5	Appendix 5: Data Display Standards & Handling Conventions
15.6	Appendix 6: Derived and Transformed Data
15.7	Appendix 7: Reporting Standards for Missing Data
15.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the ITT population, unless otherwise specified. If the ITT population and the safety populations differ, study population analyses will also be produced for the safety population.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, exposure and treatment compliance (assessed by number of administrations of study treatment) will be based on GSK Core Data Standards. In addition, summaries of baseline HES therapy, most bothersome HES symptoms and steroid perception questionnaire will be produced.

Details of the planned displays are presented in Appendix 10: List of Data Displays.

7. EFFICACY ANALYSES

The target population for the primary estimand is as defined by the study inclusion/exclusion criteria and therefore the ITT population will be the primary population for all efficacy analyses.

7.1. Primary Efficacy Analyses

7.1.1. Endpoint / Variables

The primary endpoint is the proportion of subjects who experience an HES flare during the 32-week study treatment period.

An HES flare is defined as either:

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

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

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

or

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

HES flares meeting definition a) will be captured on the 'flare details' page in the eCRF.

An increase in blood eosinophils above the pre-defined threshold level (2 x baseline value or baseline value + 2500 cells/μL) without any other clinical manifestations during the study will lead to administration of blinded active OCS treatment (see Section 2.2). If a subject receives a second course of blinded active OCS during the 32-week treatment period, the subject will be considered to be experiencing a flare. The container list for the blinded OCS treatment (indicating which container numbers contained active OCS and which contained placebo OCS) will be used to define HES flares meeting endpoint definition b).

7.1.2. Summary Measure

The difference between mepolizumab and placebo in the proportion of subjects with HES flare during the 32-week study treatment period.

7.1.3. Strategy for Intercurrent (Post-Randomization) Events

7.1.3.1. Primary Estimand

The primary treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications.

The study is designed to continue to collect data on HES flares for subjects who prematurely discontinue from their randomised study treatment. All data on HES flares collected for these subjects will be included in the primary analysis. Subjects who withdraw from the study prior to Week 32 (Visit 11) and therefore have missing data on HES flares will be included in the primary analysis as treatment failures, i.e. for the primary comparison, a subject will be classed as not experiencing an HES flare only if they have no flares reported and complete Week 32 (Visit 11).

Sensitivity analyses will be performed on the ITT population to examine the potential impact of the missing data:

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

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

7.1.3.2. Supplementary Estimand

A supplementary estimand using the 'while on treatment' strategy will be assessed for the intercurrent event of discontinuation of study medication.

Subjects discontinuing from study treatment prematurely will be included as having a HES flare if a flare is recorded with an onset date equal or prior to 28 days after the last dose of study treatment, and not having a flare otherwise.

7.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

A summary of the number and percentage of subjects with HES flares will be produced by treatment group. The total number of HES flares in each treatment group will also be presented. The summary will include all HES flares, as well as a separate breakdown of HES flares meeting definition a) and b) (see Section 7.1.1). A plot of the cumulative number of HES flares over time in each treatment group will be produced.

7.1.4.1. Statistical Methodology Specification

Primary Statistical Analyses

Endpoint

- Proportion of subjects who experience an HES flare during the 32-week study treatment period.

Model Specification

- Cochran-Mantel-Haenszel test stratified by baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region.
- Supplemented by a logistic regression analysis adjusting for covariates of baseline OCS dose (continuous scale), region, and treatment.

Model Checking & Diagnostics

- To examine the fit of the logistic regression model, deviance residuals will be calculated and plotted.

Model Results Presentation

- Number of subjects analysed in each treatment group.
- Number of subjects with ≥1 HES flare or who withdraw from the study prior to Week 32 (Visit 11).
  - Number of subjects with ≥1 HES flare.
  - Number of subjects with no HES flare who withdraw from the study prior to Week 32 (Visit 11).
- Number of subjects with no HES flare who complete Week 32 (Visit 11).
- p-value from Cochran-Mantel-Haenszel test.
- Odds ratio and 95% Confidence Interval (CI) from logistic regression model.
- p-value from logistic regression model.

Subgroup Analyses

- A logistic regression analysis will be fitted separately within each subgroup of interest defined in Section 5.4.2.
- Odds ratios and 95% confidence intervals from the logistic regression model will be presented. Analysis will be descriptive only; no p-values will be presented for the subgroup analyses. If the number of subjects in each subgroup category are small, confidence intervals may also be omitted.

Sensitivity and Supportive Statistical Analyses

- A supplementary estimand using the 'while on treatment' strategy for intercurrent events will be assessed.
- The primary analysis will be repeated using the PP population.
- Sensitivity analyses for the primary estimand to assess the impact of missing data will be performed using the ITT population as follows:
  - Subjects withdrawing from the study prematurely prior to reporting an HES flare, with the primary reason for treatment withdrawal reported as AE or Lack of Efficacy, will be classed as experiencing an HES flare. Subjects withdrawing from the study prematurely with any other reason for treatment withdrawal will be included as having a flare if one is recorded

Primary Statistical Analyses
prior to study withdrawal, and as not having a flare if no flare is recorded prior to study withdrawal. • Subjects withdrawing from the study prematurely will be included as having a flare if one is recorded prior to study withdrawal, and as not having a flare if no flare is recorded prior to study withdrawal.

7.1.5. Exploratory Modelling of Primary Endpoint

The role of baseline blood eosinophil counts on the effectiveness of mepolizumab with respect to the proportion of subjects who experience an HES flare during the 32-week study treatment period will be investigated. A logistic regression model will be fitted, including baseline blood eosinophils fitted on the $\log_e$ scale as a continuous covariate as well as a treatment-by-baseline blood eosinophils interaction term, in order to predict the odds ratio for mepolizumab vs placebo for each level of the baseline blood eosinophil count. The analysis will also be adjusted for region and baseline OCS dose, as described in Section 5.4.1. Fractional polynomial models may also be explored in order to find the best fitting model for the relationship.

7.2. Secondary Efficacy Analysis – Time to First HES Flare

7.2.1. Endpoint / Variables

The time to first HES flare will be calculated from the date of first dose of study treatment and the onset date of the first HES flare as defined in Section 15.6.4.

7.2.2. Summary Measure

The difference between mepolizumab and placebo in the time to first HES flare.

7.2.3. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. If a subject withdraws prematurely from the study prior to experiencing an HES flare, the event time will be censored at the time point at which the subject withdrew from the study. Sensitivity analyses will be performed to examine the potential impact of the missing data.

7.2.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Time to first HES flare will be graphically represented using a Kaplan-Meier plot of cumulative incidence rates over time for each treatment group.

7.2.4.1. Statistical Methodology Specification

Endpoint
• Time to first HES flare.
Model Specification
• Log-rank test stratified by baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region. • Supplemented by a Cox proportional hazards regression model allowing for covariates of baseline OCS dose (continuous scale) and region.
Model Checking & Diagnostics
• To examine the fit of the Cox proportional hazards model, martingale and deviance residuals will be calculated and plotted.
Model Results Presentation

• In each treatment group
  • Number of subject analysed.
  • Number of subjects with HES flare.

- Number of subjects censored at study withdrawal.
- Number of subjects censored at study completion.

- Stratified Log-Rank test p-value for association between treatment and time to first HES flare.
- Hazard ratio and 95% CI from Cox proportional hazards model.
- Wald chi-square p-value from Cox proportional hazards model.

Subgroup Analyses

- No subgroup analyses will be performed on this endpoint.

Sensitivity and Supportive Analyses

- Sensitivity analyses to assess the impact of missing data will be performed using the ITT population as follows:
  - Subjects withdrawing from the study prematurely prior to reporting an HES flare will be included with an HES flare on the date of study withdrawal.
  - Subjects withdrawing from the study prematurely prior to reporting an HES flare, with primary reason for treatment withdrawal reported as Adverse Event or Lack of Efficacy will be included as an HES flare on the date of study withdrawal. For subjects withdrawing from the study prematurely prior to reporting an HES flare, with any other reason for discontinuation of study treatment, the event time will be censored at the date of study withdrawal.

7.3. Secondary Efficacy Analysis – Proportion of Subject Who Experience an HES Flare During Week 20 Through Week 32

7.3.1. Endpoint / Variables

HES flare during Week 20 through Week 32 will be defined as an HES flare starting or ongoing on or after the date of the Week 20 visit up to and including the date of the Week 32 visit.

7.3.2. Summary Measure

The difference between mepolizumab and placebo in the proportion of subjects with HES flare during Week 20 through Week 32.

7.3.3. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. Subjects who withdraw prematurely from the study prior to Week 32 (Visit 11) and therefore have missing data on HES flares during Week 20 through Week 32 will be included in the analysis as treatment failures i.e., that they experience a flare during Week 20 through Week 32. Sensitivity analyses will be performed to examine the potential impact of the missing data.

7.3.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

A summary of HES flares during Week 20 through Week 32 will be produced as for the primary endpoint (see Section 7.1.4).

7.3.4.1. Statistical Methodology Specification

Endpoint
• Proportion of subjects who experience an HES flare during Week 20 through Week 32.
Model Specification
• Cochran-Mantel-Haenszel test stratified by baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region. • Supplemented by a logistic regression analysis adjusting for covariates of baseline OCS dose (continuous scale), region, and treatment.
Model Checking & Diagnostics
• To examine the fit of the logistic regression model, deviance residuals will be calculated and plotted.
Model Results Presentation
• Number of subjects analysed in each treatment group. • Number of subjects with ≥1 HES flare during Week 20 through Week 32 in each treatment group. • Test statistic and p-value for association between treatment and flare from Cochran-Mantel-Haenszel test. • Odds ratio and 95% CI from logistic regression model. • p-value from logistic regression model.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses

• Sensitivity analyses to assess the impact of missing data will be performed using the ITT population as follows:
  • Subjects withdrawing from the study prematurely prior to reporting an HES flare during Week 20 through Week 32, with the primary reason for treatment withdrawal reported as AE or Lack of Efficacy, will be classed as experiencing an HES flare during Week 20 through Week 32. Subjects withdrawing from the study prematurely with any other reason for treatment withdrawal will be included as having a flare if one is recorded during Week 20 through Week 32 prior to study withdrawal, and as not having a flare if no flare during Week 20 through Week 32 is recorded prior to study withdrawal.
  • Subjects withdrawing from the study prematurely will be included as having a flare if one is recorded during Week 20 through Week 32 prior to study withdrawal, and as not having a flare if no flare during Week 20 through Week 32 is recorded prior to study withdrawal.

7.4. Secondary Efficacy Analysis – Rate of HES Flares

7.4.1. Endpoint / Variables

The rate of HES flares will be calculated for each subject as the number of observed HES flares divided by the time (expressed in years) between the first dose of study treatment and either the Week 32 visit date if available, or otherwise the study withdrawal date (see Section 15.6.4).

The number of observed HES flares will be calculated for each subject as the number of unique starting dates for HES flares. To be considered as a separate episode of HES flare, the onset date of an HES flare must be at least 14 days apart from the resolution date of the preceding HES flare.

For flares meeting endpoint definition b) described in Section 7.1.1, each subsequent course of blinded active OCS beyond 14 days from the resolution date of the preceding flare will be considered as an additional flare (e.g., 3 courses of blinded active OCS are considered as 2 flares, 4 courses of blinded active OCS are considered as 3 flares, etc.).

See Section 15.6.4 for details of the definition of the onset and resolution date of HES flares and full details of the derivation of the rate of HES flares.

7.4.2. Summary Measure

The difference between mepolizumab and placebo in the rate/year of HES flares.

7.4.3. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. For subjects withdrawing prematurely from the study during the 32-week treatment period, all data up to the time of study withdrawal will be used to calculate the rate of HES flares. Sensitivity analyses will be performed to examine the potential impact of the missing data.

7.4.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

7.4.4.1. Statistical Methodology Specification

Endpoint
• Rate of HES flares.
Model Specification
• Wilcoxon Rank Sum test stratified by baseline OCS dose (0-≤20mg/day and >20mg/day

prednisone or equivalent) and region.

- Supplemented by an analysis using a negative binomial generalised linear model with a log-link function, including terms for baseline OCS dose (continuous scale), region, treatment and observed time (as an offset variable). The model estimated mean flare rate per year will be weighted according to the observed proportion of the categorical covariates in the study data by inclusion of the OM (obsmargins) option in the LSMEANS statement of the GENMOD procedure.

Model Checking & Diagnostics

- The fit of the negative binomial generalised linear model will be investigated by calculating and plotting standardised deviance residuals.

Model Results Presentation

- In each treatment group:
  - Median rate/year.
    - Median rate/year for HES flares meeting definition a) (see Section 7.1.1).
    - Median rate/year for HES flares meeting definition b) (see Section 7.1.1).
  - Adjusted mean rate/year from negative binomial model.
- p-value for difference between treatments in rate/year from Wilcoxon Rank Sum test.
- Rate ratio and 95% CI from negative binomial model.
- p-value from negative binomial model.

Subgroup Analyses

- No subgroup analyses will be performed on this endpoint.

Sensitivity and Supportive Statistical Analyses

- Sensitivity analyses to assess the impact of missing data will be performed using the ITT population as follows:
  - Subjects withdrawing from the study prematurely will have the missing time period imputed with the placebo flare rate for the missing time period, regardless of the reason for treatment discontinuation.
  - Subjects withdrawing from the study prematurely with primary reason for treatment discontinuation reported as AE or Lack of Efficacy, will have the missing time period imputed with the placebo flare rate for the missing time period. Subjects withdrawing from the study prematurely with a primary reason for treatment discontinuation other than AE or Lack of Efficacy will have HES flare rate calculated using available data up to study withdrawal date only.

7.5. Secondary Efficacy Analysis – Change from Baseline in Fatigue Severity BFI Item 3 (Worst Level of Fatigue in Past 24 Hours) at Week 32

7.5.1. Endpoint / Variables

The BFI has 9 items. The subject rates their fatigue level right now, their usual fatigue level over the last 24 hours and their worst level of fatigue over the last 24 hours using an 11-point rating scale anchored at 0 (no fatigue) and 10 (as bad as you can imagine). The subject also rates how, during the past 24 hours, fatigue has influenced each of the following on an 11-point rating scale anchored at 0 (does not interfere) and 10 (completely interferes): general activity, mood, walking ability, normal work, relations with other people and enjoyment of life. The subject completes item 3 (worst level of fatigue during past 24 hours) of the BFI daily and the full BFI every 7 days at home on the eDiary.

The change from baseline in fatigue severity (worst level of fatigue during past 24 hours) at Week 32 will be calculated using the mean of the 7 daily assessments of BFI item 3 up to and including the date of the Week 32 visit as the Week 32 assessment, and the mean of the 7 daily assessments of BFI item 3 up to but not including the date of first dose of study treatment as the baseline assessment. If any of the 7 daily assessments of BFI item 3 are missing for either the Week 32 time point or the baseline time point, the mean of the available daily assessments over the 7-day period will be used to calculate the change from baseline.

7.5.2. Summary Measure

The difference between mepolizumab and placebo in the change from baseline BFI item 3 at Week 32.

7.5.3. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the ‘treatment policy’ effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. Subjects with missing change from baseline BFI item 3 at Week 32 will be included in the analysis with the largest (i.e. worst) value observed for any subject. Sensitivity analyses to assess the impact of missing data will be performed.

7.5.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Summary statistics for BFI item 3 at each week of treatment will be presented, including change from baseline values. Assessment windows for each week are defined in Section 15.3.1.

The clinical relevance of changes in BFI item 3 at Week 32 will be assessed using a cumulative distribution plot showing the percentage of subjects in each treatment group with a reduction in BFI item 3 greater than equal to each value in the observed range; this will allow assessment of the treatment difference against a range of clinically important differences.

Endpoint
• Change from baseline in fatigue severity (BFI item 3) at Week 32.
Model Specification
• Wilcoxon Rank Sum test stratified by baseline fatigue severity ("severe" defined as BFI item 3 ≥7, and "not severe" defined as BFI item 3<7), baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region.
Model Checking & Diagnostics
• Not applicable.
Model Results Presentation
• Number analysed in each treatment group. • Median change from baseline BFI item 3 at Week 32 in each treatment group. • p-value for difference between treatments from Wilcoxon Rank Sum test.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses

• Repeated measures analysis including assessments at Week 4, 8, 12, 16, 20, 24, 28 and 32. In this analysis missing data will be assumed to be missing at random and will not be imputed with the largest i.e. worst value. A mixed effects model will be fitted with the following specification:
  • Time point, treatment and region included as fixed categorical effects.
  • Baseline BFI and baseline OCS dose included as continuous fixed covariates.
  • Interaction terms for baseline-by-timepoint and treatment-by-time point interaction.
  • The Kenward and Roger method (DDFM = KR) for approximating the denominator degrees of freedom to correct for bias in the estimated variance-covariance matrix.
  • REPEATED statement with TYPE=UN to specify an unstructured covariance structure for the R matrix.
  • The OBSMARGIN option on the LSMEANS statement in order to compute the adjusted geometric means with weights proportional to the input data set.

7.6. Exploratory Efficacy Analyses

Details of the planned displays for the exploratory endpoints are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

7.6.1. Proportion of Subjects Who Have an Elevated Blood Eosinophil Level That Meets the Pre-Defined Threshold During the 32-Week Study Treatment Period.

7.6.1.1. Endpoint / Variables

Subjects who have an elevated blood eosinophil level (2 x baseline value or baseline value + 2500 cells/μL) during the 32-week study treatment period will be identified from the central laboratory haematology results. Samples taken from the date of first dose of study medication up until the date of Visit 11 (Week 32) will be considered in the derivation. Baseline will be defined as in Section 5.2.

7.6.1.2. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. Subjects withdrawing from the study prematurely leading to missing blood assessments for blood eosinophil count will be included in the analysis as having an elevated blood eosinophil level that meets the pre-defined threshold.

7.6.1.3. Statistical Analyses / Methods

Endpoint
• Proportion of subjects who have an elevated blood eosinophil level during the 32-week study treatment period.
Model Specification
• Cochran-Mantel-Haenszel test stratified by baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region. • A supplementary analysis using a logistic regression analysis adjusting for covariates of baseline OCS dose (continuous scale), region, and treatment will also be performed.
Model Results Presentation
• Number of subjects analysed in each treatment group. • Number of subjects who have an elevated blood eosinophil level during the 32-week study treatment period. • Test statistic and p-value for association between treatment and endpoint from Cochran-Mantel-Haenszel test. • Odds ratio and 95% CI from logistic regression model. • p-value from logistic regression model.

Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses
• No sensitivity/supportive analyses will be performed on this endpoint.

7.6.2. FEV_1, FVC and FEV_1/FVC ratio

7.6.2.1. Endpoint / Variables

- Change from baseline FEV_1 at each visit.
- Change from baseline FVC at each visit.
- FEV_1/FVC at each visit.

7.6.2.2. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. Subjects with missing data will be assumed to be missing at random in the analysis.

7.6.2.3. Statistical Analyses / Methods

Summary statistics for FEV_1, FVC and FEV_1/FVC at each visit will presented by treatment, including change from baseline values. A separate summary and analysis excluding any data from timepoints where the subject did not withhold short-acting bronchodilators for 6 hours or long-acting bronchodilators for 12 hours will be produced. No statistical analysis will be performed on FEV_1/FVC.

Endpoint
• Change from baseline in FEV_1. • Change from baseline in FVC.
Model Specification

• Repeated measures with missing data assumed to be missing at random. A mixed effects model will be fitted with the following specification:
  ◦ Visit, treatment and region included as fixed categorical effects.
  ◦ Baseline FEV_1 (or FVC as appropriate) and baseline OCS dose included as continuous fixed covariates.
  ◦ Interaction terms for baseline-by-visit and treatment-by-visit.
  ◦ The Kenward and Roger method (DDFM = KR) for approximating the denominator degrees of freedom to correct for bias in the estimated variance-covariance matrix.
  ◦ REPEATED statement with TYPE=UN to specify an unstructured covariance structure for the R matrix.

• The OBSMARGIN option on the LSMEANS statement in order to compute the adjusted geometric means with weights proportional to the input data set.
Model Results Presentation
• Number analysed in each treatment group. • LS Mean (SE) and LS Mean Change from baseline (SE) in each treatment group. • Mean difference, 95% CI and p-value for mepolizumab vs placebo.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses
• The analysis will be repeated excluding any data from timepoints where the subject did not withhold short-acting bronchodilators for 6 hours or long-acting bronchodilators for 12 hours.

7.6.3. Echocardiogram

Echocardiogram/MUGA scans at Screening and Week 32 will be summarised by treatment for the ITT population. No statistical analysis of this endpoint will be performed.

7.6.4. Change From Baseline in HES Symptom Severity Based on HES Daily Symptoms (HES-DS) at Week 32

7.6.4.1. Endpoint / Variables

For each of the 6 symptom domains (muscle/joint pain, chills or sweats, abdominal pain or bloating, breathing symptoms, nasal or sinus symptoms and skin symptoms), the change from baseline symptom score at Week 32 will be defined using the mean of the 7 daily symptom scores up to and including the date of the Week 32 visit as the Week 32 assessment, and the mean of the 7 daily symptom scores up to but not including the date of first dose of study treatment as the baseline assessment. For each symptom domain, if any of the 7 daily symptom scores are missing for either the Week 32 time point or the baseline time point, the mean of the available daily symptom scores for the relevant symptom domain over the 7-day period will be used to calculate the change from baseline.

The change from baseline most bothersome symptom score at Week 32 will be derived using the mean domain scores at Week 32 and baseline for the up to 3 symptom domains identified by the subject as most bothersome at Week 0 (Visit 2).

7.6.4.2. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the ‘treatment policy’ effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. Subjects with missing change from baseline symptom score or missing most bothersome symptom score at Week 32 will be included in the analysis with the largest (i.e. worst) value observed for any subject.

7.6.4.3. Statistical Analyses / Methods

Summary statistics for the most bothersome symptom score and the symptom score for each symptom domain at each week of treatment will be presented, including change from baseline values. Assessment windows for each week are defined in Section 15.3.1.

Endpoint
• Change from baseline in most bothersome HES symptom severity score (HES-DS) at Week 32. • Change from baseline in HES symptom severity score (HES-DS) for each symptom at Week 32.
Model Specification
• Wilcoxon Rank Sum test stratified by median baseline symptom severity (baseline symptom severity≤median and baseline symptom severity>median), baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region.
Model Results Presentation
• Number analysed in each treatment group. • Median change from baseline at Week 32 in each treatment group. • p-value for difference between treatments from Wilcoxon Rank Sum test.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses

• Repeated measures analysis including assessments at Week 4, 8, 12, 16, 20, 24, 28 and 32. In this analysis missing data will be assumed to be missing at random and will not be imputed with the largest i.e. worst value. A mixed effects model will be fitted with the following specification:
  • Time point, treatment and region included as fixed categorical effects.
  • Baseline symptom severity and baseline OCS included as continuous fixed covariates.
  • Interaction terms for baseline-by-timepoint and treatment-by-time point interaction.
  • The Kenward and Roger method (DDFM = KR) for approximating the denominator degrees of freedom to correct for bias in the estimated variance-covariance matrix.
  • REPEATED statement with TYPE=UN to specify an unstructured covariance structure for the R matrix.
  • The OBSMARGIN option on the LSMEANS statement in order to compute the adjusted geometric means with weights proportional to the input data set.

7.6.5. Change from Baseline in BFI Total Score at Week 32

7.6.5.1. Endpoint / Variables

The full BFI is completed every 7 days at home on the eDiary. The BFI total score will be calculated as the mean of the 9 item scores recorded for the weekly assessment, as long as at least 5 of the 9 item scores are complete. The change from baseline in BFI total

score at Week 32 will be calculated using the weekly assessment windows for Week 32 and baseline defined in Section 15.3.1.

7.6.5.2. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. Subjects with missing change from baseline symptom score at Week 32 will be included in the analysis with the largest (i.e. worst) value observed for any subject.

7.6.5.3. Statistical Analyses / Methods

Summary statistics for BFI total score at each week of treatment will be presented, including change from baseline values. Assessment windows for each week are defined in Section 15.3.1.

Endpoint
• Change from baseline in BFI total score at Week 32.
Model Specification
• Wilcoxon Rank Sum test stratified by median baseline fatigue (baseline fatigue≤median and baseline fatigue>median), baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region.
Model Results Presentation
• Number analysed in each treatment group. • Median change from baseline at Week 32 in each treatment group. • p-value for difference between treatments from Wilcoxon Rank Sum test.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses

• For the change from baseline BFI total score, a repeated measures analysis including assessments at Week 4, 8, 12, 16, 20, 24, 28 and 32. In this analysis missing data will be assumed to be missing at random and will not be imputed with the largest i.e. worst value. A mixed effects model will be fitted with the following specification:
  • Time point, treatment and region included as fixed categorical effects.
  • Baseline BFI total score and baseline OCS included as continuous fixed covariates.
  • Interaction terms for baseline-by-timepoint and treatment-by-time point interaction.
  • The Kenward and Roger method (DDFM = KR) for approximating the denominator degrees of freedom to correct for bias in the estimated variance-covariance matrix.
  • REPEATED statement with TYPE=UN to specify an unstructured covariance structure for the R matrix.
  • The OBSMARGIN option on the LSMEANS statement in order to compute the adjusted geometric means with weights proportional to the input data set.

7.6.6. Clinician- and Subject-Rated Overall Response to Therapy Score (RTS) at Week 32

7.6.6.1. Endpoint / Variables

- Clinician-rated overall response to therapy (significantly improved [1], moderately improved [2], mildly improved [3], no change [4], mildly worse [5], moderately worse [6] and significantly worse [7]) at Week 32.

- Subject-rated overall response to therapy (significantly improved [1], moderately improved [2], mildly improved [3], no change [4], mildly worse [5], moderately worse [6] and significantly worse [7]) at Week 32.

7.6.6.2. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. Subjects with missing response at Week 32 will be included in the analysis with the largest (i.e. worst) value observed for any subject.

7.6.6.3. Statistical Analyses / Methods

Summary statistics for clinician- and subject- rated overall response to therapy at each visit will be presented.

Endpoint
• Clinician-rated overall response to therapy at Week 32. • Subject-rated overall response to therapy at Week 32
Model Specification
• Wilcoxon Rank Sum test stratified by baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region. • Supplemented by an ordinal logistic regression (proportional odds) analysis adjusting for covariates of baseline OCS dose (continuous scale), region and treatment.
Model Results Presentation
• Number analysed in each treatment group. • Median change from baseline at Week 32 in each treatment group. • p-value for difference between treatments from Wilcoxon Rank Sum test. • Odds ratio and 95% CI from ordinal logistic regression model. • p-value from ordinal logistic regression model.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses
• Clinician- and subject-rated overall response to therapy will also be analysed at Week 4, 8, 12, 16, 20, 24 and 28 in the same way as the Week 32 analysis.

7.6.7. Change from Baseline in Subject-Rated Symptom Severity (SSR) at Week 32

7.6.7.1. Endpoint / Variables

At each visit, subjects are asked to rate their symptoms of HES now as none (0), mild (1), moderate (2), severe (3) or very severe (4). The change from baseline at Week 32 will be calculated from the Week 32 assessment and the Week 0 assessment and expressed in terms of number of categories of improvement or worsening of symptoms i.e. 4 point improvement (-4), 3 point improvement (-3), 2 point improvement (-2), 1 point improvement (-1), no change (0), 1 point worsening (1), 2 point worsening (2), 3 point worsening (3) or 4 point worsening (4).

7.6.7.2. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. Subjects with missing SSR score at Week 32 will be included in the analysis with the largest (i.e. worst) value observed for any subject.

7.6.7.3. Statistical Analyses / Methods

Summary statistics for the SSR score at each visit will be presented, as well as the change from baseline.

Endpoint
• Change from baseline in subject-rated symptom severity (SSR) at Week 32.
Model Specification
• Wilcoxon Rank Sum test stratified by baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region. • Supplemented by an ordinal logistic regression (proportional odds) analysis adjusting for covariates of baseline OCS dose (continuous scale), region and treatment.
Model Results Presentation
• Number analysed in each treatment group. • Median change from baseline at Week 32 in each treatment group. • p-value for difference between treatments from Wilcoxon Rank Sum test. • Odds ratio and 95% CI from ordinal logistic regression model. • p-value from ordinal logistic regression model.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses
• No sensitivity analyses will be performed.

7.6.8. Change from Baseline in Modified Memorial Symptom Assessment Scale-Short Form (MSAS-SF) responses at Week 32

7.6.8.1. Endpoint / Variables

The MSAS-SF questionnaire records the distress or bother in the last week caused by each of 32 symptoms on 5-point scale (not at all [0], a little bit [1], somewhat [2], quite a bit [3], very much [4]).

- Total MSAS-SF score for each visit will be calculated as the mean of the 32 scores recorded for that visit.

- MSAS-SF global distress index (GDI) for each visit will be calculated as the mean of the scores for the 4 psychological symptoms (feeling sad, worrying, feeling irritable and feeling nervous) and 6 physical symptoms (lack of energy, pain, lack of appetite, feeling drowsy, constipation, dry mouth).

- MSAS-SF physical symptom subscale score for each visit will be calculated as the mean of the scores for 12 physical symptoms (lack of energy, pain, lack of appetite, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, feeling bloated, and dizziness).

- MSAS-SF psychological symptom subscale score for each visit will be calculated as the mean of the scores for 6 psychologic symptoms (worrying, feeling sad, feeling nervous, difficulty sleeping, feeling irritable, and difficulty concentrating).

For each score the change from baseline at Week 32 will be calculated from the assessment at Week 0 and Week 32.

7.6.8.2. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. Subjects with missing change from baseline MSAS-SF score at Week 32 will be included in the analysis with the largest (i.e. worst) value observed for any subject.

7.6.8.3. Statistical Analyses / Methods

Summary statistics for MSAS-SF scores at each visit will be presented, including change from baseline values.

Endpoint
• Change from baseline in Total Modified Memorial Symptom Assessment Scale-Short Form (MSAS-SF) score at Week 32. • Change from baseline in Modified Memorial Symptom Assessment Scale-Short Form (MSAS-SF) global distress index at Week 32.

• Change from baseline in Modified Memorial Symptom Assessment Scale-Short Form (MSAS-SF) physical symptom subscale score at Week 32. • Change from baseline in Modified Memorial Symptom Assessment Scale-Short Form (MSAS-SF) psychological symptom subscale score at Week 32.
Model Specification
• Wilcoxon Rank Sum test stratified by median baseline score (baseline score≤median and baseline score>median), baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region.
Model Results Presentation
• Number analysed in each treatment group. • Median change from baseline at Week 32 in each treatment group. • p-value for difference between treatments from Wilcoxon Rank Sum test.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses

• A repeated measures analysis including assessments at Week 4, 8, 16, 24 and 32. In this analysis missing data will be assumed to be missing at random and will not be imputed with the largest i.e. worst value. A mixed effects model will be fitted with the following specification:
  • Time point, treatment and region included as fixed categorical effects.
  • Baseline score and baseline OCS dose included as continuous fixed covariates.
  • Interaction terms for baseline-by-timepoint and treatment-by-time point interaction.
  • The Kenward and Roger method (DDFM = KR) for approximating the denominator degrees of freedom to correct for bias in the estimated variance-covariance matrix.
  • REPEATED statement with TYPE=UN to specify an unstructured covariance structure for the R matrix.
  • The OBSMARGIN option on the LSMEANS statement in order to compute the adjusted geometric means with weights proportional to the input data set.

7.6.9. Change from Baseline in Physical Function and Sleep (Patient Reported Outcome Measurement Information System [PROMIS]) at Week 32

7.6.9.1. Endpoint / Variables

- The PROMIS physical function score for each visit will be calculated as the mean of the scores for the 12 physical function items recorded for that visit, as long as at least 6 of the 12 item scores are complete. The change from baseline at Week 32 will be calculated from the Week 32 assessment and the Week 0 assessment.

- The PROMIS sleep score for each visit will be calculated as the mean of the scores for the 2 sleep items recorded for that visit; if either of the items has a missing score, the PROMIS sleep score will be assigned as missing for that visit. The change from

baseline at Week 32 will be calculated from the Week 32 assessment and the Week 0 assessment.

7.6.9.2. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated (estimand) will be the 'treatment policy' effect of initial randomised treatment. A treatment policy strategy will be used for the intercurrent events of a) discontinuation of study medication and b) receipt of alternative HES medications. Subjects with missing change from baseline PROMIS score at Week 32 will be included in the analysis with the largest (i.e. worst) value observed for any subject.

7.6.9.3. Statistical Analyses / Methods

Summary statistics for PROMIS physical function and sleep score at each visit will be presented, including change from baseline values.

Endpoint
• Change from baseline in PROMIS physical function score at Week 32. • Change from baseline in PROMIS sleep score at Week 32.
Model Specification
• Wilcoxon Rank Sum test stratified by median baseline score (baseline score≤median and baseline score>median), baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region.
Model Results Presentation
• Number analysed in each treatment group. • Median change from baseline at Week 32 in each treatment group. • p-value for difference between treatments from Wilcoxon Rank Sum test.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses

• A repeated measures analysis including assessments at Week 4, 8, 16, 24 and 32. In this analysis missing data will be assumed to be missing at random and will not be imputed with the largest i.e. worst value. A mixed effects model will be fitted with the following specification:
  • Time point, treatment and region included as fixed categorical effects.
  • Baseline score and baseline OCS included as continuous fixed covariates.
  • Interaction terms for baseline-by-timepoint and treatment-by-time point interaction.
  • The Kenward and Roger method (DDFM = KR) for approximating the denominator degrees of freedom to correct for bias in the estimated variance-covariance matrix.
  • REPEATED statement with TYPE=UN to specify an unstructured covariance structure for the R matrix.
  • The OBSMARGIN option on the LSMEANS statement in order to compute the adjusted geometric means with weights proportional to the input data set.

8. HEALTH OUTCOMES ANALYSIS

8.1. SF-36 v2

- Certified scoring of the SF-36 survey will be performed using OPTUM™ software.
- The eight domain scores (bodily pain, general health, mental health, physical functioning, role emotional, role physical, social functioning and vitality) as well as the physical and mental component summary scores provided by the software will be converted to SDTM and ADaM data sets by GSK Biostatistics.
- Domain and component summary scores will be summarised by visit, including change from baseline.
- Summaries will be performed on the ITT population.
- No statistical analysis of the SF-36 scores will be performed.

8.2. Healthcare Resource Utilization (HCRU)

- Healthcare resource utilisation associated with a HES flare will be summarised by treatment group.
- Summaries will be performed on the ITT population.
- For each resource type, the number of flares using resource, total amount of resource and mean (SD) resource per HES flare will be summarised.
- No statistical analysis of this endpoint will be performed.

8.2.1. Work Productivity and Activity Impairment

The following endpoints will be derived and summarised by treatment group and visit for the ITT population. Change from baseline will also be derived and summarised.

Endpoint	Derivation
Percentage work time missed due to health	Q2 / (Q2 + Q4)
Percentage impairment while working due to health	Q5 / 10
Percentage overall work impairment due to health	Q2 / (Q2 + Q4) + [(1- (Q2 / (Q2 + Q4))) x (Q5 / 10)]
Percentage activity impairment due to health	Q6 / 10

No statistical analysis of work productivity and activity impairment will be performed.

9. POPULATION PHARMACOKINETIC ANALYSES

Refer to Data Display Standards & Handling Conventions (Section 15.5.3 Reporting Standards for Pharmacokinetic Data).

In support of the analysis described below, a specific dataset will be generated. Specifications for the generation of the dataset will be provided in a separate document.

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK Data Standards and statistical principles.

9.1. Population of Interest

The population PK analysis will be performed on the PK population.

9.2. Strategy for Intercurrent (Post-Randomization) Events

For subjects withdrawing prematurely from study treatment, all available data will be included in the analysis.

Based on mepolizumab PK knowledge, concentrations below the limit of quantification (BLQ) of the assay is considered unlikely at the 300 mg SC dose investigated, in view of the PK sampling scheme selected in the study. Thus, any such results will be treated as missing.

Outlier data will be assessed for plausibility; however, the aim is to use all available data whenever possible. Any decision to exclude data will be fully documented and specified in the clinical study report.

9.3. Population Pharmacokinetic Methodology

Sparse blood sampling is implemented in this study for determination of mepolizumab plasma concentration and subsequent data analysis by population PK methods using the most recent population pharmacokinetics model (meta-analysis PK model of data across indications described in GlaxoSmithKline Document Number 2015N238436_00). Since mepolizumab PK following intravenous administration in HES subjects has already been evaluated within the population PK meta-analysis (using PK samples collected in previous Phase III study MHE100185), the main objectives of this population PK analysis are:

- To evaluate mepolizumab pharmacokinetics in subjects with HES following the subcutaneous administration of a 300 mg dose every 4 weeks.
- To investigate the impact of covariates of interest in the studied HES population (such as baseline characteristics, co-medication) on specific parameters (e.g. clearance) in order to identify potential sources of inter-individual variability in these parameters.
- To obtain individual plasma concentration predictions for the timepoints at which PD is measured to allow the conduct of population PKPD analyses if deemed appropriate.

Mepolizumab plasma concentration-time data (samples collected at Weeks 4, 16 and 32; at the early Withdrawal and the additional follow-up visits (if applicable)) will be analysed by population methods using nonlinear mixed-effects modelling. The analysis will be carried out using appropriate software (e.g., NONMEM or SAS).

9.3.1. Base Model

In consideration of the sparse sampling (3 samples post-start of treatment over 32 weeks: Week 4, 16 and 32) and the wealth of mepolizumab PK knowledge, the most recent population PK model will be applied directly to the dataset without estimation (e.g. maxevals=0 in NONMEM) and predictions generated, against which the model will be validated prospectively using appropriate goodness of fit tests. For example, the Anderson-Darling and Cramér–von Mises tests are accepted methods of comparing Empirical Distribution Functions for model and data (i.e., PK concentrations) to evaluate whether independent observations (i.e., observed PK concentrations from the study) are adequately described by a model (i.e., most recent population PK model).

The following will be obtained:

- A description of the key models tested during the model development will be provided and tabulated;
- Population mepolizumab plasma PK parameter estimates with 95% CI from the final model will be tabulated. Goodness of fit plots for the final model will be presented;
- Individual post-hoc PK parameter estimates (such as area under the plasma concentration-time curve over the dosing interval [AUC (0-τ)], C_{AV} [AUC (0-τ)/τ]) will be summarised descriptively and listed;
- Individual post-hoc predicted plasma concentrations will be summarised descriptively and listed;
- Accumulation ratio estimate will be assessed at Week 16 and 32.

The most recent model consists of a two-compartment pharmacokinetic model with first-order absorption and elimination. Bodyweight is incorporated into the model using allometry with fixed physiological allometric exponents of 0.75 and unity for clearance and volumes, respectively. Albumin and creatinine clearance are also included as covariates of mepolizumab clearance on physiological grounds, however their effects are small and not of clinical relevance. Details of the model can be found in report GlaxoSmithKline Document Number 2015N238436_00.

9.3.2. Investigation of Covariates

The impact of the following prospectively selected covariates on mepolizumab exposure (e.g. clearance) will be evaluated using the procedures described in Section 9.3.3.

Category	Covariates
Demographics	Weight (included in the structural model), age, race, gender, country
Baseline clinical status	Creatinine clearance, albumin (both already included in the

Category	Covariates
	current model), serum creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, total protein
Baseline disease status	Flare history, blood eosinophils and baseline OCS dose
Concomitant medications	If data permits*, e.g. immunosuppressant therapies (e.g. methotrexate, azathioprine and mycophenolate mofetil), proton pump inhibitors, statins, pain relief (e.g. paracetamol, NSAIDs), interferon alfa and antihypertensive drugs
Others	Presence/absence of anti-drug antibodies and previous biologics use (monoclonal antibodies).

*Attempt to investigate those classes of drug will be made providing data permits.

Covariate selection will be based on physiological plausibility, supported by graphical evaluation (PK parameters vs. covariates), and formally by automated linear model fitting using proc glmselect in SAS 9.2 (or higher). Individual PK parameters and covariates will be log-transformed and standardized before analysis. For forward and backward selections, significance levels of 0.1 and 0.05 will be applied respectively, in line with criteria used in previous analyses. Co-linearity between covariates will be carefully considered.

Identified covariates will then be subjected to traditional covariate analysis (with estimation step) and will follow the procedures described in Section 9.3.3. If deemed appropriate box plots of systemic clearance versus covariates of interest (e.g., immunogenicity status) will be provided.

9.3.3. Covariate Model Selection Procedures

The covariate model building will follow a step-wise process consisting of a forward and backward selection procedure. The likelihood ratio test will be used to evaluate the significance of incorporating or removing covariates into the population model based on alpha levels set *a priori*. For forward and backward selections, a significance level of 0.05 and 0.01 for first order conditional estimation with interaction (FOCE-I) will be used, respectively, in line with criteria used in previous analyses.

- **Step-wise forward addition procedure**

Each covariate will be included individually in the 'base model' to identify covariates resulting in a decrease in the objective function value (OFV) of > 3.84, $\chi 2 < 0.05$ for 1 degree of freedom (*df*) using FOCE-I. The retained covariates will then be added to the base model one by one, starting with the most significant ones until all covariates have been tested. Note, if a covariate exponent estimate is numerically small, the covariate will not be retained; irrespective of objective function. This will also be supported by examination of the goodness of fit. This will constitute the full model.

- **Backward elimination procedure**

From the full model, the significance of each covariate will be tested individually by removing covariates one by one until all non-significant covariates have been excluded. A covariate will be retained if upon removal, the OFV increase by more than 6.64 points ($\chi 2 < 0.01$ for 1 *df)* using FOCE-I. Note, a covariate may be retained in the model despite being found non-statistically significant, if there is a strong rationale for its inclusion. This will constitute the final model.

Note: centering of continuous covariates may be considered, as appropriate. The mean or median value of the subjects included in the analysis may be used for example.

The impact of the presence of anti-mepolizumab antibodies may not be formally tested as a covariate in the model, considering the low incidence observed in the mepolizumab programme to date. Instead a graphical approach will be used, if deemed appropriate.

9.3.4. Model Evaluation

The uncertainty in the parameter estimates will be assessed (e.g. from the standard error estimates provided by NONMEM or from the 95% CI estimates provided by other appropriate analysis conducted using other software). Furthermore, the model performance will be investigated using a set of goodness of fit plots as well as Visual Predictive Check (VPC) method. Other evaluation methods may be used (e.g., bootstrapping) if deemed appropriate.

10. PHARMACODYNAMIC ANALYSES

10.1. Blood Eosinophils

10.1.1. Population of Interest

Blood eosinophil analyses will be based on the Pharmacodynamic population.

10.1.2. Endpoint / Variables

Absolute and ratio to baseline blood eosinophil counts at each visit. For blood eosinophils, baseline will be defined as the latest blood eosinophil value measured by the central laboratory prior to the first dose of study treatment.

10.1.3. Summary Measure

The difference between mepolizumab and placebo in the ratio to baseline of blood eosinophils.

10.1.4. Strategy for Intercurrent (Post-Randomization) Events

For subjects withdrawing prematurely from study treatment, only the endpoint values up to and including 28 days after the last dose of study treatment will be included in the analysis ('while on treatment' estimand).

10.1.5. Statistical Analyses / Methods

- Blood eosinophil counts will be $\log_e$-transformed prior to analysis. Non-detectable blood eosinophil values of 0 GI/L, or results below the limit of quantification will be replaced by half of the lowest observed detectable (non-zero) value in the study data set, prior to log transformation.

- Absolute and ratio to baseline blood eosinophil counts will be summarised by treatment group and visit. Only results from the central laboratory will be included in the summary, however all data will be listed.

- Full details of data displays to be presented are given in Appendix 10: List of Data Displays.

10.1.5.1. Statistical Methodology Specification

Endpoint
• Ratio to baseline blood eosinophil count
Model Specification
• A mixed effects repeated measures model will be fitted to the $\log_e$ transformed blood eosinophil data with the following specification: • Visit, treatment and region included as fixed categorical effects.

• Baseline blood eosinophil count (log_e scale) and baseline OCS dose included as continuous fixed covariates. • Interaction terms for baseline (screening) blood eosinophil count-by-visit and treatment-by-visit. • The Kenward and Roger method (DDFM = KR) for approximating the denominator degrees of freedom to correct for bias in the estimated variance-covariance matrix. • REPEATED statement with TYPE=UN to specify an unstructured covariance structure for the R matrix. • The OBSMARGIN option on the LSMEANS statement in order to compute the adjusted geometric means with weights proportional to the input data set.
Model Results Presentation
• Number analysed in each treatment group. • LS Mean (SE) and LS Mean ratio to screening (SE) in each treatment group. • Mean treatment ratio, 95% CI and p-value for mepolizumab vs placebo.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses
• The MMRM model specified above will also be fitted to the log transformed absolute blood eosinophil counts and adjusted mean absolute blood eosinophil counts and 95% CI from this model will be plotted.

10.2. Serum Total IL-5

10.2.1. Population of Interest

Total IL-5 analyses will be based on the Pharmacodynamic population.

10.2.2. Endpoint / Variables

Absolute and ratio to baseline total IL-5 at Week 32

10.2.3. Summary Measure

The difference between mepolizumab and placebo in the ratio to baseline of serum total IL-5 at Week 32.

10.2.4. Strategy for Intercurrent (Post-Randomization) Events

For subjects withdrawing prematurely from study treatment, only the endpoint values up to and including 28 days after the last dose of study treatment will be included in the analysis ('while on treatment' estimand).

10.2.5. Statistical Analyses / Methods

- Total IL-5 values will be log_e-transformed prior to analysis. Values below the limit of quantification will be replaced by half the limit of quantification, prior to log

transformation. Summary statistics will include the number and percentage of BLQ values.

- Absolute and ratio to baseline total IL-5 values will be summarised by treatment group and visit (Baseline and Week 32).

- Full details of data displays to be presented are given in Appendix 10: List of Data Displays.

10.2.5.1. Statistical Methodology Specification

Endpoint
• Ratio to baseline total IL-5 at Week 32
Model Specification
• Wilcoxon Rank Sum test stratified by baseline OCS dose (0-≤20mg/day and >20mg/day prednisone or equivalent) and region.
Model Results Presentation
• Number analysed in each treatment group. • Median change from baseline at Week 32 in each treatment group. • p-value for difference between treatments from Wilcoxon Rank Sum test.
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses
• No sensitivity analyses will be performed.

11. SAFETY ANALYSES

The safety analyses will be based on the Safety population, unless otherwise specified.

11.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. Common AEs will be defined as AEs with frequency ≥3% (prior to rounding to nearest percent) in either treatment group.

The details of the planned displays are provided in Appendix 10: List of Data Displays.

11.1.1. Adverse Events of Special Interest

Adverse events of special interest (AESIs) reported by the investigator as systemic reactions (further categorised by the investigator as either allergic [type I hypersensitivity] or other systemic reactions and assessed against Sampson criteria for anaphylaxis) are collected via targeted eCRF within the study. Local injection site reactions are also collected via targeted eCRF within the study.

AESIs of opportunistic infections, malignancies, serious cardiac, vascular and thromboembolic (CVT) events and serious ischemic events will be identified from a list of relevant preferred terms maintained within a project level reference dataset created based on the MedDRA dictionary available at the time of DBF for this study. Further details of how relevant preferred terms are identified are given in the Program Safety Analysis Plan (PSAP).

Separate summary tables showing the number and percent of subjects with each type of AESI, broken down by preferred term will be created.

For each type of AESI a profile summary table will be produced containing information including, but not limited to, the number of occurrences of the event, event characteristics, time to onset, intensity, outcome and action taken.

The relative risk of each AESI between mepolizumab and placebo with 95% confidence intervals will also be presented.

Separate listings of AESIs identified by the investigator as anaphylaxis, allergic (type I hypersensitivity), other systemic reactions and local injection site reactions will be produced, as well as listings of opportunistic infections, malignancies, serious CVT events and serious ischemic events.

11.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Haematology laboratory tests and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 10: List of Data Displays.

A scatter plot of maximum ALT vs baseline ALT, and maximum ALT vs total bilirubin will be produced. In addition, if any liver stopping or liver monitoring events occur during the study, summaries of liver monitoring/stopping event reporting and hepatobiliary laboratory abnormalities will be produced.

11.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 10: List of Data Displays.

12. IMMUNOGENICITY ANALYSES

12.1. Overview of Immunogenicity Analyses

For the immunogenicity assessment, two types of anti-drug antibody (ADA) assays will be performed, a binding anti-drug antibody assay and a neutralizing antibody assay.

For the binding assay, there will be a three tiered analysis: screening, confirmation and titration. The screening assay produces a result of positive or negative relative to a screening cut point. Positive samples continue with the confirmation assay, which also produces a result of positive or negative relative to a confirmation cut point. For positive confirmation samples, a titre value will also be obtained to quantify the degree of binding in a titration assay and the sample will be tested with the neutralizing assay, which also reports results as positive or negative.

The binding ADA results at each visit will be categorised as negative, transient positive (defined as a single confirmatory positive immunogenic response that does not occur at the final study assessment) or persistent positive (defined as a confirmatory positive immunogenic response for at least 2 consecutive assessments excluding the screening visit, or a single result at the final study assessment). In addition, the highest post-baseline binding ADA confirmatory result obtained for a subject will be summarised. Subjects with both positive and negative results will be identified in the positive category. Summary statistics for the titre result by visit will also be presented.

A summary of adverse events by highest post-baseline binding ADA confirmatory result (as defined above) will be produced.

A summary of treatment emergent positive confirmatory binding ADA results in the subset of subjects who did not have a positive confirmatory binding ADA result prior to the dosing of study treatment will also be presented.

Neutralizing antibody assay results will be summarised by visit. In addition, the highest post-baseline neutralising antibody assay result during the treatment period of the study will be summarised, with subjects with both positive and negative results identified in the positive category.

Immunogenicity data will be listed for subjects with at least one positive screening binding assay.

13. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

In support of the analysis described below, a specific dataset will be generated. Specifications for the generation of the dataset will be provided in a separate document.

The details of the planned displays are presented in Appendix 10: List of Data Displays.

13.1. Population of Interest

The population PKPD analysis will be performed on the PK and PD populations.

13.2. Strategy for Intercurrent (Post-Randomization) Events

For subjects withdrawing prematurely from study treatment, all available data will be included in the analysis.

Zero values for the baseline blood eosinophil count as well as for blood eosinophil count will be replaced by half of the lowest observed detectable (non-zero) value in the study data set (consistent with approaches used in other analyses).

Outlier data will be assessed for plausibility, however the aim is to use all available data whenever possible. Any decision to exclude data will be fully documented and specified in the clinical study report.

13.3. Population Pharmacokinetic/Pharmacodynamic Methodology

If deemed appropriate, a population pharmacokinetic/pharmacodynamic analysis will be conducted.

Blood eosinophil count were measured during the course of the study over the 32 weeks treatment period and will be analysed by population methods using the most recent population PKPD model (meta-analysis PKPD model of data across indications described in GlaxoSmithKline Document Number 2015N238436_00).

The objectives of the population PKPD analysis are:

- To evaluate mepolizumab pharmacodynamics in subjects with HES following subcutaneous administration of a 300 mg dose every 4 weeks;
- To investigate the impact of covariates of interest in the studied HES population (such as baseline characteristics, co-medication) on specific parameters (e.g. maximum blood eosinophil reduction) in order to identify potential sources of inter-individual variability in these parameters.

Mepolizumab blood eosinophil count-time data (samples collected at screening, Week 2, Week 4 and every 4 weeks for the remainder of the 32-week treatment period) will be analysed by population methods using nonlinear mixed-effects modelling. The analysis will be carried out using appropriate software (e.g., NONMEM or SAS).

13.3.1. Base Model

The most recent population PKPD model will be applied directly to the dataset without estimation (e.g. maxevals=0 in NONMEM) and predictions generated against which the model will be validated prospectively using appropriate goodness of fit tests as described in Section 9.3.1 (using the observed data from the study).

The following will be obtained:

- A description of the key models tested during the model development will be provided and tabulated.
- The population PD parameter estimates with 95% CI from the final model will be tabulated. Goodness of fit plots for the final model will be presented.

The most recent population PKPD model consists of an indirect response model parameterised in term of baseline blood eosinophil count (KRO), rate of elimination of eosinophils in the blood (Kout), concentration resulting in 50% of maximum drug effect (IC_{50}) and maximum effect (Imax). Observed baseline blood eosinophil count is included as covariates of both predicted baseline and mepolizumab inhibitory response; and disease for predicted baseline blood eosinophil count. Details of the model can be found in GlaxoSmithKline Document Number 2015N238436_00 and GlaxoSmithKline Document Number 2015N255079_00 (extension of the former report).

13.3.2. Investigation of Covariates

The impact of the following prospectively selected plausible covariates on relevant parameters (i.e., baseline blood eosinophil count and maximum effect) will be evaluated.

Category	Covariates
Demographics	Age, race, gender
Baseline disease status	Flare history, blood eosinophils (already included in the current model)
Others	Baseline OCS absolute dose, presence/absence of anti-drug antibodies*, immunosuppressant therapies* (e.g. methotrexate, azathioprine and mycophenolate mofetil), interferon alfa*

*Attempt to investigate those covariates will be made providing data permits.

Covariate selection will be based on physiological plausibility, supported by graphical evaluation (PD parameters vs. covariates), and formally by automated linear model fitting using proc glmselect in SAS 9.2 (or higher). Individual PD parameters and covariates will be log-transformed and standardized before analysis. For forward and backward selections, significance levels of 0.1 and 0.05 will be applied respectively, in line with criteria used in previous analyses. Co-linearity between covariates will be carefully considered.

Identified covariates will then be subjected to traditional covariate analysis (with estimation step) and will follow the same procedures as described in Section 9.3.3 for the population PK model.

Model evaluation will be as described in Section 9.3.4 for the population PK model.

14. REFERENCES

GlaxoSmithKline Document Number 2013N171550_00 Study ID 200622. A randomised, double-blind, placebo-controlled study to investigate the efficacy and safety of mepolizumab in the treatment of adolescent and adult subjects with severe hypereosinophilic syndrome. Report Date 29-APR-2016.

GlaxoSmithKline Document Number 2015N238436_00 Study ID N/A. A population PK and PKPD meta-analysis of combined intravenous and subcutaneous mepolizumab data. Report Date 27-MAY-2015.

GlaxoSmithKline Document Number 2015N255079_00 Study ID N/A. Supplementary outputs from a population PK and PKPD meta-analysis of combined intravenous and subcutaneous mepolizumab data. Report Date 04-OCT-2015.

15. APPENDICES

15.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

Subjects with important protocol deviations considered to potentially have an effect on the primary efficacy analysis will be excluded from the Per Protocol (PP) population. The decision to exclude a subject from the PP population or exclude part of their data from the PP population will be made prior to breaking the blind.

15.1.1. Exclusions from Per Protocol Population

A subject meeting any of the following criteria will be excluded from the Per Protocol population:

Number	Exclusion Description
01	Inclusion #3 – Insufficient evidence that subject has been diagnosed with HES for at least 6 months at randomization (Visit 2).
02	Inclusion #4 – Subject did not have a history of two or more flares within the past 12 months prior to screening (Visit 1), with at least one HES flare not related to a decrease in HES therapy during the 4 weeks prior to the flare.
03	Inclusion #5 – Subject did not have a blood eosinophil count ≥1000 cells/μL collected during screening (within 4 weeks prior to randomization). Investigators were permitted to use local laboratory results to meet this inclusion criteria, therefore if the screening central laboratory blood eosinophil count is <1000 cells/μL but a local laboratory blood eosinophil count ≥1000 cells/μL is available during screening the subject will not be considered a protocol deviation or excluded from the Per Protocol population.
04	Inclusion #6 – Subject was not on a stable dose of HES therapy for the 4 weeks prior to randomization (Visit 2).
05	Incorrect study treatment administered at any point during the study i.e. subject received placebo instead of mepolizumab or vice versa.
06	Subject received a medication or herbal remedy which may alter the course of HES or interact with the study treatment with the exception of HES therapy to treat an HES flare.

15.2. Appendix 2: Schedule of Activities

15.2.1. Protocol Defined Schedule of Events

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

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

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

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

15.3. Appendix 3: Assessment Windows

15.3.1. Definition of Weekly Assessment Windows

Daily assessments of BFI item 3 and HES daily symptoms as well as weekly assessments of the full BFI will be assigned a single weekly analysis time point according to the table below.

Analysis Timepoint	Analysis Window		
	Beginning Timepoint	Ending Timepoint	Special Rules for Handling Overlapping Timepoints
Week 32	Week 32 (Visit 11) visit date – 6 days	Week 32 (Visit 11) visit date	
Week 31	Week 32 (Visit 11) visit date – 13 days	Week 32 (Visit 11) visit date – 7 days	If assessment falls into Week 31/Week 30/Week 29 and Week 28, assign assessment as Week 28. If assessment date is less than Week 28 (Visit 10) visit date, assign a relevant timepoint less than Week 28.
Week 30	Week 32 (Visit 11) visit date – 20 days	Week 32 (Visit 11) visit date – 14 days	
Week 29	Week 32 (Visit 11) visit date – 27 days	Week 32 (Visit 11) visit date – 21 days	
Week 28	Week 28 (Visit 10) visit date – 6 days	Week 28 (Visit 10) visit date	
Week 27	Week 28 (Visit 10) visit date – 13 days	Week 28 (Visit 10) visit date – 7 days	If assessment falls into Week 27/Week 26/Week 25 and Week 24, assign assessment as Week 24. If assessment date is less than Week 24 (Visit 9) visit date, assign a relevant timepoint less than Week 24.
Week 26	Week 28 (Visit 10) visit date – 20 days	Week 28 (Visit 10) visit date – 14 days	
Week 25	Week 28 (Visit 10) visit date – 27 days	Week 28 (Visit 10) visit date – 21 days	
Week 24	Week 24 (Visit 9) visit date – 6 days	Week 24 (Visit 9) visit date	
Week 23	Week 24 (Visit 9) visit date – 13 days	Week 24 (Visit 9) visit date – 7 days	If assessment falls into Week 23/Week 22/Week 21 and Week 20, assign assessment as Week 20. If assessment date is less than Week 20 (Visit 8) visit date, assign a relevant timepoint less than Week 20.
Week 22	Week 24 (Visit 9) visit date – 20 days	Week 24 (Visit 9) visit date – 14 days	
Week 21	Week 24 (Visit 9) visit date – 27 days	Week 24 (Visit 9) visit date – 21 days	
Week 20	Week 20 (Visit 8) visit date – 6 days	Week 20 (Visit 8) visit date	
Week 19	Week 20 (Visit 8) visit date – 13 days	Week 20 (Visit 8) visit date – 7 days	If assessment falls into Week 19/Week 18/Week 17 and Week 16, assign assessment as Week 16. If assessment date is less than Week 16 (Visit 7) visit date, assign a relevant timepoint less than
Week 18	Week 20 (Visit 8) visit date – 20 days	Week 20 (Visit 8) visit date – 14 days	
Week 17	Week 20 (Visit 8) visit date – 27 days	Week 20 (Visit 8) visit date – 21 days	

Analysis Timepoint	Analysis Window		
	Beginning Timepoint	Ending Timepoint	Special Rules for Handling Overlapping Timepoints
			Week 16.
Week 16	Week 16 (Visit 7) visit date – 6 days	Week 16 (Visit 7) visit date	
Week 15	Week 16 (Visit 7) visit date – 13 days	Week 16 (Visit 7) visit date – 7 days	If assessment falls into Week 15/Week 14/Week 13 and Week 12, assign assessment as Week 12. If assessment date is less than Week 12 (Visit 6) visit date, assign a relevant timepoint less than Week 12.
Week 14	Week 16 (Visit 7) visit date – 20 days	Week 16 (Visit 7) visit date – 14 days	
Week 13	Week 16 (Visit 7) visit date – 27 days	Week 16 (Visit 7) visit date – 21 days	
Week 12	Week 12 (Visit 6) visit date – 6 days	Week 12 (Visit 6) visit date	
Week 11	Week 12 (Visit 6) visit date – 13 days	Week 12 (Visit 6) visit date – 7 days	If assessment falls into Week 11/Week 10/Week 9 and Week 8, assign assessment as Week 8. If assessment date is less than Week 8 (Visit 5) visit date, assign a relevant timepoint less than Week 8.
Week 10	Week 12 (Visit 6) visit date – 20 days	Week 12 (Visit 6) visit date – 14 days	
Week 9	Week 12 (Visit 6) visit date – 27 days	Week 12 (Visit 6) visit date – 21 days	
Week 8	Week 8 (Visit 5) visit date – 6 days	Week 8 (Visit 5) visit date	
Week 7	Week 8 (Visit 5) visit date – 13 days	Week 8 (Visit 5) visit date – 7 days	If assessment falls into Week 7/Week 6/Week 5 and Week 4, assign assessment as Week 4. If assessment date is less than Week 4 (Visit 4) visit date, assign a relevant timepoint less than Week 4.
Week 6	Week 8 (Visit 5) visit date – 20 days	Week 8 (Visit 5) visit date – 14 days	
Week 5	Week 8 (Visit 5) visit date – 27 days	Week 8 (Visit 5) visit date – 21 days	
Week 4	Week 4 (Visit 4) visit date – 6 days	Week 4 (Visit 4) visit date	
Week 3	Week 4 (Visit 4) visit date – 13 days	Week 4 (Visit 4) visit date – 7 days	If assessment falls into Week 3/Week 2/Week 1 and Baseline (Week 0) or Screening, assign assessment as Baseline (Week 0) or Screening.
Week 2	Week 4 (Visit 4) visit date – 20 days	Week 4 (Visit 4) visit date – 14 days	
Week 1	Week 4 (Visit 4) visit date – 27 days	Week 4 (Visit 4) visit date – 21 days	
Baseline (Week 0)	Date of first dose of study treatment – 7 days	Date of first dose of study treatment - 1	
Screening	N/A	Date of first dose of study treatment – 8 days	

15.4. Appendix 4: Study Phases

Assessments and events will be classified according to the time of occurrence relative to the first dose of study treatment.

15.4.1. Treatment Phases for Adverse Events

Study Phase	Definition
Pre-Treatment	AE onset date/time < Date/time of first dose of study treatment
On-Treatment	Date/time of first dose of study treatment ≤ AE onset date/time ≤ Date of last dose of study treatment + 28 days
Post-Treatment	AE onset date > Date of last dose of study treatment + 28 days

NOTES:

- Please refer to Section 15.7.2.1 for handling of missing and partial dates for adverse events.

15.4.2. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before the date of first dose of study treatment
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Section 15.7.2.1 for handling of missing and partial dates for concomitant medications.

15.5. Appendix 5: Data Display Standards & Handling Conventions

15.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Area	: sb240563/mid200622
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards. • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files will be generated for the final reporting effort.	

15.5.2. Reporting Standards

General

• All data displays (Tables, Figures & Listings) will use the term “Subject” rather than “Participant” which reflects CDISC and GSK Data Display Standards terminology.
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include subject level listings in the main body of the GSK Clinical Study Report. All subject level listings should be located in the modular appendices as ICH or non-ICH listings

Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DPs) will be adopted for reporting of data based on the raw data collected but may be adjusted to a clinically interpretable number of DPs. • For FEV_1 and FVC, the mean and median (L) will be reported to 3 decimal places (i.e. to the nearest mL), SD to 4 decimal places, minimum and maximum to 2 decimal places.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.

• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.
• Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings, summaries and statistical analyses.

Unscheduled Visits
• HES flare data collected at unscheduled visits will be included in the derivation of all flare related endpoints for summary and analysis. • For summaries by visit, data recorded at an unscheduled visit will be re-assigned in the ADaM data sets to the closest nominal visit at which collection of data was scheduled, unless information already exists at that visit. Unscheduled data re-assigned to a scheduled visit will be included in analyses, summary tables and figures by scheduled visit. Unscheduled data that is not re-assigned to a scheduled visit will not be included in analyses, summary tables or figures by scheduled visit. Unscheduled data that is not re-assigned to a scheduled visit will be considered in the derivation of baseline and highest/worst case post baseline result for relevant summary tables. • Data recorded at unscheduled visits will be included in the assessment of maximum or worst case post-baseline for relevant endpoints. • All unscheduled visits will be included in listings.
Early Withdrawal Visits
• Data recorded at the early withdrawal visit will be re-assigned in the ADaM data sets to the next scheduled visit, unless information already exists at that visit. Early withdrawal data re-assigned to a scheduled visit will be included in analyses, summary tables and figures by scheduled visit. Early withdrawal visit data that is not re-assigned to a scheduled visit will not be included in analyses, summary tables or figures by scheduled visit. • Data recorded at early withdrawal visits will be included in the assessment of maximum or worst case post-baseline for relevant endpoints. • Data from all early withdrawal visits will be included in listings.

Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %

Graphical Displays
• Refer to IDSL Statistical Principals 7.01 to 7.13.

15.5.3. Reporting Standards for Pharmacokinetic Data

Pharmacokinetic Concentration Data	
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: BLQ concentration values will be imputed as per GUI_51487 for descriptive summary statistics only.
NONMEM/Pop PK	Pop-PK file (CSV and SAS format) for the POP-PK and POP-PKPD

File	analyses performed by the Clinical Pharmacology Modelling and Simulation function will be created according to the POP-PKPD Dataset Specification document.
Pharmacokinetic Parameter Data	
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1.

15.6. Appendix 6: Derived and Transformed Data

15.6.1. General

Multiple Measurements at One Analysis Time Point
• If there are two results identified at a single visit the latter of the two measurements will be flagged and used in any derivation of summary statistics. All values will be presented on listings. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from the date of the first dose of study treatment:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

15.6.2. Change from Baseline Definitions

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]
Ratio to Baseline	= Visit Value / Baseline

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 5.2 will be used for derivations for endpoints / parameters.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and result will be set to missing.

15.6.3. Study Population

Age
• GSK standard IDSL algorithms will be used for calculating age where birth day and month will be imputed 'PPD • Birth date will be presented in listings as 'YYYY'. • Age will be calculated relative to the date of the screening visit (Visit 1).
Body Mass Index (BMI)
Calculated as **Weight (kg) / [Height (m)^2]**

Baseline HES Therapy

• Baseline oral corticosteroid use and baseline oral prednisone equivalent daily dose will be derived as detailed in Section 5.4.1.1.
• Cytotoxic therapy/immunosuppressive therapy and other HES therapy will be identified by clinical review of the concomitant medications page according to the following criteria:
  ○ Medication type = “Hypereosinophilic syndrome”
  ○ Start date < Date of first dose of study treatment
  ○ Either “ongoing” or End date ≥ Date of first dose of study treatment
• Oral budesonide has negligible systemic exposure and will be counted as “Other HES therapy” rather than oral corticosteroid therapy.

Duration of HES
• Duration of HES in years will be calculated from the date of the screening visit (Visit 1) and the date of HES diagnosis as follows: Duration (years) = (Date of visit 1 – date of HES diagnosis)/365.25 • If the date of HES diagnosis is a partial date, a '01' will be used for a missing day and 'Jan' will be used for a missing month.
Exposure (therapeutic coverage)
• The number of days of exposure (therapeutic coverage) to study drug will be calculated based on the formula: Duration of exposure in days = Date of last dose of study treatment – date of first dose of study treatment + 29. • Exposure in months will be calculated using the formula: Exposure (months) = (Exposure in days / 365.25) * 12 • Total subject years exposure will be calculated using the formula: Total subject-years exposure = (Sum across subjects of exposure in days)/365.25

15.6.4. Efficacy

HES Flare

Definition of HES Flare

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

- An increase in the maintenance OCS dose by at least 10mg/day for 5 days
- An increase in or addition of any cytotoxic and/or immunosuppressive HES therapy

or

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

- The maintenance OCS dose is the dose received during the 4 weeks prior to randomisation i.e. baseline OCS therapy, which should be maintained for the duration of the treatment period. If a subject has their OCS dose reduced during the treatment period, the maintenance dose will be redefined as the new dose they have received for at least 4 weeks. If the OCS dose is increased during the treatment period, the maintenance OCS dose will not be redefined and will remain as therapy taken during the 4 weeks prior to randomisation.
- Flares meeting endpoint definition a) will be captured on the 'flare details' form in the eCRF.
- An increase in blood eosinophils above the pre-defined threshold level (2 x baseline value or baseline value + 2500 cells/μL) without any other clinical manifestations during the study will lead to administration of blinded active OCS treatment (see Section 2.2). If a subject receives a second course of blinded active OCS during the 32-week treatment period, the subject will be considered to be experiencing a flare. The container list for the blinded OCS treatment (indicating which container numbers contained active OCS and which contained placebo OCS) will be used to define HES flares meeting endpoint definition b). This container list will be incorporated into the final SDTM data sets at the end of the study, at the same time as the randomised treatment information.

HES flare onset and resolution dates

- The onset and resolution dates of HES flares meeting endpoint definition a) will be recorded on the 'Flare details' form in the eCRF.
- The start date of HES flares meeting endpoint definition b) is defined as the date of the blood draw at which the second course of blinded active OCS was triggered via schedule blood sampling for eosinophil monitoring. The resolution date for a flare meeting endpoint definition b) is the date of the first blood draw at which blood eosinophil count is below the threshold to trigger blinded active OCS (see protocol Section 6.4 for full details of blood eosinophil monitoring).

HES flare during Week 20 through Week 32

- Defined as an HES flare starting or ongoing on or after the date of the Week 20 visit (Visit 8) up to and including the date of the Week 32 visit (Visit 11).

Time to First HES Flare

- Calculated for each subject as

(Onset date of first HES flare – Date of first dose of study treatment) + 1

HES Flare

Rate of HES Flares

- For subjects completing the study, the rate of HES flares will be calculated as

$$\frac{365.25 \times Number\ of\ observed\ HES\ flares}{Date\ of\ Week\ 32\ (Visit\ 11) - Date\ of\ first\ dose\ of\ mepolizumab + 1}$$

- For subjects withdrawing prematurely from the study, the rate of HES flares will be calculated as

$$\frac{365.25 \times Number\ of\ observed\ HES\ flares}{Date\ of\ study\ withdrawal - Date\ of\ first\ dose\ of\ mepolizumab + 1}$$

The number of HES flares is the number of unique starting dates for HES flares. To be considered as a separate episode of HES flare, the start date of an HES flare must be at least 14 days apart from the resolution date of the preceding HES flare.

- For flares meeting endpoint definition b), each subsequent course of blinded active OCS beyond 14 days from the resolution date of the preceding flare will be considered as an additional flare (e.g., 3 courses of blinded active OCS are considered as 2 flares, 4 courses of blinded active OCS are considered as 3 flares, etc.).

Subjects who have an elevated blood eosinophil level (2 x baseline value or baseline value + 2500 cells/μL) during the 32-week study treatment period

- Subjects with elevated blood eosinophils either 2 x baseline value or baseline value + 2500 cells/μL during the 32-week study treatment period will be identified from the central laboratory haematology results. Samples taken from the date of first dose of study medication up until the date of Visit 11 (Week 32) will be considered in the derivation. Baseline will be defined as in Section 5.2.

Worst Level of Fatigue in Past 24 Hours (BFI Item 3)

- A BFI item 3 score for baseline and each week of treatment will be derived by taking the mean of up to 7 available daily assessments in each week of treatment.
- Assessment windows defining each week will be based on the date recorded for each BFI assessment and are defined in Section 15.3.1.

HES Symptom Severity Based on HES Daily Symptoms (HES-DS)

- For each of the 6 symptom domains (muscle/joint pain, chills or sweats, abdominal pain or bloating, breathing symptoms, nasal or sinus symptoms and skin symptoms, a symptom score for baseline and each week of treatment will be derived by taking the mean of up to 7 available daily assessments in each weekly assessment window.
- Assessment windows defining each week will be based on the date recorded for each HES-DS assessment and are defined in Section 15.3.1.
- A symptom score for most bothersome symptoms will be derived by taking the mean of the symptom scores for the up to 3 symptom domains identified by the subject as most bothersome at visit 2 (Week 0).

BFI Total Score
• The BFI total score (range 0 – 10) will be calculated as the mean of the 9 domain scores (range 0 – 10) recorded for the weekly assessment. If less than 4 domain scores are complete, the BFI total score will be set to missing.

15.6.5. Safety

Adverse Events
Drug Related AEs
AEs with relationship marked 'YES' or relationship missing.
AEs Leading to Permanent Discontinuation from Study Treatment or Withdrawal from the Study
AEs with action marked "Study treatment withdrawn" or withdrawn from study status marked "YES", or a response to either of these questions is missing.
AEs on Day of Dosing
AEs with an onset date equal to a study treatment dosing date and an onset time on or after the study treatment dosing time.
AE Time Since First Dose
• If AE onset time is missing, calculate in days as follows:- o If AE start date < Date of first dose of study treatment then Time since first dose = AE start date - Date of first dose of study treatment o If AE start date ≥ Date of first dose of study treatment then Time since first dose = AE start date – Date of first dose of study treatment +1 o Missing if AE start date or date of first dose of study treatment is missing. • If AE onset time is present, calculate in days, hours, minutes as Time since first dose = AE start date/time – Date/time of first dose of study treatment
AE Duration (Days)
• If AE onset time is missing, calculate in days as AE end date – AE start date + 1 • If AE onset time is present, calculate in days, hours and minutes as AE end date/time – AE start date/time • Missing if AE start date or end date is missing.
AEs of Special Interest
• See Section 11.1.1.
ECG
• QTc(B) will be derived from QT (uncorrected) and RR interval as $QTc(B) = \frac{QT}{\sqrt{RR}}$

15.7. Appendix 7: Reporting Standards for Missing Data

15.7.1. Premature Withdrawals

Element	Reporting Detail
General	• A subject will be considered to have **completed study treatment** if they receive study treatment at week 28 (Visit 10). • For the purpose of the primary endpoint, a subject will be considered to have **completed the study** if they continue to participate in the study until Week 32 (Visit 11). If a subject's last dose of study treatment is on Week 24 (Visit 9) or Week 28 (Visit 10) *and* the subject does not continue into the open-label extension study 205203 after completing Visit 11 assessments (32 weeks from randomization), then the protocol requires an up to 8-week additional follow-up period, concluding with the 12-weeks post last dose follow-up visit (Visit 12). Subjects who continue to participate in the study until Week 32 (Visit 11) but withdraw from the study prior to the final follow-up visit (Visit 12) will be documented separately in the study disposition table. • Subjects who discontinue study treatment or withdraw early will not be replaced in the study.
Pre-Screen and Run-in Failures	• A subject will be assigned a subject number at the time when the informed consent form (ICF) is signed. A subject who is assigned a subject number but does not complete any Visit 1 procedures will be considered a **pre-screen failure.** • **Screen failures** are defined as subjects who consent to participate in the clinical trial but are never subsequently randomised.

15.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument. These data will be indicated by the use of a "blank" in subject listing displays, unless all data for a specific visit are missing in which case the data is excluded from the listing. • BLQ is not missing data and must be displayed as such and included in all listings and summaries. For blood eosinophil and IL-5 data, see Section 10.1.5 and Section 10.2.5 respectively. For PK data, refer to Section 15.5.3.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

15.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
HES Flare and Adverse Events	• Any partial dates for HES flare and adverse events will be raised to data management. If the full date cannot be ascertained, the following assumptions will be made:

Element	Reporting Detail
	○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month. ○ However, if this imputation results in a date prior to the first dose of study treatment and the event could possibly have occurred during treatment from the partial information, then the date of the first dose of study treatment will be assumed to be the start date. ○ The event will then be considered to start on-treatment (worst case). ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • The recorded partial date will be displayed in listings.
Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

15.8. Appendix 8: Values of Potential Clinical Importance

15.8.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Age Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	12+	0.201	0.599
Haemoglobin	G/L	12+	71	199
Platelet Count	GI/L	1+	31	1499
White Blood Cell Count (WBC)	GI/L	12+	1.1	

Clinical Chemistry				
Laboratory Parameter	**Units**	**Age Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
ALT	U/L	3-12		>143 (and Total Bilirubin >43)
	U/L	13+		>239 (and Total Bilirubin >43)
Calcium	mmol/L	3+	1.50	3.24
Glucose	mmol/L	1+	2.2	27.8
Phosphorus, Inorg	mmol/L	3+	0.32	
Potassium	mmol/L	3+	2.8	6.5
Sodium	mmol/L	0+	120	160

Possible Hy's Law Cases			
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**
ALT, Bilirubin			ALT ≥ 3xULN and Bilirubin ≥ 2xULN (>35% direct)
ALT, INR			ALT ≥ 3xULN and INR > 1.5

NOTES:

- ULN = Upper Limit of Normal.

15.8.2. Urinalysis

As per GSK IDSL display standards, a subject is considered to have urinalysis results of PCI if there is an increase in Protein or an increase in Occult Blood results during the study, or if microscopy is performed.

15.9. Appendix 9: Abbreviations & Trade Marks

15.9.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
A&R	Analysis and Reporting
BFI	Brief Fatigue Index
BLQ	Below limit of quantification
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GSK	GlaxoSmithKline
HCRU	Healthcare Resource Utilisation
HES-DS	HES Daily Symptoms
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
ITT	Intent-To-Treat
MMRM	Mixed Model Repeated Measures
MSAS-SF	Modified Memorial Symptom Assessment Scale – Short Form
MUGA	Multigated Aquisition
OCS	Oral Corticosteroid
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
Pop-PK	Population PK
Pop-PKPD	Population PKPD
PROMIS	Patient Reported Outcome Measurement Information System
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RMC	Respiratory Medication Class

Abbreviation	Description
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SDTM	Study Data Tabulation Model
SoC	Standard of Care
SSR	Subject-Rated Symptom Severity
TFL	Tables, Figures & Listings

15.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
NONMEM
SAS

15.10. Appendix 10: List of Data Displays

15.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.n	1.1 to 1.n
Efficacy	2.1 to 2.n	2.1 to 2.n
Health Outcome Tables	3.1 to 3.n	3.1 to 3.n
Safety	4.1 to 4.n	4.1 to 4.n
Pharmacokinetic	5.1 to 5.n	5.1 to 5.n
Pharmacodynamic and / or Biomarker	6.1 to 6.n	6.1 to 6.n
Pharmacokinetic / Pharmacodynamic	7.1 to 7.n	7.1 to 7.n
Section	**Listings**	
ICH Listings	1 to x	

15.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 11: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Population Pharmacokinetic (PopPK)	POPPK_Fn	POPPK_Tn	POPPK_Ln
Pharmacodynamic and / or Biomarker	PD_Fn	PD_Tn	PD_Ln
Pharmacokinetic / Pharmacodynamic	PKPD_Fn	PKPD_Tn	PK/PD_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

15.10.3. Deliverables

Deliverable	Description
Headline	Headline results
SAC	Final Statistical Analysis Complete

15.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	ITT	ES1	Summary of Subject Disposition	Include Completed, Withdrawn and subsets of completed/withdrawn as follows:- Completed, Completed Week 32 and entered 205203, Completed Week 32 and Follow-up Withdrawn, Withdrawn prior to Week 32, Completed Week 32 and withdrawn prior to Follow up	SAC
1.2.	ITT	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		SAC
1.3.	ITT	*POP_T1*	Summary of Subject Accountability During 32-Week Treatment Period		SAC
1.4.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	As a subset of "Enrolled" subjects, also include the number of subjects for whom inclusion criteria #5 is based on local rather than central laboratory result. Use text "Inclusion criteria #5 based on local laboratory result [1]", and add footnote: "[1] The number of subjects for whom the screening central laboratory blood eosinophil count is <1000 cells/uL but a local laboratory blood eosinophil count ≥1000 cells/uL was used to meet study inclusion criteria."	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.5.	Enrolled	NS1	Summary of Number of Subjects by Country and Site ID		SAC
Protocol Deviation					
1.6.	ITT	DV1	Summary of Important Protocol Deviations		SAC
Population Analysed					
1.7.	ITT	SP1	Summary of Study Populations		Headline
1.8.	ITT	SP2	Summary of Exclusions from the Per Protocol Population		SAC
Demographic and Baseline Characteristics					
1.9.	ITT	DM1	Summary of Demographic Characteristics		SAC
1.10.	Enrolled	DM11	Summary of Age Ranges		SAC
1.11.	ITT	DM5	Summary of Race and Racial Combinations		SAC
1.12.	ITT	*POP_T8*	Summary of Duration of HES		SAC
Prior and Concomitant Medications/Conditions					
1.13.	ITT	*POP_T2*	Summary of Baseline HES Therapy		SAC
1.14.	ITT	*POP_T3*	Summary of Baseline Prednisone Equivalent Daily Dose		Headline
1.15.	ITT	CM1	Summary of Concomitant Medications		SAC
1.16.	ITT	MH4	Summary of Current Medical Conditions		SAC
1.17.	ITT	MH4	Summary of Past Medical Conditions		SAC
Exposure and Treatment Compliance					
1.18.	ITT	*POP_T4*	Summary of Exposure (Therapeutic Coverage) to Study Treatment		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.19.	ITT	*POP_T5*	Summary of Number of Treatments Administered		SAC
Most Bothersome HES Symptoms					
1.20.	ITT	*POP_T6*	Summary of Most Bothersome HES Related Symptoms		SAC
Steroid Perception Questionnaire					
1.21.	ITT	*POP_T7*	Summary of Steroid Perception Questionnaire		SAC

15.10.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
HES Flare					
2.1.	ITT	*EFF_T1*	Overview of HES Flares		SAC
2.2.	ITT	*EFF_T2*	Summary of Frequency of All HES Flares		SAC
2.3.	ITT	*EFF_T3*	Primary Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period (Treatment Policy Estimand)		Headline
2.4.	ITT	*EFF_T3a*	Supportive Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period (While on Treatment Estimand)		Headline
2.5.	PP	*EFF_T3*	Supportive Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period (Treatment Policy Estimand, PP Population)		Headline
2.6.	ITT	*EFF_T3b*	Sensitivity Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period (Treatment Policy Estimand, Alternative Missing Data Imputation Strategy #1)		Headline
2.7.	ITT	*EFF_T3c*	Sensitivity Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period (Treatment Policy Estimand, Alternative Missing Data Imputation Strategy #2)		Headline
2.8.	ITT	*EFF_T3*	Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period by Age (Treatment Policy Estimand)	Descriptive summary only; do not present p-values.	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.9.	ITT	*EFF_T3*	Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period by Sex (Treatment Policy Estimand)	Descriptive summary only; do not present p-values.	SAC
2.10.	ITT	*EFF_T3*	Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period by Race (Treatment Policy Estimand)	Descriptive summary only; do not present p-values.	SAC
2.11.	ITT	*EFF_T3*	Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period by Region (Treatment Policy Estimand)	Descriptive summary only; do not present p-values.	SAC
2.12.	ITT	*EFF_T3*	Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period by Baseline OCS (Treatment Policy Estimand)	Descriptive summary only; do not present p-values.	SAC
2.13.	ITT	*EFF_T3*	Analysis of Proportion of Subjects Who Experience a HES Flare During the 32-Week Treatment Period by Baseline Blood Eosinophils (Treatment Policy Estimand)	Descriptive summary only; do not present p-values.	SAC
2.14.	ITT	*EFF_T4*	Analysis of Time to First HES Flare (Treatment Policy Estimand)	Add footnote: “Note: Subjects withdrawing from the study prematurely are censored at the date of study withdrawal.”	Headline
2.15.	ITT	*EFF_T4*	Sensitivity Analysis of Time to First HES Flare (Treatment Policy Estimand, Alternative Missing Data Imputation Strategy #1)	Add footnote: “Note: Subjects withdrawing from the study prematurely prior to reporting an HES flare are included with an HES flare on the date of study withdrawal.”	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.16.	ITT	*EFF_T4*	Sensitivity Analysis of Time to First HES Flare (Treatment Policy Estimand, Alternative Missing Data Imputation Strategy #2)	Add footnote: "Note: Subjects withdrawing from the study prematurely prior to reporting an HES flare, with primary reason for treatment withdrawal reported as Adverse Event or Lack of Efficacy are included with an HES flare on the date of study withdrawal. For subjects withdrawing from the study prematurely prior to reporting an HES flare, with any other reason for discontinuation of study treatment, the event time will be censored at the date of study withdrawal."	SAC
2.17.	ITT	*EFF_T3*	Analysis of Proportion of Subjects Who Experience a HES Flare During Week 20 Through Week 32 (Treatment Policy Estimand)		SAC
2.18.	ITT	*EFF_T3*	Sensitivity Analysis of Proportion of Subjects Who Experience a HES Flare During Week 20 Through Week 32 (Treatment Policy Estimand, Alternative Missing Data Imputation Strategy #1)		SAC
2.19.	ITT	*EFF_T3*	Sensitivity Analysis of Proportion of Subjects Who Experience a HES Flare During Week 20 Through Week 32 (Treatment Policy Estimand, Alternative Missing Data Imputation Strategy #2)		SAC
2.20.	ITT	*EFF_T5*	Analysis of Rate of HES Flares (Treatment Policy Estimand)	Add footnote: "Note: For subjects withdrawing prematurely from the study during the 32-week treatment period, all data up to the time of study withdrawal is used to calculate the rate of HES flares."	Headline

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.21.	ITT	*EFF_T5*	Sensitivity Analysis of Rate of HES Flares (Treatment Policy Estimand, Alternative Missing Data Imputation Strategy #1)	Add footnote: "Note: For subjects withdrawing prematurely from the study during the 32-week treatment period, the placebo flare rate is imputed for the missing time period."	SAC
2.22.	ITT	*EFF_T5*	Sensitivity Analysis of Rate of HES Flares (Treatment Policy Estimand, Alternative Missing Data Imputation Strategy #2)	Add footnote: "Note: For subjects withdrawing prematurely from the study with primary reason for treatment withdrawal reported as AE or Lack of efficacy, the placebo flare rate is imputed for the missing time period. For all subjects withdrawing prematurely from the study with any other primary reason for treatment discontinuation, all data up to the time of study withdrawal is used to calculate the rate of HES flares."	SAC
Daily Fatigue Severity - Worst Level of Fatigue in Past 24 Hours (BFI Item 3)					
2.23.	ITT	*EFF_T6*	Summary of Mean Daily Fatigue Severity - Worst Level of Fatigue in Past 24 Hours (BFI Item 3) (Treatment Policy Estimand)	Present Baseline (week 0) up Week 32.	SAC
2.24.	ITT	*EFF_T7*	Analysis of Change from Baseline in Mean Daily Fatigue Severity - Worst Level of Fatigue in Past 24 Hours (BFI Item 3) – at Week 32 (Treatment Policy Estimand)		SAC
2.25.	ITT	*EFF_T8*	Analysis of Change from Baseline in Mean Daily Fatigue Severity - Worst Level of Fatigue in Past 24 Hours (BFI Item 3) (Treatment Policy Estimand, Mixed Model Repeated Measures)		SAC
2.26.	ITT	*EFF_T9*	Summary of P-values for Primary and Secondary Endpoints (Treatment Policy Estimand)		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Elevated Blood Eosinophil Level					
2.27.	ITT	*EFF_T10*	Analysis of Proportion of Subjects Who Have an Elevated Blood Eosinophil Count (2 x Baseline Value or Baseline Value + 2500 cells/μL) During the 32-Week Treatment Period (Treatment Policy Estimand)		SAC
FEV_1, FVC, FEV_1/FVC Ratio					
2.28.	ITT	*EFF_T6*	Summary of FEV1, FVC and FEV1/FVC	Add a by-line for parameter. Column header "Visit" rather than "Analysis Time Point".	SAC
2.29.	ITT	*EFF_T8*	Analysis of Change from Baseline in FEV1 (Treatment Policy Estimand, Mixed Model Repeated Measures)		SAC
2.30.	ITT	*EFF_T8*	Analysis of Change from Baseline in FVC (Treatment Policy Estimand, Mixed Model Repeated Measures)		SAC
2.31.	ITT	*EFF_T6*	Summary of FEV1, FVC and FEV1/FVC - Excluding Data where SABA/LABA was Taken Within 6/12 Hours Respectively	Add a by-line for parameter. Column header "Visit" rather than "Analysis Time Point".	SAC
2.32.	ITT	*EFF_T8*	Analysis of Change from Baseline in FEV1 - Excluding Data where SABA/LABA was Taken Within 6/12 Hours Respectively (Treatment Policy Estimand, Mixed Model Repeated Measures)		SAC
2.33.	ITT	*EFF_T8*	Analysis of Change from Baseline in FVC - Excluding Data where SABA/LABA was Taken Within 6/12 Hours Respectively (Treatment Policy Estimand, Mixed Model Repeated Measures)		SAC
ECHO/MUGA					
2.34.	ITT	*EFF_T16*	Summary of ECHO/MUGA		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
HES Symptom Severity (HES-DS)					
2.35.	ITT	*EFF_T6a*	Summary of Most Bothersome HES Symptom Severity Score (HES-DS)	Includes number (%) of subjects with no reported symptoms.	SAC
2.36.	ITT	*EFF_T7*	Analysis of Change from Baseline in Most Bothersome HES Symptom Severity Score (HES-DS) at Week 32 (Treatment Policy Estimand)	Scale 0 = None to 10 = As bad as you can imagine.	SAC
2.37.	ITT	*EFF_T8*	Analysis of Change from Baseline in Most Bothersome HES Symptom Severity Score (HES-DS) (Treatment Policy Estimand, Mixed Model Repeated Measures)	Scale 0 = None to 10 = As bad as you can imagine.	SAC
2.38.	ITT	*EFF_T6a*	Summary of HES Symptom Severity Score (HES-DS) by Symptom	Includes number (%) of subjects with no reported symptoms. Use T_EFF6a with Endpoint = Symptom Severity Score and by line for symptom domain. Add footnote "Note: 1. The mean of the available assessments on the 7 days up to and including the date of each study visit is used as the value for that visit. For time points between visits i.e week 1, 2, 3, 5, 6, 7, 9, 10, 11, 13, 14, 15, 17, 18, 19, 21, 22, 23, 25, 26, 27, 29, 30, 31, the number of available assessments depends on the elapsed time between visits. 2. Scale 0 = None to 10 = As bad as you can imagine."	SAC
2.39.	ITT	*EFF_T7*	Analysis of Change from Baseline HES Symptom Severity Score (HES-DS) by Symptom at Week 32 (Treatment Policy Estimand)	Use T_EFF7 with by line for symptom domain. Scale 0 = None to 10 = As bad as you can imagine	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.40.	ITT	*EFF_T8*	Analysis of Change from Baseline in HES Symptom Severity Score (HES-DS) by Symptom (Treatment Policy Estimand, Mixed Model Repeated Measures)	Use T_EFF8 with by line for symptom domain. Scale 0 = None to 10 = As bad as you can imagine.	SAC
Weekly Fatigue Severity – BFI Total Scores					
2.41.	ITT	*EFF_T6*	Summary of Total BFI Score	Present Baseline (week 0) up Week 32.	SAC
2.42.	ITT	*EFF_T7*	Analysis of Change from Baseline in Total BFI Score at Week 32 (Treatment Policy Estimand)		SAC
2.43.	ITT	*EFF_T8*	Analysis of Change from Baseline in Total BFI Score (Treatment Policy Estimand, Mixed Model Repeated Measures)		SAC
Clinical- and Subject- Rated Overall Response to Therapy					
2.44.	ITT	*EFF_T11*	Summary of Clinician-Rated Overall Response to Therapy		SAC
2.45.	ITT	*EFF_T12*	Analysis of Clinician-Rated Overall Response to Therapy (Treatment Policy Estimand)		SAC
2.46.	ITT	*EFF_T11*	Summary of Subject-Rated Overall Response to Therapy		SAC
2.47.	ITT	*EFF_T12*	Analysis of Subject-Rated Overall Response to Therapy (Treatment Policy Estimand)		SAC
Subject-Rated Symptom Severity (SSR)					
2.48.	ITT	*EFF_T13*	Summary of Subject-Rated Symptom Severity		SAC
2.49.	ITT	*EFF_T12*	Analysis of Subject-Rated Symptom Severity at Week 32 (Treatment Policy Estimand)		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Modified Memorial Symptom Assessment Scale-Short Form (MSAS-SF)					
2.50.	ITT	*EFF_T6*	Summary of MSAS-SF Total and Subscale Scores	Include by line: Total MSAS-SF Score, MSAS-SF Global Distress Index, MSAS-SF Physical Subscale Score, MSAS-SF Psychological Subscale Score. Present Baseline (week 0) up Week 32. Column header "Visit" rather than "Analysis Time Point". Add footnote: "Scale 0 = Not at all distressed or bothered/No symptoms to 4 = Very much distressed or bothered/Almost constant symptoms."	SAC
2.51.	ITT	*EFF_T7*	Analysis of Change from Baseline in MSAS-SF Total and Subscale Scores at Week 32 (Treatment Policy Estimand)	Include by line: Total MSAS-SF Score, MSAS-SF Global Distress Index, MSAS-SF Physical Subscale Score, MSAS-SF Psychological Subscale Score. Scale 0 = Not at all distressed or bothered/No symptoms to 4 = Very much distressed or bothered/Almost constant symptoms.	SAC
2.52.	ITT	*EFF_T8*	Analysis of Change from Baseline in MSAS-SF Total and Subscale Scores (Treatment Policy Estimand, Mixed Model Repeated Measures)	Include by line: Total MSAS-SF Score, MSAS-SF Global Distress Index, MSAS-SF Physical Subscale Score, MSAS-SF Psychological Subscale Score. Scale 0 = Not at all distressed or bothered/No symptoms to 4 = Very much distressed or bothered/Almost constant symptoms.	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PROMIS Physical Function and Sleep					
2.53.	ITT	*EFF_T6*	Summary of PROMIS Physical Function Score	Present Baseline (week 0) up Week 32. Column header "Visit" rather than "Analysis Time Point". Add footnote: "Scale 1 = Cannot do/unable to do to 5 = Not at all/Without any difficulty."	SAC
2.54.	ITT	*EFF_T7*	Analysis of Change from Baseline in PROMIS Physical Function Score at Week 32 (Treatment Policy Estimand)	Scale 1 = Cannot do/unable to do to 5 = Not at all/Without any difficulty.	SAC
2.55.	ITT	*EFF_T8*	Analysis of Change from Baseline in PROMIS Physical Function Score (Treatment Policy Estimand, Mixed Model Repeated Measures)	Scale 1 = Cannot do/unable to do to 5 = Not at all/Without any difficulty.	SAC
2.56.	ITT	*EFF_T6*	Summary of PROMIS Sleep Score	Present Baseline (week 0) up Week 32. Column header "Visit" rather than "Analysis Time Point". Add footnote: "Scale 1 = Not at all difficulty in falling asleep /Never trouble staying asleep to 5 = Very much difficulty in falling asleep /Always trouble staying asleep."	SAC
2.57.	ITT	*EFF_T7*	Analysis of Change from Baseline in PROMIS Sleep Score at Week 32 (Treatment Policy Estimand)	Scale 1 = Not at all difficulty in falling asleep /Never trouble staying asleep to 5 = Very much difficulty in falling asleep /Always trouble staying asleep.	SAC
2.58.	ITT	*EFF_T8*	Analysis of Change from Baseline in PROMIS Sleep Score (Treatment Policy Estimand, Mixed Model Repeated Measures)	Scale 1 = Not at all difficulty in falling asleep /Never trouble staying asleep to 5 = Very much difficulty in falling asleep /Always trouble staying asleep.	SAC

15.10.6. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
HES Flare					
2.1.	ITT	*EFF_F1*	Cumulative Number of HES Flares		Headline
2.2.	ITT	*EFF_F2*	Analysis of Proportion of Subjects with HES Flare During the 32-Week Treatment Period	Present odds ratios and 95% CI from 5 analyses of the primary endpoint on one figure: Primary estimand, While on treatment estimand, Per protocol population, Alternative missing data imputation strategy #1, Alternative missing data imputation strategy #2.	Headline
2.3.	ITT	*EFF_F3*	Kaplan-Meier Cumulative Incidence Curve for Time to First HES Flare		SAC
2.4.	ITT	*EFF_F2*	Analysis of Time to First HES Flare (Treatment Policy Estimand)	Present relative risk and 95% CI from 3 analyses corresponding to 3 missing data imputation strategies: Primary estimand, Alternative missing data imputation strategy #1, Alternative missing data imputation strategy #2	SAC
2.5.	ITT	-	Exploratory Modelling of Proportion of Subjects with HES Flare During the 32-Week Treatment Period vs Baseline Blood Eosinophils		SAC
2.6.	ITT	*EFF_F2*	Analysis of Proportion of Subjects with HES Flare During Week 20 Through Week 32 (Treatment Policy Estimand)	Present odds ratio and 95% CI from 3 analyses corresponding to 3 missing data imputation strategies: Primary estimand, Alternative missing data imputation strategy #1, Alternative missing data imputation strategy #2	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.7.	ITT	*EFF_F2*	Analysis of Rate of HES Flare (Treatment Policy Estimand)	Present rate ratio and 95% CI from 3 analyses corresponding to 3 missing data imputation strategies: Primary estimand, Alternative missing data imputation strategy #1, Alternative missing data imputation strategy #2	SAC
Worst Level of Fatigue in Past 24 Hours (BFI Item 3)					
2.8.	ITT	*EFF_F6*	Cumulative Distribution Plot for the Change from Baseline in Mean Daily Fatigue Severity - Worst Level of Fatigue in Past 24 Hours (BFI Item 3) – at Week 32		SAC
2.9.	ITT	*EFF_F4*	Change from Baseline in Fatigue Severity - Worst Level of Fatigue in Past 24 Hours (BFI Item 3) (Treatment Policy Estimand, Mixed Model Repeated Measures)	Present adjusted mean (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 12, 16, 20, 24, 28, 32. Add footnote: "Note: Adjusted for baseline (week 0) BFI item 3 score and region".	SAC
2.10.	ITT	*EFF_F5*	Change from Baseline in Fatigue Severity - Worst Level of Fatigue in Past 24 Hours (BFI Item 3) - Treatment Difference vs Placebo (Treatment Policy Estimand, Mixed Model Repeated Measures)	Present adjusted mean treatment difference (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 12, 16, 20, 24, 28, 32. Add footnote: "Note: Adjusted for baseline (week 0) BFI item 3 score and region".	SAC
FEV_1 and FVC					
2.11.	ITT	*EFF_F4*	Change from Baseline in FEV_1 (Treatment Policy Estimand, Mixed Model Repeated Measures)		SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.12.	ITT	*EFF_F5*	Change from Baseline in FEV_1 - Treatment Difference vs Placebo (Treatment Policy Estimand, Mixed Model Repeated Measures)		SAC
2.13.	ITT	*EFF_F4*	Change from Baseline in FVC (Treatment Policy Estimand, Mixed Model Repeated Measures)		SAC
2.14.	ITT	*EFF_F5*	Change from Baseline in FVC - Treatment Difference vs Placebo (Treatment Policy Estimand, Mixed Model Repeated Measures)		SAC
HES Symptom Severity (HES-DS)					
2.15.	ITT	*EFF_F4*	Change from Baseline in Most Bothersome HES Symptom Severity Score (HES-DS) (Treatment Policy Estimand, Mixed Model Repeated Measures)	Present adjusted mean (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 12, 16, 20, 24, 28, 32. Add footnote: "Note: Adjusted for baseline (week 0) most bothersome symptom score and region".	SAC
2.16.	ITT	*EFF_F5*	Change from Baseline in Most Bothersome HES Symptom Severity Score (HES-DS) - Treatment Difference vs Placebo (Treatment Policy Estimand, Mixed Model Repeated Measures)	Present adjusted mean treatment difference (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 12, 16, 20, 24, 28, 32. Add footnote: "Note: Adjusted for baseline (week 0) most bothersome symptom score and region".	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.17.	ITT	*EFF_F4*	Change from Baseline in HES Symptom Severity Score (HES-DS) by Symptom (Treatment Policy Estimand, Mixed Model Repeated Measures)	One page per domain with byline. Present adjusted mean (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 12, 16, 20, 24, 28, 32. Add footnote: "Note: Adjusted for baseline (week 0) symptom score and region".	SAC
2.18.	ITT	*EFF_F5*	Change from Baseline in HES Symptom Severity Score (HES-DS) by Symptom - Treatment Difference vs Placebo (Treatment Policy Estimand, Mixed Model Repeated Measures)	One page per domain with byline. Present adjusted mean treatment difference (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 12, 16, 20, 24, 28, 32. Add footnote: "Note: Adjusted for baseline (week 0) symptom score and region".	SAC
Weekly Fatigue Severity – BFI Total Scores					
2.19.	ITT	*EFF_F4*	Change from Baseline in Total BFI Score (Treatment Policy Estimand, Mixed Model Repeated Measures)	Present adjusted mean (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 12, 16, 20, 24, 28, 32. Add footnote: "Note: Adjusted for baseline (week 0) total BFI score and region".	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.20.	ITT	*EFF_F5*	Change from Baseline in Total BFI Score - Treatment Difference vs Placebo (Treatment Policy Estimand, Mixed Model Repeated Measures)	Present adjusted mean treatment difference (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 12, 16, 20, 24, 28, 32. Add footnote: "Note: Adjusted for baseline (week 0) total BFI score and region".	SAC
Modified Memorial Symptom Assessment Scale-Short Form (MSAS-SF)					
2.21.	ITT	*EFF_F4*	Change from Baseline in MSAS-SF Total and Subscale Scores (Treatment Policy Estimand, Mixed Model Repeated Measures)	One plot per page, 4 pages with by line: Total MSAS-SF Score, MSAS-SF Global Distress Index, MSAS-SF Physical Subscale Score, MSAS-SF Psychological Subscale Score. Present adjusted mean (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 16, 24, 32. Add footnote: "Note: Adjusted for baseline (week 0) score and region. Scale: 0 = Not at all distressed or bothered/No symptoms to 4 = Very much distressed or bothered/Almost constant symptoms."	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.22.	ITT	*EFF_F5*	Change from Baseline in MSAS-SF Total and Subscale Scores - Treatment Difference vs Placebo (Treatment Policy Estimand, Mixed Model Repeated Measures)	Either one plot per page, 4 pages with by line, or 4 lines on one plot, as data permit: Total MSAS-SF Score, MSAS-SF Global Distress Index, MSAS-SF Physical Subscale Score, MSAS-SF Psychological Subscale Score. Present adjusted mean treatment difference (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 12, 16, 20, 24, 28, 32. Add footnote: "Note: Adjusted for baseline (week 0) score and region. Scale: 0 = Not at all distressed or bothered/No symptoms to 4 = Very much distressed or bothered/Almost constant symptoms."	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PROMIS Physical Function and Sleep					
2.23.	ITT	*EFF_F4*	Change from Baseline in PROMIS Physical Function and Sleep Score (Treatment Policy Estimand, Mixed Model Repeated Measures)	One plot per page, 2 pages with by line: PROMIS Physical Function Score, PROMIS Sleep Score. Present adjusted mean (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 16, 24, 32. Add footnote: "Note: 1. Adjusted for baseline (week 0) score and region. 2. Sleep score scale 1 = Not at all difficulty in falling asleep /Never trouble staying asleep to 5 = Very much difficulty in falling asleep /Always trouble staying asleep. 3. Physical function scale 0 = Not at all distressed or bothered/No symptoms to 4 = Very much distressed or bothered/Almost constant symptoms."	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.24.	ITT	*EFF_F5*	Change from Baseline in PROMIS Physical Function and Sleep Score - Treatment Difference vs Placebo (Treatment Policy Estimand, Mixed Model Repeated Measures)	Either one plot per page, 2 pages with by line, or 2 lines on one plot, as data permit: PROMIS Physical Function Score, PROMIS Sleep Score. Present adjusted mean treatment difference (95% CI) change from baseline by time (weeks) from repeated measures model – Week 0, 4, 8, 16, 24, 32. Add footnote: "Note: 1. Adjusted for baseline (week 0) score and region. 2. Sleep score scale 1 = Not at all difficulty in falling asleep /Never trouble staying asleep to 5 = Very much difficulty in falling asleep /Always trouble staying asleep. 3. Physical function scale 0 = Not at all distressed or bothered/No symptoms to 4 = Very much distressed or bothered/Almost constant symptoms."	SAC

15.10.7. Health Outcomes Tables

Health Outcomes: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
SF-36					
3.1.	ITT	*EFF_T6*	Summary of SF-36 Health Survey Domain Scores	Include change from baseline values. Include 95% CIs for the mean.	SAC
3.2.	ITT	*EFF_T6*	Summary of SF-36 Health Survey Component Summary Scores	Include change from baseline values Include 95% CIs for the mean.	SAC
Healthcare Resource Utilisation					
3.3.	ITT	*EFF_T14*	Summary of Healthcare Resource Utilisation Associated with HES Flare		SAC
Work Productivity and Activity Impairment Questionnaire					
3.4.	ITT	*EFF_T15*	Summary of Work Productivity and Activity Impairment		SAC

15.10.8. Safety Tables

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Adverse Event Overview					
4.1.	Safety	*SAFE_T1*	Adverse Event Overview		SAC
Adverse Events					
4.2.	Safety	AE1	Summary of All On-Treatment Adverse Events by System Organ Class and Preferred Term		SAC
4.3.	Safety	AE1	Summary of All Post-Treatment Adverse Events by System Organ Class and Preferred Term		SAC
4.4.	Safety	AE3	Summary of Common (>=3% Incidence) On-Treatment Adverse Events by Overall Frequency		SAC
4.5.	Safety	AE15	Summary of Common (>=3% Incidence) On-Treatment Non-Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
4.6.	Safety	AE5A	Summary of All On-Treatment Adverse Events by Maximum Intensity by System Organ Class and Preferred Term		SAC
4.7.	Safety	AE1	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term		SAC
4.8.	Safety	AE5A	Summary of All Drug-Related Adverse Events by Maximum Intensity by System Organ Class and Preferred Term		SAC
4.9.	Safety	AE1	Summary of Non-Serious Drug-Related Adverse Events by System Organ Class and Preferred Term		SAC
4.10.	Safety	AE1	Summary of On-Treatment Adverse Events by Highest Post-Baseline Binding Antibody Result	Add in row with n in each binding antibody result category.	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
4.11.	Safety	AE3	Summary of All Adverse Events Leading to Permanent Discontinuation from Study Treatment by Overall Frequency		SAC
4.12.	Safety	AE3	Summary of All Adverse Events Leading to Withdrawal from the Study by Overall Frequency		SAC
4.13.	Safety	AE1	Summary of Adverse Events Reported on the Day of Dosing by System Organ Class and Preferred Term		SAC
4.14.	Safety	AE7	Listing of Subject Numbers for Individual On-Treatment Adverse Events		SAC
4.15.	Safety	AE7	Listing of Subject Numbers for Individual Post-Treatment Adverse Events		SAC
4.16.	Safety	AE2	Listing of Relationship of Adverse Event, System Organ Classes, Preferred Terms and Verbatim Text		SAC
Serious Adverse Events					
4.17.	Safety	AE3	Summary of Fatal Serious Adverse Events by Overall Frequency		Headline
4.18.	Safety	AE3	Summary of Drug-Related Fatal Serious Adverse Events by Overall Frequency		SAC
4.19.	Safety	AE3	Summary of Non-Fatal Serious Adverse Events by Overall Frequency		SAC
4.20.	Safety	AE3	Summary of All Serious Adverse Events by Overall Frequency		Headline
4.21.	Safety	AE1	Summary of All On-Treatment Serious Adverse Events by System Organ Class and Preferred Term		SAC
4.22.	Safety	AE1	Summary of All Post-Treatment Serious Adverse Events by System Organ Class and Preferred Term		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
4.23.	Safety	AE1	Summary of All Pre-Treatment Serious Adverse Events by System Organ Class and Preferred Term		SAC
4.24.	Safety	AE16	Summary of All Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
4.25.	Safety	AE1	Summary of All Drug-Related Serious Adverse Events by System Organ Class and Preferred Term		SAC
Adverse Events of Special Interest					
4.26.	Safety	*SAFE_T5*	Summary of On-Treatment Serious AEs and AEs of Special Interest Incidence, Relative Risk and Risk Difference – Mepolizumab 300mg SC vs Placebo		SAC
4.27.	Safety	AE1	Summary of On-Treatment Adverse Events Reported by the Investigator as Meeting the Criteria for Anaphylaxis		SAC
4.28.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Reported by the Investigator as Meeting the Criteria for Anaphylaxis		SAC
4.29.	Safety	AE1	Summary of On-Treatment Adverse Events Defined by the Investigator as Systemic Reactions - Allergic (Type I Hypersensitivity) and Other Systemic		SAC
4.30.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Defined by the Investigator as Systemic Reactions - Allergic (Type I Hypersensitivity) and Other Systemic		SAC
4.31.	Safety	AE1	Summary of On-Treatment Adverse Events Defined by the Investigator as Systemic Reactions - Allergic (Type I Hypersensitivity)		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
4.32.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Defined by the Investigator as Systemic Reactions - Allergic (Type I Hypersensitivity)		SAC
4.33.	Safety	AE1	Summary of On-Treatment Adverse Events Defined by the Investigator as Systemic Reactions – Other Systemic		SAC
4.34.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Defined by the Investigator as Systemic Reactions - Other Systemic		SAC
4.35.	Safety	AE1	Summary of On-Treatment Adverse Events Defined by the Investigator as Local Injection Site Reactions		SAC
4.36.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Defined by the Investigator as Local Injection Site Reactions		SAC
4.37.	Safety	AE1	Summary of On-Treatment Adverse Events Categorised as Serious Cardiac, Vascular and Thromboembolic Events		SAC
4.38.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Categorised as Serious Cardiac, Vascular and Thromboembolic Events		SAC
4.39.	Safety	AE1	Summary of On-Treatment Adverse Events Categorised as Serious Ischemic Events		SAC
4.40.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Categorised as Serious Ischemic Events		SAC
4.41.	Safety	AE1	Summary of On-Treatment Adverse Events Categorised as Malignancies		SAC
4.42.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Categorised as Malignancies		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
4.43.	Safety	AE1	Summary of On-Treatment Adverse Events Categorised as Opportunistic Infections		SAC
4.44.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Categorised as Opportunistic Infections		SAC
Laboratory – Haematology					
4.45.	Safety	LB1	Summary of Haematology Changes from Baseline by Visit	Include baseline values	SAC
4.46.	Safety	LB3	Summary of Haematology Shifts from Baseline Relative to Normal Range by Visit	Include worst case post-baseline. If there are unscheduled assessments add footnote: "Note: Worst case post baseline Includes scheduled and unscheduled assessments."	SAC
4.47.	Safety	LB3	Summary of Haematology Shifts from Baseline Relative to PCI Criteria by Visit	Include worst case post-baseline. If there are unscheduled assessments add footnote: "Note: Worst case post baseline Includes scheduled and unscheduled assessments."	SAC
Laboratory – Clinical Chemistry					
4.48.	Safety	LB1	Summary of Clinical Chemistry Changes from Baseline by Visit	Include baseline values	SAC
4.49.	Safety	LB3	Summary of Clinical Chemistry Shifts from Baseline Relative to Normal Range by Visit	Include worst case post-baseline. If there are unscheduled assessments add footnote: "Note: Worst case post baseline Includes scheduled and unscheduled assessments."	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
4.50.	Safety	LB3	Summary of Clinical Chemistry Shifts from Baseline Relative to PCI Criteria by Visit	Include worst case post-baseline. If there are unscheduled assessments add footnote: "Note: Worst case post baseline Includes scheduled and unscheduled assessments."	SAC
Laboratory – Urinalysis					
4.51.	Safety	UR1	Summary of Worst Case Urinalysis Results Post-Baseline Relative to Baseline		SAC
Laboratory: Hepatobiliary (Liver)					
4.52.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting		SAC
4.53.	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities		SAC
ECG					
4.54.	Safety	EG1	Summary of ECG Findings by Visit	Include worst case post-baseline. If there are unscheduled assessments add footnote: "Note: Worst case post baseline Includes scheduled and unscheduled assessments."	SAC
4.55.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit	Include baseline values	SAC
4.56.	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category	QTc(B) and QTc(F) If there are unscheduled assessments add footnote: "Note: Includes scheduled and unscheduled assessments."	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
4.57.	Safety	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category	QTc(B) and QTc(F) If there are unscheduled assessments add footnote: "Note: Includes scheduled and unscheduled assessments."	SAC
Vital Signs					
4.58.	Safety	VS1	Summary of Vital Signs by Visit		SAC
4.59.	Safety	VS1	Summary of Change from Baseline in Vital Signs by Visit	Include baseline values	SAC
Immunogenicity					
4.60.	Safety	*SAFE_T3*	Summary of Binding Antibody by Visit	Include highest post baseline result.	SAC
4.61.	Safety	*SAFE_T3*	Summary of Binding Antibody By Visit – Subjects Without Positive Result Prior to Dosing	Post-Week 0 visits only, plus highest post baseline result.	SAC
4.62.	Safety	*SAFE_T4*	Summary of Neutralising Antibody by Visit	Include highest post baseline result.	SAC

15.10.9. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events					
4.1.	Safety	AE10	Common (>=3% Incidence) On-Treatment Adverse Events and Relative Risk		SAC
4.2.	Safety	SAFE_F1	Relative Risk of On-Treatment Serious Adverse Events and AEs of Special Interest Mepolizumab 300mg SC vs Placebo		SAC
Laboratory					
4.3.	Safety	LIVER14	Scatter Plot of Maximum vs Baseline for ALT	If there are unscheduled assessments add footnote: “Note: Maximum Value includes scheduled and unscheduled assessments.”	SAC
4.4.	Safety	LIVER9	Scatter Plot of Maximum Total Bilirubin vs Maximum ALT	If there are unscheduled assessments add footnote: “Note: Maximum Value includes scheduled and unscheduled assessments.”	SAC

15.10.10. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
5.1.	PK	PK01	Summary of Plasma Mepolizumab Concentration-Time Data (Observed and Predicted)		SAC
5.2.	PK	PK06	Summary Statistics of Individual Model Predicted Plasma Mepolizumab Pharmacokinetic Parameters (Non-transformed and Log-transformed)		SAC
5.3.	PK	-	Description and Evaluation of Key PK Models Tested	Provided by CPMS	SAC
5.4.	PK	-	Population PK Parameter Estimates with 95% CI of Final PK Model	Provided by CPMS	SAC
5.5.	PK	-	Demographics Summary	Provided by CPMS	SAC
5.6.	PK	-	Samples Summary	Provided by CPMS	SAC
5.7.	PK	-	Accumulation Ratio Estimate at Week 16 and 32	Provided by CPMS	SAC

15.10.11. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
5.1.	PK	-	Plasma Mepolizumab Concentration-Time Profiles (by Treatment)	Provided by CPMS	SAC
5.2.	PK	-	Model Goodness of Fit Plots	Provided by CPMS	SAC
5.3.	PK	-	Continuous Covariate Correlation Plot	Provided by CPMS	SAC
5.4.	PK	-	Categorical Covariate Correlation Plot	Provided by CPMS	SAC
5.5.	PK	-	Automated Covariate Selection	Provided by CPMS	SAC
5.6.	PK	-	Visual Predictive Check	Provided by CPMS	SAC
5.7.	PK	-	Observed Plasma Mepolizumab Concentration-Time Profiles by Anti-Drug Antibody Status	Provided by CPMS	SAC
5.8.	PK	-	Plasma Mepolizumab Observed/Predicted Concentration-Time Profiles (by Subject)	Provided by CPMS	SAC
5.9.	PK	-	Box Plot of Systemic Clearance versus Covariates of Interest	Provided by CPMS	SAC

15.10.12. Pharmacodynamic Tables

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Blood Eosinophils					
6.1.	PD	*PD_T1*	Summary of Blood Eosinophil Count	Include absolute blood eosinophils at Screening, Baseline and Week 2 through Week 32, and ratio to baseline values for Week 2 through Week 32. Number of decimal places as follows: geometric mean (2), SD logs (3), median (2), min (2), max (2).	SAC
6.2.	PD	*PD_T2*	Analysis of On-Treatment Ratio to Baseline Blood Eosinophils (While on Treatment Estimand, Mixed Model Repeated Measures)	Include Week 2 through Week 32.	SAC
IL-5					
6.3.	PD	*PD_T1*	Summary of Serum Total IL-5	Include absolute and ratio to baseline values. Include summary statistics for the number and % of BLQ values.	SAC
6.4.	PD	*PD_T3*	Analysis of On-Treatment Ratio to Baseline Serum Total IL-5 at Week 32 (While on Treatment Estimand)		SAC

15.10.13. Pharmacodynamic Figures

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Blood Eosinophils					
6.1.	PD	*EFF_F4*	On-Treatment Absolute Blood Eosinophils (While on Treatment Estimand, Mixed Model Repeated Measures)	No reference line. Include screening and baseline unadjusted geometric mean values without 95% CI. Week 2 onwards adjusted estimates from MMRM model with 95% CI.	SAC
6.2.	PD	*EFF_F4*	On-Treatment Ratio to Baseline Blood Eosinophils (While on Treatment Estimand, Mixed Model Repeated Measures)	Reference line at 1.	SAC
6.3.	PD	*EFF_F5*	On-Treatment Ratio to Baseline Blood Eosinophils – Treatment Difference vs Placebo (While on Treatment Estimand, Mixed Model Repeated Measures)	Reference line at 1.	SAC

15.10.14. Pharmacokinetic / Pharmacodynamic Tables

Pharmacokinetic / Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
7.1.	PK and PD	-	Description and Evaluation of Key PKPD Models Tested	Provided by CPMS	SAC
7.2.	PK and PD	-	Population PD Parameter Estimates with 95% CI of Final PKPD Model	Provided by CPMS	SAC
7.3.	PK and PD	-	Demographics Summary	Provided by CPMS	SAC
7.4.	PK and PD	-	Samples Summary	Provided by CPMS	SAC

15.10.15. Pharmacokinetic / Pharmacodynamic Figures

Pharmacokinetic / Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
7.1.	PK and PD	-	Blood Eosinophil Count-Time Profiles	Provided by CPMS	SAC
7.2.	PK and PD	-	Model Goodness of Fit Plots	Provided by CPMS	SAC
7.3.	PK and PD	-	Continuous Covariate Correlation Plot	Provided by CPMS	SAC
7.4.	PK and PD	-	Categorical Covariate Correlation Plot	Provided by CPMS	SAC
7.5.	PK and PD	-	Automated Covariate Selection	Provided by CPMS	SAC
7.6.	PK and PD	-	Visual Predictive Check	Provided by CPMS	SAC
7.7.	PK and PD	-	Observed Blood Eosinophil Count -Time Profiles by Anti-Drug Antibody Status	Provided by CPMS	SAC
7.8.	PK and PD	-	Observed/Predicted Blood Eosinophil Count-Time Profiles (by Subject)	Provided by CPMS	SAC

15.10.16. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure		SAC
2.	ITT	ES2	Listing of Reasons for Study Withdrawal		SAC
3.	ITT	SD2	Listing of Reasons for Study Treatment Discontinuation		SAC
4.	ITT	BL1	Listing of Subjects for Whom the Treatment Blind was Broken		SAC
5.	ITT	TA1	Listing of Planned and Actual Treatments		SAC
Protocol Deviations					
6.	ITT	DV2	Listing of Important Protocol Deviations		SAC
7.	ITT	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
Populations Analysed					
8.	ITT	SP3	Listing of Subjects Excluded from Any Population	Include Per Protocol, Safety, PK, PD	SAC
Demographic and Baseline Characteristics					
9.	ITT	DM2	Listing of Demographic Characteristics		SAC
10.	ITT	DM9	Listing of Race		SAC
11.	ITT	MH2	Listing of Medical Conditions		SAC
Prior and Concomitant Medications					
12.	ITT	CP_CM3	Listing of Concomitant Medications	Flag baseline HES therapy on listing.	SAC
Exposure and Treatment Compliance					
13.	ITT	EX3	Listing of Exposure Data	Exposure to Mepolizumab/Placebo only.	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Burden of HES					
14.	ITT	*POP_L1*	Listing of Most Bothersome HES Related Symptoms		SAC
15.	ITT	*POP_L2*	Listing of Steroid Perception Questionnaire		SAC
Efficacy					
16.	ITT	*EFF_L1*	Listing of Investigator Reported HES Flare		SAC
17.	ITT	*EFF_L2*	Listing of Blinded OCS Therapy		SAC
18.	ITT	*EFF_L3*	Listing of Fatigue Severity (BFI)		SAC
19.	ITT	*EFF_L4*	Listing of $FEV_{1,}$ FVC and FEV1/FVC		SAC
20.	ITT	*EFF_L5*	Listing of Echocardiogram/MUGA		SAC
21.	ITT	*EFF_L6*	Listing of Symptom Severity (HES-DS)		SAC
22.	ITT	*EFF_L7*	Listing of Subject- and Clinician-Rated Overall Response to Therapy		SAC
23.	ITT	*EFF_L8*	Listing of Subject-Rated Symptom Severity		SAC
24.	ITT	*EFF_L9*	Listing of MSAS-SF Total and Subscale Scores		SAC
25.	ITT	*EFF_L10*	Listing of PROMIS Physical Function and Sleep Score		SAC
Healthcare Resource Utilisation					
26.	ITT	*EFF_L11*	Listing of SF-36 Health Survey		SAC
27.	ITT	*EFF_L12*	Listing of Healthcare Resource Utilisation Associated with HES Flare		SAC
28.	ITT	*EFF_L13*	Listing of Work Productivity and Activity Impairment		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events					
29.	Safety	AE8	Listing of All Adverse Events	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC
Serious and Other Significant Adverse Events[1]					
30.	Safety	AE8	Listing of Fatal Serious Adverse Events	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC
31.	Safety	AE8	Listing of Non-Fatal Serious Adverse Events	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC
32.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC
33.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC
34.	Safety	AE8	Listing of Adverse Events Reported on the Day of Dosing	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC
35.	Safety	AE8	Listing of Adverse Events Reported by the Investigator as Meeting the Criteria for Anaphylaxis	Add phase: Pre-treatment, on-treatment, post-treatment. Add injection reaction symptoms and number of doses prior to event. Include treatment in by-line.	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
36.	Safety	AE8	Listing of Adverse Events Defined by the Investigator as Systemic Reactions - Allergic (Type I Hypersensitivity)	Add phase: Pre-treatment, on-treatment, post-treatment. Add injection reaction symptoms and number of doses prior to event. Include treatment in by-line.	SAC
37.	Safety	AE8	Listing of Adverse Events Defined by the Investigator as Systemic Reactions – Other Systemic	Add phase: Pre-treatment, on-treatment, post-treatment. Add injection reaction symptoms and number of doses prior to event. Include treatment in by-line.	SAC
38.	Safety	AE8	Listing of Adverse Events Defined by the Investigator as Local Injection Site Reactions	Add phase: Pre-treatment, on-treatment, post-treatment. Add injection reaction symptoms and number of doses prior to event. Include treatment in by-line.	SAC
39.	Safety	AE8	Listing of Adverse Events Categorised as Serious Cardiac, Vascular and Thromboembolic Events	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC
40.	Safety	AE8	Listing of Adverse Events Categorised as Serious Ischemic Events	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC
41.	Safety	AE8	Listing of Adverse Events Categorised as Malignancies	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
42.	Safety	AE8	Listing of Adverse Events Categorised as Opportunistic Infections	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC
Hepatobiliary (Liver)					
43.	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events		SAC
44.	Safety	SU2	Listing of Substance Use for Subjects with Liver Stopping Events		
All Laboratory					
45.	Safety	LB5	Listing of Haematology Data for Subjects with Any Value of Potential Clinical Importance		SAC
46.	Safety	LB5	Listing of Clinical Chemistry Data for Subjects with Any Value of Potential Clinical Importance		SAC
47.	Safety	LB14	Listing of Laboratory Data with Character Results		SAC
48.	Safety	UR2A	Listing of Urinalysis Data for Subjects with Any Value of Potential Clinical Importance		SAC
ECG					
49.	Safety	EG3	Listing of All ECG Values for Subjects Meeting Protocol Defined QTc Stopping Criteria		SAC
Immunogenicity					
50.	Safety	*SAFE_L1*	Listing of Immunogenicity Data for Subjects with at Least One Positive Screening Binding Assay		SAC
Pharmacokinetic					
51.	PK	-	Listing of Data and Subjects Excluded from Analysis	Provided by CPMS	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
52.	PK	-	Final PK Model Listings	Provided by CPMS	SAC
Pharmacodynamic					
53.	Safety	*PD_L1*	Listing of Blood Eosinophils *(unit)*		SAC
54.	Safety	*PD_L2*	Listing of Serum Total IL-5 *(unit)*		SAC
Pharmacokinetic / Pharmacodynamic					
55.	PK and PD	-	Listing of Data and Subjects Excluded from Analysis	Provided by CPMS	SAC
56.	PK and PD	-	Final PKPD Model Listings	Provided by CPMS	SAC

[1] For deaths and any cardiovascular events, subject profiles will be produced as per GSK IDSL standard template.

15.11. Appendix 11: Example Mock Shells for Data Displays

Available upon request