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

Title	:	Reporting and Analysis Plan for Study 205203: A multi-centre, open-label extension, safety study of mepolizumab in participants with hypereosinophilic syndrome (HES) from Study 200622
Compound Number	:	SB240563
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 205203.
- This RAP defines the content of the 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 205203:

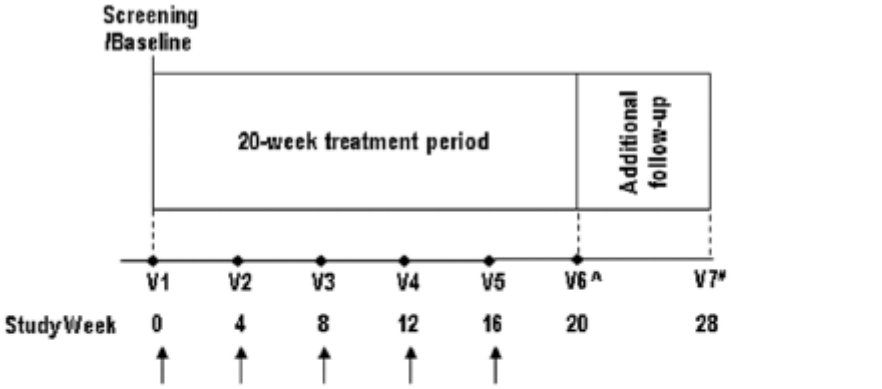
Protocol Revision Chronology:		
2016N289833_00	02-NOV-2016	Original
2016N289833_01	13-JAN-2017	Protocol Amendment 1: A change to the EudraCT# was made to reflect the correct EudraCT# associated with the protocol.
2016N289833_02	16-Nov-2017	Protocol Amendment 2: Optional biomarker sub-study has been added. The text was updated considering that investigators may adjust the participants' background HES therapy per standard of care starting at Visit 2. GSK tracking numbers were replaced with the term 'mepolizumab HES expanded access'.

2. SUMMARY OF KEY PROTOCOL INFORMATION

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

Objectives	**Endpoints**
Primary Objectives	**Primary Endpoints**
• To describe the long-term safety profile of mepolizumab in participants with HES who took part in Study 200622.	**Primary** • Adverse events (AEs) [serious and non-serious] • Anti-drug antibody **Other Safety** • Vital signs • 12-lead ECG • Hematological and clinical laboratory tests
Exploratory Objectives	**Exploratory Endpoints**
• To assess the effect of long-term use of mepolizumab on multiple clinical outcomes.	• Rate of HES flare • Change in the mean daily OCS dose from Weeks 0-4 to Weeks 16-20 • Proportion of participants who achieve a mean daily OCS (prednisone/prednisolone or equivalent) dose of ≤7.5mg during Weeks 16-20
• To assess the effect of long-term use of mepolizumab on a PD marker	• Blood eosinophil levels

2.2. Study Design

Overview of Study Design and Key Features	
 ↑: Mepolizumab treatment (300mg SC per administration) V: Visit ^: Participants who continue with mepolizumab treatment via MHE104317/MHE112562 after Study 205203 will have the last assessment on Week 20 (Visit 6). #: Participants who do not continue with mepolizumab via MHE104317/MHE112562 after Study 205203 will have additional follow-up 12 weeks after the last dose (Visit 7).	
Design Features	• Multi-centre, open-label extension, 20-week treatment period, safety study of mepolizumab in adolescent and adult participants with HES who took part in the phase 3 study 200622. • Visit 1 for study 205203 is the exit visit (32 weeks after randomisation) for study 200622. • Investigators will be blinded to the blood eosinophil count from the sample obtained at visit 1 (first dosing visit), in order to maintain the blinding of study 200622, after which eosinophil counts will be unblinded starting from visit 2. • Investigators may adjust the participants' background HES therapy per standard of care starting at visit 2 (approximately 4 weeks after the first dose of open-label mepolizumab). • Participants who withdraw from study treatment prematurely should continue in the study per protocol until 20 weeks from first dose of open-label mepolizumab. • Participants who complete assessments at visit 6 (week 20) may continue with mepolizumab treatment via MHE104317/MHE112562, where local regulation permits. Study participants who do not continue with MHE104317/MHE112562 will have an additional follow-up assessment 12 weeks after the last dose of mepolizumab.
Dosing	• 300 mg SC mepolizumab every 4 weeks (5 administrations) while continuing their HES therapy. • The final dose of study treatment will be administered at Visit 5 (Week 16) with completion of the study treatment period achieved at the next 4-weekly visit.

Overview of Study Design and Key Features	
Time & Events	• See Appendix 1: Schedule of Activities
Treatment Assignment	• All participants are assigned to 300mg SC mepolizumab. • Between 80 and 120 participants will be randomised in study 200622. Those participants who complete required assessments for 32 weeks starting from randomisation may be evaluated for eligibility to study 205203.
Interim Analysis	• An external Independent Data Monitoring Committee (IDMC) will review ongoing data from study 205203 as potential supporting data for the overall assessment of safety for use of mepolizumab in the 200622 study population. The safety data analyses for the IDMC reviews will be performed by an independent statistical analysis data centre (SDAC). The IDMC will not issue recommendations for the conduct of study 205203. • No other interim analysis is planned.
Main subject entry criteria	• Study 200622 participants who meet one of the following criteria: i. Completion of the 32-week treatment period in study 200622 ii. Participants withdrawn from study treatment prematurely during the 200622 study, but continue in the study per protocol until 32 weeks from randomisation.

2.3. Statistical Hypotheses / Statistical Analyses

No formal statistical hypothesis testing is planned.

2.4. Changes to the Protocol Defined Statistical Analysis Plan

- More detail was added to the protocol defined endpoint, change in mean daily OCS dose from Weeks 0-4 to Weeks 16-20. This additionally includes the change in mean daily OCS dose from Weeks 0-4 to Weeks 4-8, Weeks 8-12 and Weeks 12-16.
- An additional endpoint of the proportion of patients who achieve a mean daily OCS (prednisone/prednisolone or equivalent) dose reduction of 50% or more from Week 0-4 to Week 16-20 will be reported, for those subjects with a mean OCS dose during Week 0-4 greater than 0mg.

3. PLANNED ANALYSES

3.1. Interim Analyses

- An external Independent Data Monitoring Committee (IDMC) will periodically review unblinded safety data from study 200622, in accordance with the IDMC Charter. Data from study 205203 will also be provided for information to the IDMC as potential supporting data for the overall assessment of safety for use of mepolizumab in the 200622 study population. The safety data analyses for the IDMC reviews will be performed by an independent statistical analysis data centre (SDAC). The IDMC will not issue recommendations for the conduct of study 205203. GSK will evaluate if IDMC recommendations from study 200622 will require changes to study 205203.

- No other interim analysis is planned for this study.

3.2. Final Analyses

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

1. All participants 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.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Participants Enrolled	• All participants who sign the ICF and for whom a record exists on the data base	• Screen failures
Safety	• All participants who received at least one dose of open-label mepolizumab.	• Safety • Efficacy
Pharmacodynamic (PD)	• All screened participants who had a baseline blood eosinophil measurement and at least one post-treatment eosinophil measurement.	• Blood eosinophils

Refer to Appendix 8: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

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.

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 freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

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 electronic case report form (eCRF).

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Summaries will be presented by the actual treatment the participant received in the randomised double-blind study (200622). With the exception of pharmacokinetic and pharmacodynamic data, summaries will also be presented for all subjects receiving open-label mepolizumab.

Treatment group descriptors will be assigned as follows:

Treatment Group Descriptions			
RandAll NG from Study 200622		Data Displays for Reporting	
Code	Description	Description	Order [1]
P	Placebo	300mg SC Prev. Placebo	1
A	Mepolizumab 300mg SC	300mg SC Prev. Mepo	2
N/A	N/A	300mg SC Total	3

NOTES:

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

5.2. Baseline Definitions

- Baseline will be defined as the latest assessment prior to open-label mepolizumab with a non-missing value, including those from unscheduled visits. If time is not collected, visit 1 assessments are assumed to be taken prior to first dose of open-label mepolizumab and used as the baseline.
- Where the exit visit for study 200622 (32 weeks post randomisation) is performed on the same day as visit 1 for study 205203, clinical safety laboratory assessments (including PD assessment of blood eosinophils), PK, immunogenicity and vital signs may not be repeated as part of visit 1 for study 205023. In these cases, the assessments at the exit visit for study 200622 will be defined as the baseline for study 205203 and will be transferred from the 200622 SDTM data sets to the Analysis Data Model (ADaM) reporting data sets for study 205203.
- In order to allow appropriate central ECG monitoring throughout the 205203 study, sites will be requested to conduct an ECG assessment prior to the first dose of open-label mepolizumab at visit 1 of study 205203, even if an ECG assessment was done on the same day as part of the exit visit for study 200622. The visit 1 ECG in study 205203 will be defined as the baseline. If more than one ECG is performed prior to open-label mepolizumab as part of visit 1 in study 205203, for each ECG parameter the mean of the available pre-dose values on the date of visit 1 in study 205203 will be assigned as the baseline value for that parameter. Additional ECGs on the date of visit 1 will be captured as unscheduled assessments with the same date as visit 1 in the clinical study data base; all visit 1 and unscheduled visits occurring prior to open-

label mepolizumab on the date of visit 1 in study 205203 will be considered to derive the baseline value.

5.3. Multicentre Studies

- In this multicentre global study, enrolment will be presented by investigative site and country.
- The following regions will be defined with consideration for standard of care medical practice. These regions correspond to the strata used for randomisation in study 200622.
  - USA
  - Argentina, Mexico and Brazil
  - Rest of World

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

- Where adjusted flare rates are presented (see Section 9.1.1.4), estimates will be adjusted for region and for baseline oral prednisone equivalent daily dose from study 200622.

5.4.2. Examination of Subgroups

No subgroup analyses will be performed.

5.5. Multiple Comparisons and Multiplicity

Analysis of the study data will be descriptive. No adjustment for multiplicity will be made.

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
13.1	Appendix 1: Schedule of Activities
13.2	Appendix 2: Study Phases and Treatment Emergent Adverse Events
13.3	Appendix 3: Data Display Standards & Handling Conventions
13.4	Appendix 4: Derived and Transformed Data
13.5	Appendix 5: Reporting Standards for Missing Data
13.6	Appendix 6: 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 Safety population, unless otherwise specified.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 8: List of Data Displays.

7. SAFETY ANALYSES

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

7.1. 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. The details of the planned displays are provided in Appendix 8: List of Data Displays.

A summary of AEs reported by highest post-baseline binding antibody result (as defined in Section 8.1) will be produced.

7.2. Adverse Events of Special Interest Analyses

- 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 database freeze 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 participants 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 be limited to, the number of occurrences of the event, event characteristics, time to onset, intensity, outcome and action taken.
- 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.

7.3. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 8: List of Data Displays.

7.4. 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 8: List of Data Displays.

8. IMMUNOGENICITY ANALYSES

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

8.1. 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 assay results at each visit will be summarised negative or positive. In addition, the highest post-baseline binding ADA assay 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 assay confirmatory result (as defined above) will be produced.

A summary of treatment emergent positive confirmatory binding ADA assay results in the subset of subjects who did not have a positive confirmatory binding ADA assay 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 result.

9. EFFICACY ANALYSES

9.1. Exploratory Efficacy Analyses

9.1.1. Rate of HES Flares

9.1.1.1. Endpoint / Variables

Definition of HES Flare

A HES flare is defined as an HES-related clinical manifestation based on a physician-documented change in clinical signs or symptoms (worsening symptoms and/or elevated blood eosinophil level) resulting in the need for either of the following:

- An increase from the most recent dose in the maintenance OCS dose (prednisone/prednisolone equivalent) by at least 10mg/day for 5 days

- An increase in or addition of any cytotoxic and/or immunosuppressive HES therapy from/to the most recent dose of HES therapy.

To be considered as an HES flare, the most recent dose of HES therapy must not have changed for at least 4 weeks. This ensures that failed reductions in HES therapy are not misclassified as an HES flare.

The definition of HES flare for this study (205203) is different from that for the preceding, randomized Study 200622. This difference in definitions is due to the requirement during Study 200622 to avoid decreases in background HES therapy that may confound a blinded subject's clinical status as well as the requirement during Study 200622 to blind blood eosinophil levels. In Study 205203, all participants will receive mepolizumab and investigators will be unblinded to blood eosinophil levels starting 4 weeks after the first dose (Visit 2) so that they may adjust background HES therapy as per standard of care (SoC).

Derivation of Endpoint

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 in Study 205203 and either the Week 20 visit date if available, or otherwise the study withdrawal date (see Section 13.4.4).

The rate of HES flares will also be calculated separately using data from Study 200622 only, for those subjects continuing into Study 205203.

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.

9.1.1.2. Summary Measure

The rate/year of HES flares.

9.1.1.3. 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 discontinuation of study medication. For subjects withdrawing prematurely from the study during the 20-week treatment period, all data up to the time of study withdrawal will be used to calculate the rate of HES flares.

9.1.1.4. Statistical Analyses / Methods

Endpoint
Rate of HES flares.
Model Specification
• Analysis using a negative binomial generalised linear model with a log-link function, including terms for baseline OCS dose from study 200622 (continuous scale), region 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. • A separate model will be fitted to data from Study 200622 for those subjects continuing into Study 205203.
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
• Median rate/year on raw data values for Study 200622 (Week 0 – Week 32, double-blind) and Study 205203 (Week 32 – Week 52, open-label). • Adjusted mean rate/year from negative binomial model and 95% confidence interval for Study 200622 (Week 0 – Week 32, double-blind) and Study 205203 (Week 32 – Week 52, open-label).
Subgroup Analyses
• No subgroup analyses will be performed on this endpoint.
Sensitivity and Supportive Statistical Analyses
• No sensitivity analyses will be performed

9.1.2. Change in mean daily OCS dose from Weeks 0-4 to Weeks 16-20

9.1.2.1. Endpoint / Variables

The mean daily OCS (prednisone or equivalent) dose for each 4 week period (Week 0-4, Week 4-8, Week 8-12, Week 12-16 and Week 16-20) for each subject will be calculated as the sum of the daily doses of OCS during each period divided by the total number of days, 28. For each subject, the prednisone equivalent daily dose for each day will be determined as described in Section 13.4.4.

Subjects withdrawing from the study prematurely will have mean daily OCS (prednisone or equivalent) dose calculated using available data up to study withdrawal date only (divided by the number of days for which there is available data).

The change in the mean daily OCS dose from Week 0-4 to Week 16-20 will be calculated for each subject as the mean daily OCS dose for Week 16-20 minus the mean daily OCS dose for Week 0-4. The change in the mean daily OCS dose from Week 0-4 to each 4-week period (Week 4-8, Week 8-12 and Week 12-16) will be calculated using the same formula. The change in mean daily OCS dose will be summarised separately for a) all subjects and b) for subjects with a mean Week 0-4 OCS dose > 0mg.

9.1.2.2. Summary Measure

The change in the mean daily OCS dose from Week 0-4 to each 4-week period (Week 4-8, Week 8-12, Week 12-16 and Week 16-20).

9.1.2.3. 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 event of discontinuation of study medication. For subjects withdrawing prematurely from the study, all data up to the time of study withdrawal will be used to calculate the daily OCS (prednisone or equivalent) dose. Subjects that withdraw from the study prior to each 4-week period will not be included in the summary statistics for that 4-week period.

9.1.2.4. Statistical Analyses / Methods

Summary statistics for mean daily OCS (prednisone or equivalent) dose for Week 0-4, Week 4-8, Week 8-12, Week 12-16 and Week 16-20 will be presented, including change in the mean daily OCS dose.

The summary statistics to be reported for each four-week period are: minimum, maximum, mean, standard deviation and sample size (n). The same summary statistics will be reported for the change in mean daily OCS.

9.1.3. Proportion of participants who achieve a mean daily OCS (prednisone or equivalent) dose of 7.5mg or less during Weeks 16-20

9.1.3.1. Endpoint / Variables

Subjects who achieve a mean daily OCS (prednisone/prednisolone or equivalent) dose of 7.5mg or less during each four-week period (Week 0-4, Week 4-8, Week 8-12, Week 12-16 and Week 16-20) will be identified from the concomitant medications results, as defined in Section 13.4.4.

9.1.3.2. 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 discontinuation of study medication. For subjects withdrawing prematurely from the study, all data up to the time of study withdrawal will be used to calculate the mean daily OCS (prednisone or equivalent) dose and derive the above endpoint. Subjects that withdraw from the study prior to each 4-week period will not be included in the summary statistics for that 4-week period.

9.1.3.3. Statistical Analyses / Methods

The number and percentage of subjects who achieve a mean daily OCS (prednisone/prednisolone or equivalent) dose of 7.5mg or less during Week 16-20 will be presented. The number and percentage of subjects who achieve a mean daily OCS dose of 7.5mg or less during Week 0-4, Week 4-8, Week 8-12 and Week 12-16 will also be tabulated.

9.1.4. Proportion of participants who achieve a mean daily OCS (prednisone or equivalent) reduction of 50% or more during Weeks 16-20

9.1.4.1. Endpoint / Variables

Subjects who achieve a mean daily OCS (prednisone/prednisolone or equivalent) reduction of 50% or more throughout each four-week period (Week 4-8, Week 8-12, Week 12-16 and Week 16-20) will be identified from the concomitant medications results, as defined in Section 13.4.4. This endpoint will be summarised for subjects with a mean Week 0-4 OCS dose > 0mg only.

9.1.4.2. 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 discontinuation of study medication. For subjects withdrawing prematurely from the study, all data up to the time of study withdrawal will be used to calculate the mean daily OCS (prednisone or equivalent) dose and derive the above endpoint. Subjects that withdraw from the study prior to each 4-week period will not be included in the summary statistics for that 4-week period.

9.1.4.3. Statistical Analyses / Methods

The number and percentage of subjects who achieve a mean daily OCS (prednisone/prednisolone or equivalent) dose of reduction of 50% or more during Week 16-20 will be presented. The number and percentage of subjects who achieve a mean daily OCS dose of reduction of 50% or more during Week 4-8, Week 8-12 and Week 12-16 will also be tabulated.

10. PHARMACOKINETIC ANALYSES

10.1. Primary Pharmacokinetic Analyses

10.1.1. Endpoint / Variables

10.1.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 13.3.3 Reporting Standards for Pharmacokinetic Data).

No pharmacokinetic analyses are planned for this study. However Pharmacokinetic samples for determination of mepolizumab plasma concentrations will be collected at the same time as immunogenicity samples to help interpretation of immunogenicity impact. Pharmacokinetic concentrations will be summarised by previous treatment group from study 200622, immunogenicity status and visit. All pharmacokinetic concentration data will be listed.

11. PHARMACODYNAMIC ANALYSES

11.1. Blood Eosinophils

11.1.1. Population of Interest

Blood eosinophil analyses will be based on the Pharmacodynamic population.

11.1.2. 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 205203 study treatment.

11.1.3. Summary Measure

The blood eosinophil ratio to baseline.

11.1.4. 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).

11.1.5. Statistical Analyses / Methods

- Blood eosinophil counts will be $\log_e$-transformed prior to analysis. The log transformation for values of 0 GI/L will be based on a value of 0.005 GI/L

- Absolute and ratio to baseline blood eosinophil counts will be summarised by previous treatment group from study 200622 and visit. Descriptive statistics will

include: Minimum, maximum, median, geometric mean on the original scale and standard deviation on $\log_e$-transformed data.

- Geometric mean blood eosinophil counts will be plotted by previous treatment group, immunogenicity status and visit.

- Only results from the central laboratory will be included in the summary, however all data will be listed.

Details of the planned displays are provided in Appendix 8: List of Data Displays and will be based on GSK Data Standards and statistical principles.

12. REFERENCES

GlaxoSmithKline Document Number 2016N289833_01 Study ID 205203. Clinical Protocol for Study 205203: A multi-centre, open-label extension, safety study to describe the long-term clinical experience of mepolizumab in participants with hypereosinophilic syndrome (HES) from Study 200622. Report Date 13-JAN-2017.

13. APPENDICES

13.1. Appendix 1: Schedule of Activities

13.1.1. Protocol Defined Schedule of Events

Procedure	Screening/Baseline	20-Week Treatment Period					WD (4 weeks post-last dose) ± 1 wk	Study Visit 7 Additional follow-up (12 weeks post-last dose ± 1 wk	Flare	Notes
Study Visit	1	2	3	4	5	6				
Study Weeks	0	4 ± 1 wk	8 ± 1 wk	12 ± 1 wk	16 ± 1 wk	20 ± 1 wk				
Informed consent	X									
Inclusion and exclusion criteria	X									
Demography	X									
Full physical examination including height and weight	X									
Past and current medical conditions	X									
Urine pregnancy test (WOCBP only) – serum test if locally required	X	X	X	X	X	X	X	X		Test is required for WOCBP on study treatment until the last follow-up.
Clinical safety laboratory assessments (include liver chemistries)	1	2	2	2	2	1	1		2	1: Hematology, chemistry, aldolase, troponin, urinalysis 2: Hematology, chemistry, aldolase, troponin
PK	X					X	X	X		
Immunogenicity (Anti-drug antibody)	X					X	X	X		
12-lead ECG	X					X	X			

Procedure	Screening/Baseline	20-Week Treatment Period					WD (4 weeks post-last dose) ± 1 wk	Study Visit 7 Additional follow-up (12 weeks post-last dose ± 1 wk	Flare	Notes
Study Visit	1	2	3	4	5	6				
Study Weeks	0	4 ± 1 wk	8 ± 1 wk	12 ± 1 wk	16 ± 1 wk	20 ± 1 wk				
Vital signs	X	X	X	X	X	X	X		X	
HES Core Assessments/HES flare details	X	X	X	X	X	X	X		X	
Study treatment	X	X	X	X	X					
AE review	X	X	X	X	X	X	X	X	X	
SAE review	X	X	X	X	X	X	X	X	X	
Concomitant medication review	X	X	X	X	X	X	X	X	X	

wk: week

- The baseline visit is the exit visit (32 weeks after randomization) for Study 200622. Assessments that are captured as part of the exit visit for Study 200622 do not have to be repeated. Information will be transferred accordingly.
- Biological sample collection (for clinical safety laboratory, PK, and immunogenicity) is done prior to administration of study treatment on dosing visits (Visits 1 2, 3, 4, 5) as specified in the SoA.
- WD: Prematurely discontinuation of mepolizumab (~4 weeks after the last dose of mepolizumab).
- Visit 7 - Additional follow-up is required 12 weeks after the last dose of mepolizumab for participants who do not continue with mepolizumab via MHE104317/MHE112562 at that time.
- Participants who prematurely discontinue study treatment will attend 4-weekly study visits (e.g., Visit 2, 3, 4, 5) to complete all assessments/procedures as noted in the SoA except for administration of study treatment and pre-dose pregnancy test for women of childbearing potential (WOCBP). For additional assessments at 4 weeks and 12 weeks after the last dose of

mepolizumab (duplicate assessments in 4-weekly study visits and 4 weeks/12 weeks post-last dose assessments are completed only once), refer to 'WD' and 'Visit 7- Additional follow-up'.

- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

13.2. Appendix 2: Study Phases and Treatment Emergent Adverse Events

Assessments and events will be classified according to the time of occurrence relative to the first dose of open-label mepolizumab.

Time	Subjects completing the study (Week 20 visit)	Subjects not completing the study (Predicted Week 20 visit date = Date of first dose + 140 days)
Total observed time	Week 20 visit date – date of first dose + 1 day	Study withdrawal date – date of first dose + 1 day
Time on treatment (days)	Minimum(Week 20 visit date, Date of last dose + 28 days) - Date of first dose + 1 day	Minimum(Study withdrawal date, Date of last dose + 28 days) - Date of first dose + 1 day
Time off treatment (days)	Week 20 visit date – Minimum(Week 20 visit date, Date of last dose + 28 days)	Study withdrawal date – Minimum(Study withdrawal date, Date of last dose + 28 days)
Missing time	0	Predicted Week 20 visit date – Study withdrawal date

13.2.1. Treatment Phases for Adverse Events

Treatment State	Definition
Pre-Treatment	• AE start date < Date of first dose of open-label mepolizumab or if AE onset date/time is available • AE start date/time < Date/time of first dose of open-label mepolizumab
On-Treatment	• Date of first dose of open-label mepolizumab ≤ AE start date ≤ Date of last dose of open-label mepolizumab + 28 days or if AE onset date/time is available • Date/time of first dose of open-label mepolizumab ≤ AE start date/time ≤ Date/time of last dose of open-label mepolizumab + 28 days • Any adverse event with missing start date will be assumed to be “On-Treatment”. • Any adverse event with partial start date will be assumed to be “On-Treatment” unless there is evidence to the contrary (e.g. month/year of onset is present and is earlier than the month/year of the first dose of study treatment).
Post-Treatment	• AE start date > Date of last dose of open-label mepolizumab + 28 days or if AE onset date/time is available • AE start date/time > Date/time of last dose of open-label mepolizumab + 28 days

13.2.2. 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 13.5.2 for handling of missing and partial dates for concomitant medications.

13.3. Appendix 3: Data Display Standards & Handling Conventions

13.3.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Area	: sb240563/mid205203
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.	

13.3.2. 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.
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 the rate of HES flares • 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.

13.3.3. 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.

13.4. Appendix 4: Derived and Transformed Data

13.4.1. General

Multiple Measurements at One Analysis Time Point
• May arise when unscheduled visits are re-assigned to a nominal visit (see Section 13.1.1). If there is data at the nominal visit, the nominal visit data will be used in the summary tables and figures. All assessments will be listed. • Participants having both High and Low values for Normal Ranges at any post-baseline visit 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. • If multiple ECG assessments are performed at a single time point, for each ECG parameter, the mean of the parameter values from replicate ECGs will be used in the derivation of any summary statistics for that ECG parameter. All data will be listed.
Study Day

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

13.4.2. 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

13.4.3. Study Population

Age
• GSK standard IDSL algorithms will be used for calculating age where birth day and month will be imputed '30th June'. • 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]**
Extent of Exposure
• Number of days of exposure to open-label mepolizumab will be calculated based on the

formula:

Duration of Exposure in Days = Date of Last Dose of Open-Label Mepolizumab – Date of First Dose of Open-Label Mepolizumab + 29.

13.4.4. Efficacy

HES Flare

Definition of HES Flare

A HES flare is defined as an HES-related clinical manifestation based on a physician-documented change in clinical signs or symptoms (worsening symptoms and/or elevated blood eosinophil level) resulting in the need for either of the following:

- An increase from the most recent dose in the maintenance OCS dose (prednisone/prednisolone equivalent) by at least 10mg/day for 5 days
- An increase in or addition of any cytotoxic and/or immunosuppressive HES therapy from/to the most recent dose of HES therapy.

To be considered as an HES flare, the most recent dose of HES therapy must not have changed for at least 4 weeks. This ensures that failed reductions in HES therapy are not misclassified as an HES flare.

The start date for an HES flare will be defined as the date of therapy escalation confirmed by the investigator attributable to an HES-related clinical manifestation.

When a subject experiences an HES flare, the investigator will monitor the change in disease control per routine medical care (e.g., follow-up call) and record the resolution of the flare including the end date. Investigators are encouraged, as medically appropriate, to return the subject's treatment regimen to the baseline (Visit 2) after the flare has resolved.

In the event of disease worsening for which the investigator suspects an HES flare between scheduled clinic visits, when possible, the subject will return to the clinic to have the unscheduled 'Flare' visit assessment completed as described in the SoA. When attending the clinic visit at the time of a suspected HES flare is not possible, the investigator should make every effort to evaluate the subject via telephone and complete the HES Core Assessments (Section 9.1.2). If an escalation of therapy is initiated by a non-study physician, the investigator should confirm that the escalation in therapy is attributable to an HES-related clinical manifestation.

Investigators will be required to record details pertaining to the HES flare event in the CRF from Visit 1 until 20 weeks after the first dose of mepolizumab. This should include details regarding the clinical symptoms resulting in the flare with detail of the required intervention(s), e.g., OCS dose increase, or addition or escalation of immunosuppressive or cytotoxic therapy. In addition, all other relevant clinical, laboratory or other diagnostic investigations required to confirm the flare must be captured in the CRF.

The definition of HES flare for this study (205203) is different from that for the preceding, randomized Study 200622. This difference in definitions is due to the requirement during Study 200622 to avoid decreases in background HES therapy that may confound a blinded subject's clinical status as well as the requirement in Study 200622 to blind blood eosinophil levels. In Study 205203, all participants will receive mepolizumab and investigators will be unblinded to blood eosinophil levels starting 4 weeks after the first dose (Visit 2) so that they may adjust background HES therapy as per SoC.

Rate of HES Flares

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

$$\frac{365.25 \times Number\ of\ observed\ HES\ flares}{Date\ of\ Week\ 20\ (Visit\ 6) - Date\ of\ first\ dose\ of\ mepolizumab + 1}$$

- 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.

Oral Prednisone Equivalent Daily Dose

- For each subject, oral prednisone equivalent daily dose (mg) on each day of the study will be identified from the concomitant medications page
- Partial start and end dates for concomitant medications will be handled as described in Section 13.5.2.
- 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.
- Only corticosteroids recorded with route = "PO" will be considered as oral corticosteroids.
- Subjects not receiving OCS therapy on any day of the study will be assigned a prednisone equivalent daily dose of 0 mg for that day.
- 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

Mean Daily OCS Dose
Change in the mean daily OCS dose from Weeks 0-4 to Weeks 16-20
• The mean daily OCS dose for weeks 0-4 will be calculated as $\frac{Sum\ of\ daily\ OCS\ dose\ for\ weeks\ 0-4}{28}$ • The mean daily OCS dose for weeks 16-20 will be calculated as $\frac{Sum\ of\ daily\ OCS\ dose\ for\ weeks\ 16-20}{28}$ • The change in the mean daily OCS dose from Weeks 0-4 to Weeks 16-20 will be the difference of mean daily OCS dose for weeks 16-20 minus mean daily OCS dose for weeks 0-4

13.4.5. 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.
AE Duration (Days)
• AE end date – AE start date + 1 • Missing if AE start date or end date is missing.
AEs of Special Interest
• See Section 7.2.

13.5. Appendix 5: Reporting Standards for Missing Data

13.5.1. Premature Withdrawals

Element	Reporting Detail
General	• A subject will be considered to have **completed study treatment** if they receive study treatment at week 16 (Visit 5). • Subjects who discontinue study treatment or withdraw early will not be replaced in the study.

13.5.2. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events and HES Flare	• Any partial dates for adverse events or HES flare will be raised to data management. If the full dated cannot be ascertained, the following assumptions will be made: o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month. o However, if this imputation results in a date prior to the first dose of open-label mepolizumab and the event could possibly have occurred during open-label mepolizumab treatment from the partial information, then the date of the first dose of mepolizumab will be assumed to be the start date. o The event will then be considered to start on-treatment (worst case). o 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. Such events will be considered to have started after the first dose of open-label mepolizumab. • 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.

13.6. Appendix 6: Values of Potential Clinical Importance

13.6.1. 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
While 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.

13.6.2. 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.

13.7. Appendix 7: Abbreviations & Trade Marks

13.7.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
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
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SDSP	Study Data Standardization Plan

Abbreviation	Description
SDTM	Study Data Tabulation Model
SoA	Schedule of Activities
SoC	Standard of Care
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings

13.7.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

13.8. Appendix 8: List of Data Displays

13.8.1. 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
Safety	3.1 to 3.n	3.1 to 3.n
Pharmacokinetic	4.1 to 4.n	4.1 to 4.n
Pharmacodynamic and / or Biomarker	6.1 to 6.n	6.1 to 6.n
Section	**Listings**	
ICH Listings	1 to x	

13.8.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 9: 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
Pharmacodynamic and / or Biomarker	PD_Fn	PD_Tn	PD_Ln

NOTES:

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

13.8.3. Deliverables

Deliverable	Description
SAC	Final Statistical Analysis Complete

13.8.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	Safety	ES1	Summary of Subject Disposition	Include Completed, Withdrawn and subsets of completed/withdrawn as follows:- Completed, Completed Week 20, Completed Week 20 and Follow-up Withdrawn, Withdrawn prior to Week 20, Completed Week 20 and withdrawn prior to Follow up	SAC
1.2.	Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		SAC
1.3.	Safety	*POP_T1*	Summary of Subject Accountability During 20-Week Treatment Period		SAC
1.4.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure		SAC
1.5.	Enrolled	NS1	Summary of Number of Subjects by Country and Site ID		SAC
Protocol Deviation					
1.6.	Safety	DV1	Summary of Important Protocol Deviations		SAC
Population Analysed					
1.7.	Safety	SP1	Summary of Study Populations		SAC
Demographic and Baseline Characteristics					
1.8.	Safety	DM1	Summary of Demographic Characteristics		SAC
1.9.	Enrolled	DM11	Summary of Age Ranges		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.10.	Safety	DM5	Summary of Race and Racial Combinations		SAC
Prior and Concomitant Medications/Conditions					
1.11.	Safety	CM1	Summary of Concomitant Medications		SAC
Exposure and Treatment Compliance					
1.12.	Safety	*POP_T2*	Summary of Exposure (Therapeutic Coverage) to Study Treatment		SAC
1.13.	Safety	*POP_T3*	Summary of Number of Treatments Administered		SAC

13.8.5. Safety Tables

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Adverse Events					
2.1.	Safety	AE1	Summary of All On-Treatment Adverse Events by System Organ Class and Preferred Term		SAC
2.2.	Safety	AE1	Summary of All Post-Treatment Adverse Events by System Organ Class and Preferred Term		SAC
2.3.	Safety	AE3	Summary of Common (>=3% Incidence) On-Treatment Adverse Events by Overall Frequency		SAC
2.4.	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
2.5.	Safety	AE5A	Summary of All On-Treatment Adverse Events by Maximum Intensity by System Organ Class and Preferred Term		SAC
2.6.	Safety	AE1	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term		SAC
2.7.	Safety	AE5A	Summary of All Drug-Related Adverse Events by Maximum Intensity by System Organ Class and Preferred Term		SAC
2.8.	Safety	AE1	Summary of Non-Serious Drug-Related Adverse Events by System Organ Class and Preferred Term		SAC
2.9.	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
2.10.	Safety	AE3	Summary of All Adverse Events Leading to Permanent Discontinuation from Study Treatment by Overall Frequency		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Adverse Events					
2.11.	Safety	AE3	Summary of All Adverse Events Leading to Withdrawal from the Study by Overall Frequency		SAC
2.12.	Safety	AE1	Summary of Adverse Events Reported on the Day of Dosing by System Organ Class and Preferred Term		SAC
2.13.	Safety	AE7	Listing of Subject Numbers for Individual On-Treatment Adverse Events		SAC
2.14.	Safety	AE7	Listing of Subject Numbers for Individual Post-Treatment Adverse Events		SAC
2.15.	Safety	AE2	Listing of Relationship of Adverse Event, System Organ Classes, Preferred Terms and Verbatim Text		SAC
Adverse Event Overview					
2.16.	Safety	*SAFE_T1*	Adverse Event Overview		SAC
Serious Adverse Events					
2.17.	Safety	AE3	Summary of Fatal Serious Adverse Events by Overall Frequency		SAC
2.18.	Safety	AE3	Summary of Drug-Related Fatal Serious Adverse Events by Overall Frequency		SAC
2.19.	Safety	AE3	Summary of Non-Fatal Serious Adverse Events by Overall Frequency		SAC
2.20.	Safety	AE3	Summary of All Serious Adverse Events by Overall Frequency		SAC
2.21.	Safety	AE1	Summary of All On-Treatment Serious Adverse Events by System Organ Class and Preferred Term		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
2.22.	Safety	AE1	Summary of All Post-Treatment Serious Adverse Events by System Organ Class and Preferred Term		SAC
2.23.	Safety	AE1	Summary of All Pre-Treatment Serious Adverse Events by System Organ Class and Preferred Term		SAC
2.24.	Safety	AE16	Summary of All Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC
2.25.	Safety	AE1	Summary of All Drug-Related Serious Adverse Events by System Organ Class and Preferred Term		SAC
Adverse Events of Special Interest					
2.26.	Safety	AE1	Summary of On-Treatment Adverse Events Reported by the Investigator as Systemic Reactions Meeting the Criteria for Anaphylaxis		SAC
2.27.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Reported by the Investigator as Systemic Reactions Meeting the Criteria for Anaphylaxis		SAC
2.28.	Safety	AE1	Summary of On-Treatment Adverse Events Reported by the Investigator as Systemic Reactions - Allergic (Type I Hypersensitivity) and Other Systemic		SAC
2.29.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events by the Investigator as Systemic Reactions - Allergic (Type I Hypersensitivity) and Other Systemic		SAC
2.30.	Safety	AE1	Summary of On-Treatment Adverse Events Reported by the Investigator as Systemic Reactions - Allergic (Type I Hypersensitivity)		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
2.31.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Reported by the Investigator as Systemic Reactions - Allergic (Type I Hypersensitivity)		SAC
2.32.	Safety	AE1	Summary of On-Treatment Adverse Events Reported by the Investigator as Systemic Reactions – Other Systemic		SAC
2.33.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Reported by the Investigator as Systemic Reactions - Other Systemic		SAC
2.34.	Safety	AE1	Summary of On-Treatment Adverse Events Reported by the Investigator as Local Injection Site Reactions		SAC
2.35.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Reported by the Investigator as Local Injection Site Reactions		SAC
2.36.	Safety	AE1	Summary of On-Treatment Adverse Events Categorised as Serious Cardiac, Vascular and Thromboembolic Events		SAC
2.37.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Categorised as Serious Cardiac, Vascular and Thromboembolic Events		SAC
2.38.	Safety	AE1	Summary of On-Treatment Adverse Events Categorised as Serious Ischemic Events		SAC
2.39.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Categorised as Serious Ischemic Events		SAC
2.40.	Safety	AE1	Summary of On-Treatment Adverse Events Categorised as Malignancies		SAC
2.41.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Categorised as Malignancies		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
2.42.	Safety	AE1	Summary of On-Treatment Adverse Events Categorised as Potential Opportunistic Infections		SAC
2.43.	Safety	*SAFE_T2*	Summary Profile of On-Treatment Adverse Events Categorised as Potential Opportunistic Infections		SAC
Laboratory – Haematology					
2.44.	Safety	LB1	Summary of Haematology Changes from Baseline by Visit	Include baseline values	SAC
2.45.	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
2.46.	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					
2.47.	Safety	LB1	Summary of Clinical Chemistry Changes from Baseline by Visit	Include baseline values	SAC
2.48.	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
2.49.	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					
2.50.	Safety	UR1	Summary of Worst Case Urinalysis Results Post-Baseline Relative to Baseline		SAC
Laboratory: Hepatobiliary (Liver)					
2.51.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting		SAC
2.52.	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities		SAC
ECG					
2.53.	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
2.54.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit	Include baseline values	SAC
2.55.	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
2.56.	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					
2.57.	Safety	VS1	Summary of Vital Signs by Visit		SAC
2.58.	Safety	VS1	Summary of Change from Baseline in Vital Signs by Visit	Include baseline values	SAC
Immunogenicity					
2.59.	Safety	*SAFE_T3*	Summary of Binding Antibody by Visit	Include highest post baseline result.	SAC
2.60.	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
2.61.	Safety	*SAFE_T4*	Summary of Neutralising Antibody by Visit	Include highest post baseline result.	SAC

13.8.6. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Laboratory					
2.1.	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

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.2.	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

13.8.7. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
HES Flare					
3.1.	Safety	*EFF_T1*	Overview of HES Flares		SAC
3.2.	Safety	*EFF_T2*	Summary of Frequency of All HES Flares		SAC
3.3.	Safety	*EFF_T3*	Summary of Rate of HES Flares by Study (Study 200622 and Study 205203) (Treatment Policy Estimand)		SAC
3.4.	Safety	*EFF_T4*	Summary of Mean Prednisone Equivalent Daily OCS Dose Over Time		SAC
3.5.	Safety	*EFF_T5*	Summary of Change from Week 0-4 in Mean Prednisone Equivalent Daily OCS Dose Over Time		SAC
3.6.	Safety	*EFF_T5*	Summary of Change from Week 0-4 in Mean Prednisone Equivalent Daily OCS Dose Over Time – Subjects with Mean Week 0-4 OCS Dose >0mg		SAC
3.7.	Safety	*EFF_T6*	Proportion of Subjects Who Achieve a Mean Daily OCS Dose =<7.5mg Over Time		SAC
3.8.	Safety	*EFF_T7*	Proportion of Subjects Who Achieve a Mean Daily OCS Dose Reduction of >=50% Over Time – Subjects with Mean Week 0-4 OCS Dose >0mg		SAC

13.8.8. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
HES Flare					
3.1.	Safety	*EFF_F1*	Cumulative Number of HES Flares		SAC

13.8.9. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.1.	Safety	PK01	Summary of Plasma Mepolizumab Concentration-Time Data (by previous treatment group from study 200622 and by immunogenicity status)		SAC

13.8.10. Pharmacodynamic Tables

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Blood Eosinophils					
6.1.	PD	*PD_T1*	Summary of On-Treatment Blood Eosinophil Count	Include absolute blood eosinophils at Screening, Baseline and Week 4 through Week 20. Number of decimal places as follows: geometric mean (2), SD logs (3), median (2), min (2), max (2).	SAC
6.2.	PD	*PD_T2*	Summary of On-Treatment Ratio to Baseline Blood Eosinophils	Include Week 4 through Week 20.	SAC

13.8.11. 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	No reference line. Include screening and baseline unadjusted geometric mean values.	SAC
6.2.	PD	*EFF_F4*	On-Treatment Ratio to Baseline Blood Eosinophils	Reference line at 1.	SAC

13.8.12. 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.	Safety	ES2	Listing of Reasons for Study Withdrawal		SAC
3.	Safety	SD2	Listing of Reasons for Study Treatment Discontinuation		SAC
Protocol Deviations					
4.	Safety	DV2	Listing of Important Protocol Deviations		SAC
5.	Safety	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
Populations Analysed					
6.	Safety	SP3	Listing of Subjects Excluded from Any Population	Include Safety, PD	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Demographic and Baseline Characteristics					
7.	Safety	DM2	Listing of Demographic Characteristics		SAC
8.	Safety	DM9	Listing of Race		SAC
Prior and Concomitant Medications					
9.	Safety	CP_CM3	Listing of Concomitant Medications	Flag baseline HES therapy on listing.	SAC
Exposure and Treatment Compliance					
10.	Safety	EX3	Listing of Exposure Data	Exposure to Mepolizumab only	SAC
Efficacy					
11.	Safety	*EFF_L1*	Listing of Investigator Reported HES Flare		SAC
Adverse Events					
12.	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]					
13.	Safety	AE8	Listing of Fatal Serious Adverse Events	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC
14.	Safety	AE8	Listing of Non-Fatal Serious Adverse Events	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC
15.	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

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
16.	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
17.	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
18.	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
19.	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
20.	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

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
21.	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
22.	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
23.	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
24.	Safety	AE8	Listing of Adverse Events Categorised as Malignancies	Add phase: Pre-treatment, on-treatment, post-treatment. Include treatment in by-line.	SAC
25.	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)					
26.	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
All Laboratory					
27.	Safety	LB5	Listing of Haematology Data for Subjects with Any Value of Potential Clinical Importance		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
28.	Safety	LB5	Listing of Clinical Chemistry Data for Subjects with Any Value of Potential Clinical Importance		SAC
29.	Safety	LB14	Listing of Laboratory Data with Character Results		SAC
30.	Safety	UR2A	Listing of Urinalysis Data for Subjects with Any Value of Potential Clinical Importance		SAC
ECG					
31.	Safety	EG3	Listing of All ECG Values for Subjects Meeting Protocol Defined QTc Stopping Criteria		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Immunogenicity					
32.	Safety	*SAFE_L1*	Listing of Immunogenicity Data for Subjects with at Least One Positive Screening Binding Assay Result		SAC
Pharmacokinetic					
33.	Safety		Listing of Plasma Concentration		SAC
Pharmacodynamic					
34.	Safety	*PD_L1*	Listing of Blood Eosinophils (unit)		SAC

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

13.9. Appendix 9: Example Mock Shells for Data Displays

Data Display Specification will be made available on Request.