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

Title	:	Reporting and Analysis Plan for study 200363: An open-label study to characterize the pharmacokinetics and pharmacodynamics of mepolizumab administered subcutaneously in children from 6 to 11 years of age with severe eosinophilic asthma
Compound Number	:	Mepolizumab (SB-240563)
Effective Date	:	09-DEC-2016

Description :

- The purpose of this RAP is to describe the planned PK, PD and safety analyses and output to be included in the Clinical Study Report (CSR) for study 200363.
- This RAP will be provided to the study team members to convey the content of the Part A and Part B Statistical Analysis Complete (SAC) deliverables.

Author's Name and Functional Area:

PPD Principal Statistician, Clinical Statistics	09-DEC-2016
PPD Director, Clinical Pharmacology Modeling & Simulation (CPMS)	09-DEC-2016

Final Approval:

Approved via email by

PPD	Director, Clinical Statistics	09-DEC-2016

Agreed by Core RAP team (via e-mail):

PPD		Project Physician Lead, Respiratory Therapeutic Unit
		Medical Monitor, Respiratory Therapeutic Unit
		Clinical Investigation Leader, Respiratory Therapeutic Unit
		Director, Safety Evaluation & Risk Management
		Senior Director, Clinical Pharmacology Modeling & Simulation
		Manager, Clinical Programming

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	• The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the CSR for study 200363

Protocol	• This RAP is based on protocol amendment 4 for study 200363 (GSK Document Number: 2014N216964_04) dated 05/MAY/2016 and the latest version of the electronic Case Report Form (eCRF) [eCRF Version 4.0].
	• The study protocol consists of two study parts with each study part to be reported sequentially:
	  • Pharmacokinetic/Pharmacodynamic Phase (Part A)
	  • Long-Term Safety / Long-Term Pharmacodynamic Phase (Part B)

Primary Objectives	Part A: • To characterize the pharmacokinetics of mepolizumab administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma • To characterize the pharmacodynamics of mepolizumab administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma Part B: • To assess the long-term (52 weeks) safety and tolerability of mepolizumab when administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma
Primary Endpoints	Part A: • Population-PK model derived estimates of clearance, area under the plasma-concentration time curve (AUC(0-inf)), maximum plasma concentration (Cmax), and terminal phase elimination half-life (t1/2) of mepolizumab • Change from baseline in blood eosinophil count at week 12 Part B: • Incidence of Adverse Events • Frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies • Incidence of clinically significant changes in vital sign measurements • Incidence of clinically significant changes in clinical laboratory parameters
Secondary Objectives	Part A: • To compare the bodyweight-adjusted clearance between adults and subjects aged 6 to 11 years old with severe eosinophilic asthma when mepolizumab is administered subcutaneously • To characterize asthma control following subcutaneous administration of mepolizumab to subjects aged 6 to 11 years old with severe eosinophilic asthma • To assess the safety and tolerability of mepolizumab when administered subcutaneously to subjects aged 6 to 11 years old with

Overview	Key Elements of the RAP
	severe eosinophilic asthma Part B: • To characterize the long-term (52 weeks) durability of pharmacodynamics of mepolizumab administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma
Secondary Endpoints	Part A: • Bodyweight-adjusted clearance estimates obtained by population PK methods. • Change from Baseline in ACQ-7 measured at week 12 • Change from Baseline in ACQ-7 measured at week 4,8,16 and 20 • Change from Baseline in C-ACT measured at week 12 • Change from Baseline in C-ACT measured at week 4,8, 16 and 20 • Incidence of Adverse Events (AEs) • Incidence of clinically significant changes in clinical laboratory parameters • Frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies • Incidence of clinically significant changes in vital sign measurements Part B: • Change from Baseline in absolute blood eosinophil count at weeks 32, 44, 56, 68, 72 and 80.
Study Design	Part A: • This is a multi-centre, open-label study that will assess the pharmacokinetics and pharmacodynamics of three 4-weekly doses of mepolizumab, either 40 or 100mg SC depending on subject bodyweight, administered subcutaneously to subjects with severe eosinophilic asthma aged 6-11 years. • Approximately 40 male or female subjects with severe eosinophilic asthma, aged 6 to 11 years inclusive at screening (Visit 1), will be screened to achieve approximately 28 eligible subjects entering the treatment phase to allow availability of 20 evaluable subjects; with a minimum of six subjects enrolled in the < 40 kg bodyweight group. An evaluable subject is defined to be a subject who has received all three doses of mepolizumab and has had all PK and PD assessments completed through to Visit 6 (week 12). Part B: • This is a long-term safety / pharmacodynamic phase in which extended treatment for a further 52 weeks will be offered on an optional basis to those subjects eligible for continued treatment. Subjects will receive either 40 or 100mg depending on subject bodyweight, administered SC every 4 weeks to subjects with severe eosinophilic asthma aged 6-11 years. At the end of the 52 weeks extended treatment in Part B, subjects will have an Exit Visit 4 weeks after last dose and a Follow-Up visit 12 weeks after last dose. • All subjects who completed Part A and meet the eligibility criteria for Part B will be allowed to participate in Part B.

Overview	Key Elements of the RAP
Planned Analyses	Part A: • A complete analysis of part A for an interim report in accordance with all Part A study objectives and endpoints will be performed after all subjects have completed Part A of the study. All outputs will be considered the final analyses for Part A. Part B: • A complete analysis of part B for a final report in accordance with all Part B study objectives and endpoints will be performed after all subjects have completed Part B of the study.
Analysis Populations	Part A: • All Subjects Enrolled (ASE): All subjects for whom a record exists on the study database. • Safety Population: All subjects receiving at least one dose of mepolizumab beginning at Visit 2. • Pharmacokinetic (PK) Population: All subjects receiving at least one dose of mepolizumab beginning at Visit 2 and having at least one blood sample taken at Visit 3 or thereafter with measurable mepolizumab plasma concentration. • Pharmacodynamic (Blood Eosinophils) (PDe) Population: All subjects receiving at least one dose of mepolizumab beginning at Visit 2 and having at least one Part A blood sample taken for blood eosinophil count. • Pharmacodynamic (Outcome Assessments) (PDo) Population: All subjects receiving at least one dose of mepolizumab beginning at Visit 2 and having at least one Part A assessment of pharmacodynamic outcomes (ACQ-7, C-ACT, asthma exacerbation, FEV_1, IgE or IL-5). • Pharmacokinetic / Pharmacodynamic (PKPD) : All subjects receiving at least one dose of mepolizumab beginning at Visit 2 and having at least one blood sample taken at Visit 3 or thereafter with measurable mepolizumab plasma concentration and who also have a baseline PDe measurement and at least one post-treatment PDe measurement. Part B: • Safety Population: All subjects receiving at least one dose of study medication beginning at Visit 9. • Pharmacodynamic (Blood Eosinophils) (PDe) Population: All subjects receiving at least one dose of mepolizumab beginning at Visit 9 and having at least one Part B one blood sample taken for blood eosinophil count. • Pharmacodynamic (Outcome Assessments) (PDo) Population: All subjects receiving at least one dose of mepolizumab beginning at Visit 9 and having at least one Part B assessment of pharmacodynamic outcomes (ACQ-7, C-ACT, asthma exacerbation, or FEV1).

Overview	Key Elements of the RAP
Hypothesis	• Formal hypothesis testing will not be performed for this study. An estimation approach will be adopted to evaluate the objectives.
Primary Analyses	Part A: • PK samples will be analysed by population-PK methods based on the PK population. A number of pharmacokinetic parameters will be fixed from adult values in the model in support of the sparse sampling implemented in the study and the relatively small sample size. In particular meaningful estimation of absorption and distribution parameters is unlikely based on the sampling scheme. The population-PK parameter estimates (AUC(0-inf), clearance, Cmax and t1/2) with 95% confidence intervals from the final model will be tabulated. • In addition, the individual PK parameter estimates (also called post-hoc individual PK parameter estimates) (AUC(0-inf), clearance, Cmax and t1/2) will be summarised including 95% CIs. • The absolute blood eosinophil count and ratio of blood eosinophil count to baseline will be summarised using summary statistics including 95% CIs, for all post-dosing study visits. Part B: • Safety data including adverse events, vital signs, clinical laboratory, electrocardiogram (ECG), and immunogenicity data will be summarised.
Secondary Analyses	Part A: • Bodyweight-adjusted clearance in this study from subjects aged 6 to 11 years old will be compared with historical values from adults with severe eosinophilic asthma when mepolizumab is administered subcutaneously. For this purpose, the bodyweight-adjusted clearance obtained from the population PK model of data from this study will be presented in a separate table with 90% CI. This point estimate and 90% CI will be compared with the historic value in adults of 0.22 L/day (corresponding to an apparent clearance of 0.29 L/day assuming an absolute bioavailability of 75%), around which a proposed 80-125% interval was applied (i.e., 0.18-0.28 L/day). • Change from baseline in the overall ACQ-7 and C-ACT score will be summarised including 95% CIs. In addition the proportion of subjects meeting the minimally clinically significant change (reduction from baseline of ≥0.5 in the overall ACQ-7 score) will be presented. Part B: • The absolute blood eosinophil count and ratio of blood eosinophil count to baseline will be summarised using summary statistics including 95% CIs, for all post-dosing study visits.
Safety	• Safety data including adverse events, vital signs, clinical laboratory, electrocardiogram (ECG), and immunogenicity data will be summarised.

2. SUMMARY OF KEY PROTOCOL INFORMATION

The study protocol consists of two study parts which are to be reported sequentially:

- Pharmacokinetic/Pharmacodynamic Phase (Part A)
- Long-Term Safety / Long-Term Pharmacodynamic Phase (Part B)

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Any changes from the originally planned statistical analysis specified in the protocol amendment 4 (dated 05/MAY/2016) are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• Part B endpoint listed as 'Change from Week 20 (Visit 9) in absolute blood eosinophil count at weeks 32, 44, 56, 68, 72 and 80'	• Part B endpoint listed as 'Change from Baseline in absolute blood eosinophil count at weeks 32, 44, 56, 68, 72 and 80'	• Patients will not have returned to their pre-mepolizumab treatment baseline at the start of part B [Week 20 (Visit 9)] and therefore individual patient comparisons back to Baseline (Week 0) are more of interest
• Part B endpoint listed as 'Change from Week 20 (Visit 9) in ACQ-7 and C-ACT at weeks 32, 44, 56, 68, 72 and 80.'	• Part B endpoint listed as 'Change from Baseline in ACQ-7 and C-ACT at weeks 32, 44, 56, 68, 72 and 80.'	• Patients will not have returned to their pre-mepolizumab treatment baseline at the start of part B [Week 20 (Visit 9)] and therefore individual patient comparisons back to Baseline (Week 0) are more of interest

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

2.2.1. Pharmacokinetic/Pharmacodynamic Phase (Part A)

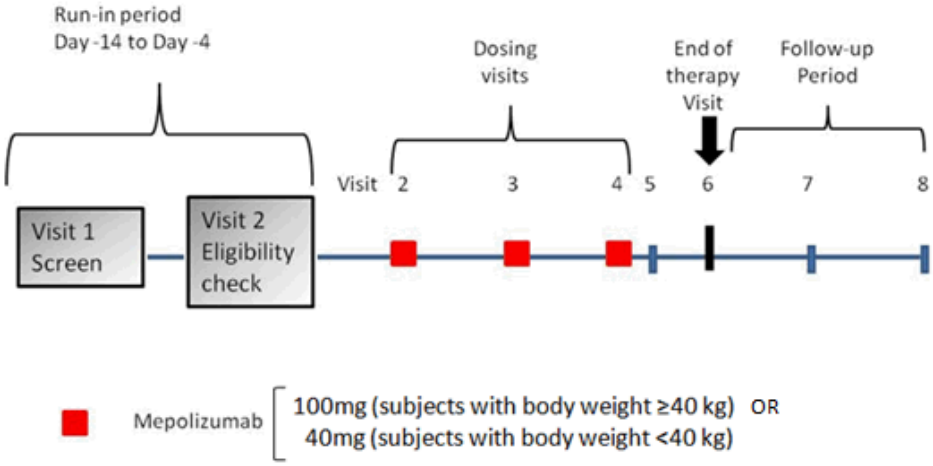
Objectives	Endpoints
Primary	
• To characterize the pharmacokinetics of mepolizumab administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma	Population-PK model derived estimates of clearance, area under the plasma-concentration time curve (AUC(0-inf), maximum plasma concentration (Cmax), and terminal phase elimination half-life (t1/2) of mepolizumab
• To characterize the pharmacodynamics of mepolizumab administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma	• Change from baseline in blood eosinophil count at week 12

Objectives	Endpoints
Secondary	
• To compare the bodyweight-adjusted clearance between adults and subjects aged 6 to 11 years old with severe eosinophilic asthma when mepolizumab is administered subcutaneously	• Bodyweight-adjusted clearance estimates obtained by population PK methods.
• To characterize asthma control following subcutaneous administration of mepolizumab to subjects aged 6 to 11 years old with severe eosinophilic asthma	• Change from Baseline in ACQ-7 measured at week 12 • Change from Baseline in ACQ-7 measured at weeks 4,8, 16 and 20 • Change from Baseline in C-ACT measured at week 12
• To assess the safety and tolerability of mepolizumab when administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma	• Change from Baseline in C-ACT measured at week 4, 8, 16 and 20 • Incidence of Adverse Events • Incidence of clinically significant changes in clinical laboratory parameters • Frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies • Incidence of clinically significant changes in vital sign measurements
Exploratory	
• To assess the number of asthma exacerbations that occur during the study following subcutaneous administration of mepolizumab to subjects aged 6 to 11 years old with severe eosinophilic asthma	• Number of asthma exacerbations that occur while on treatment (week 0-week 12). • Number of asthma exacerbations that occur on- treatment and post-treatment (week 0 – week 20)
• To assess Forced expiratory volume in 1 second (FEV1) following subcutaneous administration of mepolizumab to subjects aged 6 to 11 years old with severe eosinophilic asthma	• Change from Baseline in FEV1 measured at week 12

2.2.2. Long-Term Safety/Long-Term Pharmacodynamic Phase (Part B)

Objectives	Endpoints
Primary	
To assess the long-term (52 weeks) safety and tolerability of mepolizumab when administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma	• Incidence of Adverse Events • Frequency of positive anti-mepolizumab binding antibodies and neutralizing antibodies • Incidence of clinically significant changes in vital sign measurements • Incidence of clinically significant changes in clinical laboratory parameters
Secondary	
• To characterize the long-term (52 weeks) durability of pharmacodynamics of mepolizumab administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma	• Change from Baseline in absolute blood eosinophil count at weeks 32, 44, 56, 68, 72 and 80.
Exploratory	
• To assess the number of asthma exacerbations that occur during the long-term (52 weeks) part of the study following subcutaneous administration of mepolizumab to subjects aged 6 to 11 years old with severe eosinophilic asthma	• Incidence of asthma exacerbations
• To characterize the long-term (52 weeks) asthma control following subcutaneous administration of mepolizumab to subjects aged 6 to 11 years old with severe eosinophilic asthma	• Change from Baseline in ACQ-7 and C-ACT at weeks 32, 44, 56, 68, 72 and 80.

2.3. Study Design

Overview of Study Design and Key Features	
Part A:  	
Design Features	Part A: • This is a multi-centre, open-label study that will assess the pharmacokinetics and pharmacodynamics of three 4-weekly doses of mepolizumab, either 40 or 100mg SC depending on subject bodyweight, administered subcutaneously to subjects with severe eosinophilic asthma aged 6-11 years. • Approximately 40 male or female subjects with severe eosinophilic asthma, aged 6 to 11 years inclusive at screening (Visit 1), will be screened to achieve approximately 28 eligible subjects entering the treatment phase to allow availability of 20 evaluable subjects; with a minimum of six subjects enrolled in the < 40 kg bodyweight group. An evaluable subject is defined to be a subject who has received all three doses of mepolizumab and has had all PK and PD assessments completed through to Visit 6 (week 12). Part B: • This is a long-term safety / pharmacodynamic phase in which extended treatment for a further 52 weeks will be offered on an optional basis to those subjects eligible for continued treatment. Subjects will receive either 40 or 100mg depending on subject bodyweight, administered SC every 4 weeks to subjects with severe eosinophilic asthma aged 6-11 years. At the end of the 52 weeks extended treatment in Part B, subjects will have an Exit Visit 4 weeks after last dose and a Follow-Up visit 12 weeks after last dose. • All subjects who completed Part A and meet the eligibility criteria for Part B will be allowed to participate in Part B. • Countries participating in this study include: Japan, Poland, United States and United Kingdom.
Dosing	Part A: • Mepolizumab will be administered as either 40mg (subjects <40kg at

Overview of Study Design and Key Features	
	Visit 2) or 100 mg SC (subjects ≥40kg at Visit 2) at week 0 (Visit 2), week 4 (Visit 3) and week 8 (Visit 4) which will provide therapeutic coverage through to week 12 (Visit 6). The mepolizumab dose received throughout Part A will remain unchanged irrespective of bodyweight changes. Part B: • Within Part B the subject's dose will be adjusted to 100mg SC from the time the subject's bodyweight reaches 40 kg. Subjects will receive either mepolizumab 40 or 100 mg SC, (depending on subject bodyweight measured at Visit 9; 40 mg for subjects <40 kg and 100 mg for subjects ≥ 40 kg). Subjects with bodyweight <40 kg at Visit 9 should be weighed at each subsequent visit and have their dose adjusted to 100mg once their bodyweight reaches 40 kg. Subjects weighing ≥40kg at Visit 9 will receive the 100mg dose at all subsequent treatment visits and will not be weighed again.
Planned Analyses	Part A: • A complete analysis of part A for an interim report in accordance with all Part A study objectives and endpoints will be performed after all subjects have completed Part A of the study. All outputs will be considered the final analyses for Part A. Part B: • A complete analysis of part B for a final report in accordance with all Part B study objectives and endpoints will be performed after all subjects have completed Part B of the study.

2.4. Statistical Hypotheses

Formal hypothesis testing will not be performed for this study. An estimation approach will be adopted to evaluate the objectives.

3. PLANNED ANALYSES

3.1. Part A Analysis

A complete analysis of part A for an interim report in accordance with all Part A study objectives and endpoints will be performed after all subjects have completed Part A of the study and after the completion of the following sequential steps detailed below.

All outputs will be considered the final analyses for Part A

1. All subjects have completed Part A (upon completion of all study procedures or premature discontinuation of the study) as defined in the protocol for study 200363.
2. All required database cleaning activities have been completed and database release and database freeze has been declared by Data Management.

3.2. Part B Analysis

A complete analysis of part B for a final report in accordance with all Part B study objectives and endpoints after all subjects have completed Part B of the study. The database will be locked after all subjects have completed all Part B assessments and the required database cleaning activities have been completed. Once this has been achieved the database will be frozen. Statistical outputs generated following the interim report (Part A) will not be reproduced.

4. ANALYSIS POPULATIONS

Table 2 Analysis Populations

Population	Definition / Criteria	Analyses Evaluated
Part A		
All Subjects Enrolled (ASE)	• All subjects for whom a record exists on the study database.	• Pre-screen failures • Screen failures • Run-in failures
Safety	• All subjects receiving at least one dose of mepolizumab beginning at Visit 2.	• Study Population • Safety • Immunogenicity
Pharmacokinetic (PK)	• All subjects receiving at least one dose of mepolizumab beginning at Visit 2 and having at least one blood sample taken at Visit 3 or thereafter with measurable mepolizumab plasma concentration.	• Pharmacokinetic
Pharmacodynamic (Blood Eosinophils) (PDe)	• All subjects receiving at least one dose of mepolizumab beginning at Visit 2 and having at least one Part A blood sample evaluable for blood eosinophil count.	• Blood eosinophil count
Pharmacodynamic (Outcome Assessments) (PDo)	• All subjects receiving at least one dose of mepolizumab beginning at Visit 2 and having at least one Part A assessment of pharmacodynamic outcomes (ACQ-7, C-ACT, asthma exacerbation, FEV_1, IgE or IL-5).	• ACQ-7 • C-ACT • Asthma exacerbations • FEV_1 • Immunoglobulin E (IgE) • IL-5
Pharmacokinetic / Pharmacodynamic (PKPD)	• All subjects receiving at least one dose of mepolizumab beginning at Visit 2 and having at least one blood sample taken at Visit 3 or thereafter with measurable mepolizumab plasma concentration and who also have	• PKPD

Population	Definition / Criteria	Analyses Evaluated
	a baseline PDe measurement and at least one post-treatment PDe measurement.	
Part B		
Safety	• All subjects receiving at least one dose of study medication beginning at Visit 9.	• Study Population • Safety • Immunogenicity
Pharmacodynamic (Blood Eosinophils) (PDe)	• All subjects receiving at least one dose of mepolizumab beginning at Visit 9 and having at least one Part B blood sample taken for blood eosinophil count.	• Blood eosinophil count
Pharmacodynamic (Outcome Assessments) (PDo)	• All subjects receiving at least one dose of mepolizumab beginning at Visit 9 and having at least one Part B assessment of pharmacodynamic outcomes (ACQ-7, C-ACT, asthma exacerbation, or FEV1).	• ACQ-7 • C-ACT • Asthma exacerbations • FEV1

NOTES :

- Please refer to Appendix 10: List of Data Displays which details the population to be used for each of the displays being generated.

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 by the study team prior to DBR to ensure all important deviations are captured and categorised in the protocol deviations dataset.
  - This dataset will be the basis for the summaries and listings of protocol deviations.
- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be listed and summarised.
- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on the data as recorded on the inclusion/exclusion page of the eCRF.
- The study endpoints will be reported using the populations detailed in Section 4 of this document regardless of whether the subjects deviate from the protocol. If there are subjects with protocol deviations that may potentially impact either the PK or the PD endpoints, exploratory sensitivity analyses may be considered (See Section 7).

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 3 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 3 Overview of Appendices

Section	Component
10.1	Appendix 1: Protocol Deviation Management
10.2	Appendix 2: Time & Events
10.3	Appendix 3: Assessment Windows & Visit Slotting
10.4	Appendix 4: Treatment Phases
10.5	Appendix 5: Data Display Standards & Handling Conventions
10.6	Appendix 6: Derived and Transformed Data
10.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
10.8	Appendix 8: Population Pharmacokinetic Analyses
Other RAP Appendices	
10.9	Appendix 9: Abbreviations & Trade Marks
10.10	Appendix 10: List of Data Displays
10.11	Appendix 11: Example Mock Shells for Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

Table 4 and Table 5 and provide an overview of the planned study population displays, with full details of data displays being presented in Appendix 10: List of Data Displays.

The study population listings and summaries will be based on the Safety population unless otherwise specified in Appendix 10: List of Data Displays.

Table 4 Overview of Study Population Summaries (Part A)

Endpoint / Parameter	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Analysis populations	Y[1]		
Reasons for screen or run-in failures	Y		Y
Failed inclusion/exclusion criteria for screen or run-in failures	Y		
Failed inclusion/exclusion criteria for Safety Population	Y		Y
Subjects by country and site	Y		
Reason for premature study withdrawal	Y		Y
Demographic and Baseline Characteristics			
Demographic characteristics	Y		Y
Age Ranges	Y		
Race and racial combinations	Y		Y[3]
Race and racial combinations details	Y		
Medical Conditions			
Past medical conditions	Y		
Current medical conditions	Y		
Cardiovascular assessments (family history)	Y		
Baseline Disease Characteristics			
Asthma exacerbation history[2]	Y		
Asthma history and baseline disease characteristics	Y		
Lung function results (screening and baseline)	Y		
Prior and concomitant medications			
Asthma concomitant medications (taken before/during run-in, during treatment, post-treatment) by Respiratory Medication Class [4]	Y		
Non-asthma concomitant medications taken during treatment	Y		
Relationship between ATC level 1, Ingredient and verbatim text			Y
Protocol deviations			
Important protocol deviations	Y		Y

NOTES :

- Y = Yes display generated.
- [1] To include summary of subjects moving into study Part B
- [2] Asthma exacerbation recorded in 12 months prior to Screening
- [3] Listing of race
- [4] Multi-ingredient medications will be presented according to their combination Anatomical Therapeutic Chemical (ATC) classification rather than the classification of the ingredients.

Table 5 Overview of Study Population Summaries (Part B)

Endpoint / Parameter	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Analysis Populations	Y		
Reason for premature study withdrawal	Y		Y
Prior and concomitant medications			
Asthma concomitant medications (during treatment, post-treatment) by Respiratory Medication Class [1]	Y		
Non-Asthma concomitant medications taken during treatment	Y		
Relationship between ATC level 1, Ingredient and verbatim text			Y
Protocol deviations			
Important Protocol Deviations	Y		Y

NOTES :

- Y = Yes display generated.
- [1] Multi-ingredient medications will be presented according to their combination Anatomical Therapeutic Chemical (ATC) classification rather than the classification of the ingredients.

7. PRIMARY ANALYSES

This section contains the details of the planned primary Pharmacokinetic (PK) and Pharmacodynamic (PD) analyses using the study populations defined in Section 4. If there are protocol deviations that are thought to potentially impact the primary PK and/or PD endpoints, an exploratory sensitivity analysis may be considered. Any sensitivity analyses performed will be documented in the clinical study report.

All safety analyses are detailed within Section 8.2.

Full details of data displays are presented in Appendix 10: List of Data Displays.

Table 6 Overview of Planned Primary Analysis (Part A)

Endpoint / Parameter/ Display Type]	Untransformed							Log-transformed						
	Pop-PK model			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
PK														
PK Plasma Concentrations (Observed and Predicted)				Y	Y[1]	Y[2]	Y							
Individual PK Parameter Estimates (also called post-hoc individual PK parameter estimates)				Y			Y				Y			
Population PK parameter estimates	Y													
Goodness of fit test/plots	Y	Y												
Endpoint / Parameter/Display Type]	**Raw Data**							**Ratio of Post Dosing Visit to Baseline**						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Blood Eosinophil Count														
Blood Eosinophil Count (Part A)				Y	Y		Y				Y	Y		

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data/predicted data.
- Individual = Represents FL related to any displays of individual subject (observed raw data/predicted data).

[1] Model Predicted Mepolizumab Individual Plasma Concentration Time Profiles with Individual Observed Plasma Concentrations and Plasma Concentration Population Prediction from Final Model by Treatment

[2] Model Predicted Mepolizumab Individual Plasma Concentration Time Profiles with Individual Observed Plasma Concentrations and Plasma Concentration Population Prediction from Final Model by Subject

7.1. Population PK Analysis (Part A)

7.1.1. Overview of Planned Population PK Analysis

This study is conducted to support the extrapolation of the safety and efficacy data observed in adults in the Phase III Mepolizumab Programme to the paediatric population. To this purpose, one of the PK objectives of the study is to characterize the pharmacokinetics of mepolizumab administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma.

A sparse PK sampling scheme has been implemented in this study and the PK samples collected will be analysed by population PK methods, using appropriate software, and based on the PK population defined, unless otherwise specified. All subjects who are in the PK population, i.e. who have at least one measurable PK concentration recorded, will

be included in this analysis. In order to model the paediatric data collected, a number of pharmacokinetic parameters in the model will be fixed using adult values because of the sparse sampling implemented in this paediatric study and the relatively small sample size selected. In particular estimation of absorption and distribution parameters is unlikely to be meaningful based on the proposed sampling scheme.

A description of the key models tested during the model development will be provided and tabulated. The population PK parameter estimates (AUC(0-inf), clearance, Cmax and t1/2) with 95% CI from the final model will be tabulated (for mepolizumab overall (Mepolizumab SC)). Goodness of fit plots for the final model will be presented.

Additionally, the individual PK parameter estimates (also called model-predicted post-hoc individual PK parameter estimates) for $AUC_{(0\text{-inf})}$, clearance, C_{max} and $t_{1/2}$ as well as the individual observed and predicted plasma PK concentrations will be listed and summarised by mepolizumab dose and mepolizumab overall using descriptive statistics. The summary of the model-predicted post-hoc individual PK parameter estimates will include summary statistics for untransformed and $\log_e$-transformed data. See details of the summary statistics in Section 10.5.3.

A summary of plasma concentration data will be produced only including summary statistics for untransformed data. Observed and model predicted concentrations will be presented graphically by treatment and subject. Furthermore, a plot of model predicted (5^{th}, 50^{th}, and 95^{th} Percentiles) mepolizumab plasma concentrations with individual observed plasma concentrations for the final PK model for model evaluation will be generated.

In support of the described analysis, a specific dataset will be generated. Further details of the population PK analysis are provided in Appendix 8: Population Pharmacokinetic Analyses.

Any subjects and/or PK concentration excluded from this analysis will be flagged in the data listings and documented in the clinical study report.

7.2. Analysis of Blood Eosinophil Count (Part A)

The blood eosinophil count (primary PD endpoint in this study) is recorded during the laboratory investigations under hematology data at the visits indicated in the Appendix 2: Time & Events. Week 12 is the primary timepoint of interest for blood eosinophil count and ratio of blood eosinophil count to baseline.

The absolute blood eosinophil count, and ratio to baseline will be summarised using geometric mean and other descriptive statistics and listed for each mepolizumab dose and overall by visit for the PDe population. Additionally the geometric mean ratio to baseline in blood eosinophil count (including 95% CI) for each mepolizumab dose and overall by visit will be presented graphically. See details of the summary statistics in Section 10.5.3.

8. SECONDARY ANALYSES

8.1. Secondary and Exploratory Analyses

Table 7 provides an overview of the planned analysis of secondary and exploratory endpoints with further details of data displays being presented in Appendix 10: List of Data Displays.

All safety analyses are detailed within Section 8.2.

Table 7 Overview of Planned Secondary and Exploratory Analyses

Endpoint / Parameter/Display Type]	Raw Data							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Secondary Endpoints														
Part A														
Body-weight-adjusted clearance				Y										
ACQ-7 score				Y							Y	Y		
C-ACT score				Y							Y	Y		
Part B														
Blood Eosinophil Count				Y	Y		Y				Y[1]	Y[1]		
Exploratory Endpoints														
Part A														
ACQ-7 responder/non-responder category											Y			
ACQ-5 score				Y							Y	Y		
ACQ-5 responder/non-responder category											Y			
FEV_1				Y							Y	Y		
Overview of Exacerbations				Y										
Exacerbations (on-treatment) (Week 0 – Week 12)				Y										
Exacerbations (on- and post-treatment) (Week 0 – Week 20)				Y			Y							
Time to first exacerbation (Week 0 – Week 20)				Y[2]								Y[2]		
Total IgE				Y							Y[1]			
Total IL-5				Y			Y				Y[1]	Y[1]		
PK Plasma Concentrations (Observed and Predicted)					Y[3]	Y[4]								
PK model goodness of fit test/plots	Y	Y												

Endpoint / Parameter/Display Type]	Raw Data							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
PKPD Plasma Concentrations (Observed and Predicted)					Y[3]	Y[4]								
PKPD model goodness of fit test/plots	Y	Y												
Part B														
ACQ-7 score				Y							Y			
ACQ-7 responder/non-responder category											Y			
ACQ-5 score				Y							Y			
ACQ-5 responder/non-responder category											Y			
C-ACT score				Y							Y			
FEV_1				Y							Y			
Overview of Exacerbations				Y										
Exacerbations (on-treatment) (Week 20 – Week 72)				Y			Y							
Time to first exacerbation (Week 20 –Week 72)				Y[2]										

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data/predicted data.
- Individual = Represents FL related to any displays of individual subject (observed raw data/predicted data).

[1] To be presented as a Ratio to Baseline

[2] Kaplan-Meier estimates

[3] Model Predicted Mepolizumab Individual Plasma Concentration Time Profiles with Individual Observed Plasma Concentrations and Plasma Concentration Population Prediction from Final Model by Treatment

[4] Model Predicted Mepolizumab Individual Plasma Concentration Time Profiles with Individual Observed Plasma Concentrations and Plasma Concentration Population Prediction from Final Model by Subject

8.1.1. Body-Weight-Adjusted Clearance

The secondary PK objective of the study is to compare the bodyweight-adjusted clearance in this study from subjects aged 6 to 11 years old with historical values for adults with severe eosinophilic asthma when mepolizumab is administered subcutaneously. To this purpose, the point estimate for the bodyweight-adjusted clearance parameter derived as part of the primary objective (Section 7) will be presented in an additional table with a 90% CI. This point estimate and 90% CI for subjects aged 6 to 11 years will be compared with the historic adult estimated body-weight adjusted clearance of 0.22 L/day (corresponding to an apparent clearance of 0.29 L/day assuming

an absolute bioavailability of 75%), around which a proposed 80-125% interval was applied i.e. 0.18-0.28 L/day. The historic adult value is based on previous estimates obtained in studies conducted in adult subjects with severe eosinophilic asthma (i.e. 0.22 L/day as analysed in study MEA115588 [GSK Document Number: 2013N178278_02] adjusted for an estimated bioavailability of 75%).

8.1.2. Asthma Control Questionnaire

The ACQ-7 score (mean of 7 items) and change from baseline in ACQ-7 score will be summarised by visit, mepolizumab dose and mepolizumab overall for the PDo population. For an overview of the ACQ-7 questionnaire and scoring algorithm please refer to Section 10.6.5.

The ACQ-5 score (mean of 5 symptom items) and change from baseline in ACQ-5 score will be summarised by visit, mepolizumab dose and mepolizumab overall for the PDo population. For an overview of the ACQ-5 questionnaire and scoring algorithm please refer to Section 10.6.5.

8.1.3. Childhood Asthma Control Test (C-ACT)

The C-ACT score (sum of 7 items) and change from baseline in C-ACT score will be summarised by visit, mepolizumab dose and mepolizumab overall for the PDo population. For an overview of the C-ACT questionnaire and scoring algorithm please refer to Section 10.6.5.

8.1.4. Analysis of Blood Eosinophil Count (Part B)

The absolute blood eosinophil count and ratio of blood eosinophil count to baseline will be summarised using descriptive statistics and listed for each mepolizumab dose and overall by visit for the PDe population as presented within Part A (See Section 7.2).

The same baseline definition (latest value recorded prior to the first dose of mepolizumab in Part A) will be used in the analyses of both Part A and Part B data, as described within Section 10.5.2.

8.1.5. Forced expiratory volume in 1 second (FEV_1)

FEV_1 recorded at post-dose visits and change from baseline will be listed and summarised by mepolizumab dose group and mepolizumab overall for each visit.

8.1.6. Asthma Exacerbations

All asthma exacerbation data will be listed. Number of asthma exacerbations that occur while on-treatment (week 0-week 12) and number of asthma exacerbations that occur on-treatment and post-treatment (week 0 – week 20) will be summarised by mepolizumab dose group and mepolizumab overall. Additionally the number of asthma exacerbations that occur during Part B (Week 20 –Week 72) will be summarised by mepolizumab dose group and mepolizumab overall. Further summaries will be presented as listed in Table 7.

8.1.7. Total Immunoglobulin-E (IgE)

Total IgE will be summarised by mepolizumab dose group and mepolizumab overall for each visit.

8.1.8. Total Interleukin-5 (IL-5)

Total IL-5 will be summarised by mepolizumab dose group and mepolizumab overall for each visit.

8.2. Safety Analyses

8.2.1. Overview of Planned Adverse Event Analyses

Safety analyses will be based on the Safety population unless otherwise specified in Appendix 10: List of Data Displays. The safety displays to be created as part of the RAP include all the required and relevant displays identified as per the RAP Core Safety Reporting Template Version 1.0.

Table 8 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 10: List of Data Displays. The same displays will be produced for both study Part A and study Part B data.

Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Table 8 Overview of Planned Adverse Event Analyses

Endpoint	Absolute			
	Summary		Individual	
	T	F	F	L
Exposure				
Number of treatments administered and time on-treatment	Y			Y
Adverse Event				
Overview of Adverse Events	Y			
AEs by SOC and Maximum Intensity	Y			Y
On-Treatment AEs by Overall Frequency	Y			
All Drug-Related AEs by SOC and Maximum Intensity	Y			
Number of subjects & occurrences of common non-serious AEs[1] by SOC and PT	Y			
Subject Numbers for Individual AEs				Y
Relationship between AE SOCs, PT & verbatim text				Y
AEs by Highest Antidrug Antibody Result At Any Time Post Baseline	Y			
Serious and Other Significant AEs				
Fatal Serious AEs	Y			Y
Non-Fatal Serious AEs	Y			Y
Reasons for Considering as a Serious Adverse Event				Y
Serious AEs by SOC	Y			
Drug-Related Serious AEs by SOC and Maximum Intensity	Y			
AEs leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by Overall Frequency	Y			Y
Number of Subjects and Occurrences of Serious, Drug-Related Serious, Fatal Serious, and Drug-Related Fatal Serious AEs	Y			
AEs of Special Interest (On-Treatment) [2]				
Systemic Reactions (Hypersensitivity and Non-Allergic)	Y			Y
Local Injection Site Reactions	Y			Y
AEs meeting Anaphylaxis Criteria	Y			Y
Serious Cardiac, Vascular and Thromboembolic (CVT) AEs	Y			Y
Serious Ischemic AEs	Y			Y
Malignancies	Y			Y
Opportunistic Infections	Y			Y
Cardiovascular Events				
All Cardiovascular Events	Y			Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated. PT = Preferred Term, SOC = System Organ Class
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

[1] Common AEs will be defined as AEs with frequency ≥3% (prior to rounding to nearest percent) in overall mepolizumab treatment group.

[2] On-treatment Summary Profiles of each type of AE of Special Interest will also be presented.

8.2.1.1. Adverse Events of Special Interest

Adverse events of special interest (AESIs) are adverse events associated with the identified and potential risks of mepolizumab. AESIs of anaphylaxis reactions, systemic reactions, and local injection site reactions are collected via targeted eCRF within the

study. Events captured on the eCRF as systemic reactions will be further categorized as allergic/hypersensitivity reactions or non-allergic reactions. Events with preferred terms such as injection related reaction or administration related reaction will be considered non-allergic reactions. All remaining events will be considered allergic/hypersensitivity reactions.

AESIs of opportunistic infections, malignancies, serious 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 subjects with each type of AESI, broken down by preferred term will be created. Information will be reported as part of the standard AE tables for AESIs of infections, serious infections, neoplasms, cardiac disorders and serious cardiac disorders.

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

A listing of any subjects with systemic events identified by the investigators as meeting the criteria for anaphylaxis as outlined by the 2006 Joint National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Second Symposium on Anaphylaxis [Sampson, 2006] will be provided.

8.2.1.2. Cardiovascular Events

Cardiovascular events will be captured on targeted CV event pages of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

8.2.2. Overview of Planned Clinical Laboratory Analyses

Safety analyses will be based on the Safety population unless otherwise specified in Appendix 10: List of Data Displays. The safety displays to be created as part of the RAP include all the required and relevant displays identified as per the RAP Core Safety Reporting Template Version 1.0.

Table 9 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 10: List of Data Displays.

Table 9 Overview of Planned Clinical Laboratory Analyses

Endpoint	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Immunogenicity								
Immunogenicity (ADA and NAb results)	Y			Y				
Treatment Emergent ADA results	Y							
Clinical Chemistry								
Change from Baseline in Clinical Chemistry by Visit					Y			
Chemistry Results (Change from Baseline Relative to Normal Range)	Y				Y			
Haematology								
Change from Baseline in Haematology by Visit					Y			
Haematology Results (Change from Baseline Relative to Normal Range)	Y				Y			
Urinalysis								
Urinalysis Data				Y				
Hepatobiliary (Liver)								
Liver Monitoring/Stopping Event Reporting				Y				
Chemistry Results for Subjects Meeting Liver Monitoring/Stopping Event Criteria				Y				
Medical Conditions for Subjects with Liver Stopping Events				Y				
Listing of Substance Use for Subjects with Liver Stopping Events				Y				
Hepatobiliary Laboratory Abnormalities	Y			Y				
Scatter Plot of Maximum vs. Baseline for ALT		Y						
Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin		Y						

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

8.2.2.1. Immunogenicity

Immunogenicity is a measure of the immune response to a therapeutic drug (e.g. a monoclonal antibody) resulting in generation of anti-drug antibodies. Clinical samples are tested in a sequence of binding anti-drug antibody (ADA) and neutralising antibody assays:

a) Screening assay. Each sample is tested for the presence of anti-drug antibodies (ADA assay) and initially declared positive or negative according to assay cut-off criteria. Negative samples are not tested further. Positive samples are then tested in the confirmation ADA assay.
b) Confirmation assay. Each positive sample from the screening assay is either confirmed positive in this assay (ADA assay), or is declared negative and are not tested further. Positive ADA samples are then tested in the titer assay and neutralization (NAb) assay.
c) Titration assay. Each positive sample from the ADA confirmation assay is serially diluted to provide a titre, corresponding to the highest dilution factor that still yields a positive test result.
d) Neutralising assay. Each positive sample from the ADA confirmation assay is tested with the neutralising antibody assay and found as either positive or negative in this assay (NAb assay).

The mepolizumab ADA (screening/confirmation/titration) assay version 2011N122789 is performed at a Alliance Pharma (method 120711M01.V02). The mepolizumab Nab assay version 2011n129752 is being performed within GSK.

- A table will be produced summarising the number and percentage of negative and confirmed positive subjects ADA samples by treatment group and visit in the Safety population. The table will also summarise the highest assay result obtained post-baseline for each subject.
- A similar table will also be produced summarising results for the neutralising antibody assay in the Safety Population, by treatment group and visit.
- An additional summary of treatment emergent positive confirmatory binding antibody assay and results in the subset of subjects who did not have a positive confirmatory binding antibody assay result prior to the first dose of study treatment will also be presented.
- All immunogenicity results (i.e. ADA screening and confirmatory assay results, titre values, neutralising antibody results and observed mepolizumab concentration) will be listed.

8.2.3. Overview of Planned Other Safety Analyses

The safety analyses will be based on the Safety population unless otherwise specified in Appendix 10: List of Data Displays. The safety displays to be created as part of the RAP include all the required and relevant displays identified as per the RAP Core Safety Reporting Template Version 1.0.

Table 10 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 10: List of Data Displays.

Table 10 Overview of Planned Other Safety Analyses

Endpoint	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
ECG								
ECG Findings	Y			Y				
Change from Baseline in ECG Values by Visit					Y			
Actual and Change From Baseline QTc(F) Values by Category	Y				Y			
Vital Signs								
Change From Baseline in Vital Signs by Visit					Y			

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

9. REFERENCES

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10. APPENDICES

Section	Appendix
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 10.1	Appendix 1: Protocol Deviation Management
Section 10.2	Appendix 2: Time & Events
Section 10.3	Appendix 3: Assessment Windows & Visit Slotting
Section 10.4	Appendix 4: Treatment Phases
Section 10.5	Appendix 5: Data Display Standards & Handling Conventions
Section 10.6	Appendix 6: Derived and Transformed Data
Section 10.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
Section 10.8	Appendix 8: Population Pharmacokinetic Analyses
Other RAP Appendices	
Section 10.9	Appendix 9: Abbreviations & Trade Marks
Section 10.10	Appendix 10: List of Data Displays
Section 10.11	Appendix 11: Example Mock Shells for Data Displays

10.1. Appendix 1: Protocol Deviation Management

- As detailed in Section 4.1 protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (PDMP) and important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be listed and summarised.

- A Per Protocol Population will not be defined for this study. However if there are subjects with protocol deviations that may potentially impact either the PK or the PD endpoints, exploratory sensitivity analyses may be considered (See Section 7). Any additional sensitivity analyses will be documented in the CSR.

10.2. Appendix 2: Time & Events

10.2.1. Time & Events Table Pharmacokinetic/Pharmacodynamic Phase (Part A)

Procedure	Pre-Screen[1]	Screening	Treatment Period				Exit Visit[3]	Follow-up		Early Withdrawal
Visit Number	0	1	2	3	4	5	6	7	8[8]	
Week of Study (visit window ± 3 days, ±1 day Visit 5))	Prior to or same day as Visit 1	(up to 14 days prior to Visit 2)	0	4	8	9	12	16	20	
Subject Screen										
Informed consent	X									
Inclusion and exclusion criteria		X	X							
Demography	X									
Medical history, including bronchodilator reversibility history[4]		X								
Past and current medical conditions		X								
Asthma exacerbation history		X								
Safety Assessments										
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Hematology (including eosinophils)		X	X	X	X	X	X	X	X	X
Clinical Chemistry		X		X	X		X		X	X
12-lead ECG		X		X			X			X
Vital signs		X	X	X	X	X	X	X	X	X
Bodyweight			X							
Brief physical examination		X								
Adverse events		X	X	X	X	X	X	X	X	X
Cardiovascular events		X	X	X	X	X	X	X	X	X
Liver events		X	X	X	X	X	X	X	X	X
Laboratory Assessments										
Urinalysis		X							X	X
Pregnancy Test		U	U[5]	U[5]	U[5]		U	U	U	U
HBsAg and hepatitis C antibody		X[6]								
Serum IgE (total and specific)			X[5]							
PK blood sample				X[5]	X[5]	X	X	X	X	X

Procedure	Pre-Screen[1]	Screening	Treatment Period				Exit Visit[3]	Follow-up		Early Withdrawal
Visit Number	0	1	2	3	4	5	6	7	8[8]	
Week of Study (visit window ± 3 days, ±1 day Visit 5))	Prior to or same day as Visit 1	(up to 14 days prior to Visit 2)	0	4	8	9	12	16	20	
IL5 serum sample			X[5]				X			
Blood sample for immunogenicity[2,7]			X[5]					X	X[2]	X
Outcomes Assessments										
FEV1		X	X	X	X		X	X	X	X
ACQ-7			X	X	X		X	X	X	X
C-ACT			X	X	X		X	X	X	X
Assessment of exacerbation	X	X	X	X	X	X	X	X	X	X
Investigational Product										
Mepolizumab SC dose administered			X	X	X					
Study Administration										
Email to GSK Operational Lead	X	X	X	X	X	X	X	X	X	X
Complete eCRF	X	X	X	X	X	X	X	X	X	X

1. Pre-screen must be completed prior to or on the same day as Screen Visit.
2. For subjects who had a positive anti-mepolizumab antibody response at the 12 week post-last-dose follow-up assessment (Visit 8) (or last study visit at which immunogenicity was assessed if the Follow-up (Visit 8) immunogenicity sample is not available) an attempt will be made to obtain a serum sample for anti-mepolizumab antibodies at least 4 months after the last dose of study drug in Part A or upon completion of Part A, whichever is later.
3. Exit visit should be performed as close as possible to the planned week 12 visit date.
4. Therapy history to include a detailed review of prior biologics received for treatment of asthma, including prior investigational anti-IL5 or anti-IL13 preparations.
5. During the treatment period, all lab samples and procedures should be obtained prior to study treatment administration.
6. A positive Hepatitis B Surface Antigen and Hepatitis C antibody is exclusionary
7. This immunogenicity sample must always be collected 12 weeks (± 7 days) post-last-dose of study treatment; therefore, for subjects who withdraw from study treatment early, this sample must be collected 12 weeks (± 7 days) after their confirmed last dose of study treatment (i.e., prior to Visit 8). In the event that this sample collection date coincides with an Early Withdrawal Visit, only one immunogenicity sample should be collected.
8. Visit 8 to be performed 12 weeks post last dose. For subjects continuing into the long-term extension phase Part B, Visit 9 should be conducted on the same day as Visit 8 once all of the visit 8 assessments have been completed. Assessments performed at Visit 8 that are also listed for Visit 9 should not be duplicated if Visit 8 and Visit 9 are performed on the same day.

10.2.2. Time and Events Table Long-Term Safety / Pharmacodynamic Phase (Part B)

Procedure	Eligibility Check / First Dose	Treatment Period												Exit Visit	Follow-up	Early Withdrawal
Visit	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	
Week of Study (visit window ± 5 days)	20	24	28	32	36	40	44	48	52	56	60	64	68	72	80	
Subject Screen																
Informed consent	X[1]															
Inclusion and exclusion criteria	X[1]															
Safety Assessments																
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology (including eosinophils) [2]	X			X			X			X			X	X	X	X
Clinical Chemistry[2]	X			X			X			X			X	X		X
12-lead ECG														X		X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bodyweight	X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cardiovascular events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[2]																
Urinalysis	X[1]					X								X		X
Pregnancy Test	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Blood sample for immunogenicity[2]							X						X		X	X
Outcomes Assessments																
FEV1	X[1]			X			X			X			X	X	X	X
ACQ-7	X[1]			X			X			X			X	X	X	X
C-ACT	X[1]			X			X			X			X	X	X	X
Assessment of exacerbation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedure	Eligibility Check / First Dose	Treatment Period												Exit Visit	Follow-up	Early Withdrawal
Visit	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	
Week of Study (visit window ± 5 days)	20	24	28	32	36	40	44	48	52	56	60	64	68	72	80	
Investigational Product																
Mepolizumab SC dose administered	X	X	X	X	X	X	X	X	X	X	X	X	X			
Study Administration																
Email to GSK Operational Lead	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	X

1. Bodyweight will be measured at Visit 9 and at each visit until such time as the subject reaches 40kg in weight. Subjects with bodyweight ≥40Kg at Visit 9 will not be weighed again during Part B.
2. All laboratory samples should be collected prior to the administration of study medication

10.3. Appendix 3: Assessment Windows & Visit Slotting

10.3.1. Study Part (Part A and Part B)

Data will be collected across two study parts (Part A and Part B) within a single study database. Data will be attributed to an individual study part according to the time of occurrence/assessment relative to specific visits.

Data points collected at scheduled clinic visits will be attributed to the correct study part utilising the collected visit label.

Spontaneous events (such as adverse events, exacerbations and unscheduled visits) will be attributed to an individual study part as follows:

Study Part	Definition
Part A	Visit 0 (Pre-screening) visit date ≤ Date & time ≤ Visit 8 (Week 20) visit date
Part B	Visit 9 (Week 20) visit date < Date & time ≤ Visit 23 (Week 80) visit date
Note: Visit 8 and Visit 9 will be performed on the same date	

10.3.2. Part A Data Cut Date

When reporting study Part A, a data cut date will be applied to all data collected within the Case Report Form (CRF) prior to SDTM conversion. This cut date subset the data to only those assessments/visits prior to the last subject completing the Visit 8 (Week 20) visit date (LSLV Part A).

All external vendor data (e.g. Labs, ECGs, Immunogenicity) will not be possible to subset and therefore data will be present within the SDTM datasets past this data cut date.

When creating ADaM datasets all dates beyond this applied data cut date will be removed and will be documented clearly within the ADaM dataset metadata.

10.3.3. Assessment Windows

Clinic visits are scheduled to take place as specified in Appendix 2: Time & Events. Measurements outside visit windows will not be excluded from analyses. For all clinic visits, nominal visit days and times will be used for reporting, such that if a subject recorded values that were outside of the ±7 day window for a visit they will still be reported under that visit.

10.3.4. Early Withdrawal Visits

If a subject withdraws from the study at a scheduled visit (i.e. completes an Early Withdrawal Visit), where endpoint data were scheduled to be collected, the data will be summarised and analysed (as appropriate) together with data from subjects who did not withdraw from the study. If a subject withdraws from the study at a scheduled visit at which endpoint data were not scheduled to be collected, or if a subject withdraws

between scheduled visits, data will be slotted to the nearest adjacent visit where the endpoint data was scheduled to be collected (if data at that visit were not recorded) according to the Time and Events schedule (Appendix 2: Time & Events).

For example, if a subject prematurely withdraws from the study and completed the Early Withdrawal Visit at Visit 5 (Week 9) and completes an Early Withdrawal Visit which includes an FEV1 assessment, the FEV1 data collected will need to be re-assigned to an adjacent visit where FEV1 data is scheduled for collection. In this case the FEV1 data will be reassigned to Visit 4 (Week 8) (if data at that visit were not recorded) as this is the closest nominal visit at which collection of FEV1 data is scheduled.

10.3.5. Unscheduled Visits

For unscheduled visits, similar logic will be applied. If a subject has an unscheduled assessment then this data would be slotted to the closest adjacent scheduled visit but only if information already exists at that visit. If an unscheduled visit occurred between two scheduled visits for which data has been reported, then the data from the unscheduled visit will remain in the unscheduled visit and will not be used in summary tables and analyses (except for endpoints using any post-baseline data) but will be presented in any relevant listings.

10.4. Appendix 4: Treatment Phases

10.4.1. Treatment Phases (Adverse Events)

Adverse events will be classified according to time of occurrence relative to the first and last dose of mepolizumab within specific study parts.

Treatment Phase	Definition
Pre-Treatment	AE Onset Date & time < First Part A dose of mepolizumab If mepolizumab treatment is never started then all AEs will be classified as pre-treatment.
On-Treatment (Part A)	First Part A dose of mepolizumab ≤ AE Onset Date & time ≤ Last Part A dose of mepolizumab + 28 days If an AE start date is missing or partial then the AE will be considered on-treatment unless there is evidence to the contrary (e.g. month/year of onset date is present and is earlier than the month/year of First Part A dose of mepolizumab).
Post-treatment (Part A)	For subjects entering Part B: Last Part A dose of mepolizumab + 28 days < AE Onset Date & time < First dose of Part B mepolizumab For subjects not entering Part B: Last Part A dose of mepolizumab + 28 days < AE Onset Date & time ≤ Visit 8 (Week 20) visit date
On-Treatment (Part B)	First dose of Part B mepolizumab ≤ AE Onset Date & time ≤ Last Part B dose of mepolizumab + 28 days If an AE start date is missing or partial then the AE will be considered on-treatment unless there is evidence to the contrary (e.g. month/year of onset date is present and is earlier than the month/year of First Part B dose of mepolizumab).
Post-treatment (Part B)	AE Onset Date & time > Last Part B dose of mepolizumab + 28 days
Onset Time Since 1st Dose (Days)*	If Treatment Start Date > AE Onset Date = AE Onset Date - First Part A dose of mepolizumab If Treatment Start Date ≤ AE Onset Date = AE Onset Date - First Part A dose of mepolizumab + 1 If Treatment Start Date or AE Onset Date is missing = missing.
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	If relationship is marked 'YES' on Inform/eCRF OR value is missing.
* Note: will be derived as time since 1st dose of mepolizumab utilising the First Part A dose of mepolizumab for both study parts A and B	

10.4.2. Treatment Phases (Exacerbations)

Exacerbation data will be classified according to time of occurrence/assessment relative to the first and last dose of mepolizumab and the participation of subjects within to specific study parts (as dictated by attendance dates of specific visits).

Treatment Phase	Definition
Pre-Treatment	Exacerbation Onset Date & time < First Part A dose of mepolizumab If mepolizumab treatment is never started then all exacerbations will be classified as pre-treatment.
On-Treatment (Part A)	Subjects completing Part A: First Part A dose of mepolizumab ≤ Exacerbation Onset Date & time ≤ Visit 6 (Week 12) visit date Subjects discontinuing study treatment/withdrawing early from Part A: First Part A dose of mepolizumab ≤ Exacerbation Onset Date & time ≤ Earliest of (1) Last Part A dose of mepolizumab + 28 days or (2) Early Withdrawal visit date
Post-treatment (Part A)	Subjects completing Part A and entering Part B: Visit 6 (Week 12) visit date < Exacerbation Onset Date & time < First dose of Part B mepolizumab Subjects completing Part A and not entering Part B: Visit 6 (Week 12) visit date < Exacerbation Onset Date & time ≤ Visit 8 (Week 20) visit date Subjects discontinuing study treatment/withdrawing early from Part A: Earliest of (1) Last Part A dose of mepolizumab + 28 days or (2) Early Withdrawal visit date < Exacerbation Onset Date & time ≤ Visit 8 (Week 20) visit date
On-Treatment (Part B)	Subjects completing Part B: First Part B dose of mepolizumab ≤ Exacerbation Onset Date & time ≤ Visit 22 (Week 72) visit date Subjects discontinuing study treatment/withdrawing early from Part B: First Part B dose of mepolizumab ≤ Exacerbation Onset Date & time ≤ Earliest of (1) Last Part B dose of mepolizumab + 28 days or (2) Early Withdrawal visit date
Post-treatment (Part B)	Subjects completing Part B: Exacerbation Onset Date & time > Visit 22 (Week 72) visit date Subjects discontinuing study treatment/withdrawing early from Part B: Exacerbation Onset Date & time > Earliest of (1) Last Part B dose of mepolizumab + 28 days or (2) Early Withdrawal visit date
Onset Time Since 1st Dose (Days)*	If Treatment Start Date > Exacerbation Onset Date = Exacerbation Onset Date - First Part A dose of mepolizumab If Treatment Start Date ≤ Exacerbation Onset Date = Exacerbation Onset Date - First Part A dose of mepolizumab + 1 If Treatment Start Date or AE Onset Date is missing = missing.
Duration (Days)	Exacerbation Resolution Date – Exacerbation Onset Date + 1
* Note: will be derived as time since 1st dose of mepolizumab utilising the First Part A dose of mepolizumab for both study parts A and B	

10.4.3. Treatment Phases (Concomitant Medications)

Concomitant medications will be classified according to time of occurrence relative to the first and last dose of mepolizumab within specific study parts.

Treatment/Study Phase	Definition
Taken Before the Run-in	If Con-med Start Date < Date of Visit 1
Taken During the Run-in	• If Con-med Start Date < Date of Visit 1 and Con-med Stop Date ≥ Date of Visit 1, or • If Date of Visit 1 ≤ Con-med Start Date < First Part A dose of mepolizumab
Taken During Treatment (Part A)	• If Con-med Start Date < First Part A dose of mepolizumab and Con-med Stop Date ≥ First Part A dose of mepolizumab, or • If First Part A dose of mepolizumab≤ Con-med Start Date ≤ Last Part A dose of mepolizumab+ 28 days • If the con-med start or stop date is missing or partial then the con-med will be considered on-treatment unless there is evidence to the contrary (e.g. month/year of con-med stop date is present and is before the month/year of the first Part A dose of mepolizumab).
Started During Treatment (Part A)	Subset of con-meds Taken During Treatment (Part A) for which: First Part A dose of mepolizumab ≤ Con-med Start Date ≤ Last Part A dose of mepolizumab + 28 days
Taken Post Treatment (Part A)	• Con-med Stop Date > Last Part A dose of mepolizumab + 28 days
Taken During Treatment (Part B)	• If Con-med Start Date < First Part B dose of mepolizumab and Con-med Stop Date ≥ First Part B dose of mepolizumab, or • If First Part B dose of mepolizumab≤ Con-med Start Date ≤ Last Part B dose of mepolizumab+ 28 days • If the con-med start or stop date is missing or partial then the con-med will be considered on-treatment unless there is evidence to the contrary (e.g. month/year of con-med stop date is present and is before the month/year of the first Part B dose of mepolizumab).
Started During Treatment (Part B)	Subset of con-meds Taken During Treatment (Part B) for which: First Part B dose of mepolizumab ≤ Con-med Start Date ≤ Last Part B dose of mepolizumab + 28 days
Taken Post Treatment (Part B)	• Con-med Stop Date > Last Part B dose of mepolizumab + 28 days
Time Since 1st Dose (Days)*	If Treatment Start Date > Con-med Start Date = Con-med Start Date - First Part A dose of mepolizumab If Treatment Start Date ≤ Con-med Start Date = Con-med Start Date - First Part A dose of mepolizumab + 1 If Treatment Start Date or Con-med Start Date is missing = missing.
Duration (Days)	Con-med Stop Date –Con-med Start Date + 1
* Note: will be derived as time since 1st dose of mepolizumab utilising the First Part A dose of mepolizumab for both study parts A and B	

A medication will be summarised in every treatment/study phase in which it was taken, so for example a medication that was started in the run-in and stopped during treatment will appear in both the during the run-in and during treatment tables

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Study Treatment & Display Descriptors

For all displays subjects will be presented in the treatment group received during the study.

10.5.1.1. Part A

All displays will be presented by mepolizumab dose group within Part A (Mepolizumab 40 mg and 100mg SC) and overall, when appropriate.

Treatment Group Descriptions			
RandAll NG[1]		Data Displays for Reporting	
Code	Description	Description[3]	Order [2]
N/A	N/A	Mepolizumab 40 mg SC	1
		Mepolizumab 100 mg SC	2
		Mepolizumab SC	3

NOTES:

1. This is not a randomised study and treatment group descriptions are not required for RandAll NG
2. Order represents treatments being presented in TFL, as appropriate.
3. 'Mepolizumab SC' group includes all subjects who received at least one dose of mepolizumab regardless of dose.

10.5.1.2. Part B

All displays will be presented by mepolizumab dose group within Part B and overall. Note: Subjects which are switched from 40mg to 100mg SC during Part B will be presented separately [Mepolizumab 40/100 mg SC].

Treatment Group Descriptions			
RandAll NG[1]		Data Displays for Reporting	
Code	Description	Description[3]	Order [2]
N/A	N/A	Mepolizumab 40 mg SC	1
		Mepolizumab 100 mg SC	2
		Mepolizumab 40/100 mg SC	3
		Mepolizumab SC	4

NOTES:

1. This is not a randomised study and treatment group descriptions are not required for RandAll NG
2. Order represents treatments being presented in TFL, as appropriate.
3. 'Mepolizumab SC' group includes all subjects who received at least one dose of mepolizumab regardless of dose.

10.5.2. Baseline Definition & Derivations

10.5.2.1. Definition of Baseline

- The baseline value for each assessment will be the latest value recorded prior to the first dose of mepolizumab.
- If an assessment was performed on the same day as the first dose of study treatment but it is known that the assessment was done after administration of treatment (i.e. because time of assessment is available and is after time of first dose) then this value will not be used as the baseline value.
- The same baseline definition (latest value recorded prior to the first dose of mepolizumab in Part A) will be used in the analyses of both Part A and Part B data.

10.5.2.2. Derivations of Change from Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
Ratio to baseline	= Post-Dose Visit Value / Baseline
Maximum Change from Baseline	= Highest Post-Dose Value - Baseline

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 10.5.2.1 will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- The baseline definition will be footnoted on all change from baseline displays.

10.5.3. Reporting Process & Standards

Reporting Process	
Software	
The currently supported versions of SAS software will be used to perform all data analyses, generate tables, figures and listings.	
Reporting Area (Part A)	
HARP Server	: UK1SAL00175
HARP Area	: /arenv/arprod/sb240563/mid200363/part_a
Quality Control (QC) Spread sheet	: /arenv/arwork/sb240563/mid200363/part_a/document
Reporting Area (Part B)	
HARP Server	: UK1SAL00175
HARP Area	: /arenv/arprod/sb240563/mid200363/final
Quality Control (QC) Spread sheet	: /arenv/arwork/sb240563/mid200363/final/document

Reporting Process
Analysis Datasets
• Analysis datasets will be created according to CDISC standards (current versions of SDTM IG & ADaM IG). • 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 only for summary tables

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics
Formats
• All data will be reported according to the actual treatment the subject received (see Section 10.5.1). • The reported precision of data will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of decimal places.
Planned and Actual Time
• Reporting for tables and figures : • Nominal visits (planned time relative to dosing) will be used in summary figures and summary tables. Actual time relative to dosing will be used in individual subject figures. • 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 data listings • Scheduled visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings, summaries and statistical analyses. The impact of any major deviation from the planned assessment times and/or scheduled visit days on the summaries, figures, analyses will be assessed as appropriate.
Unscheduled Visits
• When possible unscheduled assessments will be slotted to the closest adjacent scheduled visit. If an unscheduled visit occurs between two completed scheduled visits, the data from the unscheduled visit will not be used in summary tables which are based on by-visit assessments. The information from the unscheduled visit will be included in 'any time post-baseline' summaries and will also be presented in any relevant listings. See Section 10.3 for further details.

Reporting Standards	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N (number of subjects in the treatment group), n (number of subjects with non-missing values), frequency, %
Reporting of Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 Refer to GUI_51487 for further details of handling NQ/BQL values
Reporting of Pharmacokinetic Parameters	
Descriptive Summary Statistics	The following summary statistics will be presented for all parameters: N, n, mean, median, SD, min and max In addition the following summary statistics will be presented for all parameters with the exception of t1/2. N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data and [between] geometric coefficient of variation (CVb (%)) will be reported. [1] CV_b (%) = $\sqrt{}$ (exp(SD^2) – 1) * 100 (SD = SD of log transformed data)
Reporting of Blood Eosinophil Count	
Descriptive Summary Statistics	The following summary statistics will be presented for blood eosinophil count: N, n, geometric mean, 95% CI of geometric mean, SD (natural log scale), median, min and max
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

10.6. Appendix 6: Derived and Transformed Data

10.6.1. General

Multiple Measurements at One Time Point
• There are no scheduled multiple measurements, however, if multiple measurements are recorded at a given time point the following process will be followed, unless a process for selection of the measurement for the visit is specified. • Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time window the value closest to the target day for that window will be used. If values are the same distance from the target then the mean will be taken. • 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.
Study Day
Calculated as the number of days from first mepolizumab dose: • Ref Date = Missing Study Day = Missing • Ref Date < First mepolizumab dose Study Day = Ref Date – First dose of mepolizumab • Ref Data ≥ First mepolizumab dose Study Day = Ref Date – (First dose of mepolizumab) + 1

10.6.2. Study Population

Demographics
Age
• Only year of birth was collected for subjects; actual birth data was not collected. • GSK standard IDSL algorithms will be used for calculating age where birth date of all subjects will be imputed as '30th June'. • Birth date will be presented in listings as 'YYYY'. • Each subject's derived age will be calculated as an integer value based on their imputed date of birth relative to the date of the subject's screening visit (Visit 1) [(30th June of the year of birth reported on eCRF – date of Screening)/365.25] • Derived age may not represent the actual age of a subject at entry to the study • All tables which include age will describe this as "derived age" and will include a footnote to indicate that a) actual age was not collected, b) age was derived using a value of 30th June for birth date and c) this may not represent the actual age of a subject at entry to the study.
Body Mass Index (BMI)
• Calculated as Weight (kg) / [Height $(m)^2$

Disease parameters
Percent Predicted FEV1
• FEV1 % of predicted normal will be derived using the Global Lung Function Initiative 2012 look-up tables [Quanjer, 2012]

Disease parameters
FEV_1/FVC Ratio
• Pre- and post-bronchodilator FEV_1/FVC ratio will be calculated as the ratio of the FEV_1 and FVC values.
Blood Eosinophils
• Blood eosinophil count will be log transformed prior to analysis. Summary statistics will include geometric mean and a measure of spread (SD or SE) on the natural log scale. • If a blood eosinophil count of zero is reported, it will be imputed with half of the lowest possible blood eosinophil count, where applicable, prior to log transforming the data (Note: this imputation has typically been 0.5 * 0.01 GI/L = 0.005 GI/L for previous mepolizumab studies).
Categories defined based on databased information regarding blood eosinophil counts in the previous 12 months and observed blood eosinophil counts at the Screening visit.
• Historical and Screening: Blood eosinophil count ≥300 cells/µl in previous 12 months and ≥150 cells/µl at Screening • Historical Only: Blood eosinophil count ≥300 cells/µl in previous 12 months and <150 cells/µl at Screening • Screening Only: Blood eosinophil count <300 cells/µl or missing or unknown in previous 12 months and ≥150 cells/µl at Screening
Baseline OCS daily dose
• Only corticosteroids administered via oral, intravenous (IV) and intramuscular (IM) routes are to be considered when calculating a subject's total daily prednisone/prednisolone asthma maintenance dose at baseline. All steroids administered via a sublingual route will also be considered as oral. • The corticosteroid conversion factors shown below will be used, regardless of the route of administration, to scale each corticosteroid dose to a prednisone equivalent dose. These three routes of administration (oral, IV and IM) are to be considered equivalent as it has been noted that the bioavailability of methylprednisolone is considered to be roughly equivalent following administration as an oral, IV or IM steroid.

Standardised Medication Name	**Scaling Factor**
Betamethasone	8.33
Betamethasone Dipropionate	8.33
Betamethasone Sodium Phosphate	8.33
Cortisone	0.2
Cortisone Acetate	0.2
Cortivazol	17
Deflazacort	0.833
Dexamethasone	6.67
Dexamethasone Sodium Phosphate	6.67
Fludrocortisone Acetate	0
Hydrocortisone	0.25
Hydrocortisone Sodium Succinate	0.25
Hydrocortisone Sodium Phosphate	0.25

Standardised Medication Name	Scaling Factor
Meprednisone	1
Methylprednisolone	1.25
Methylprednisolone Acetate	1.25
Methylprednisolone Sodium Succinate	1.25
Methylprednisone	1.25
Methylprednisone Acetate	1.25
Methylprednisolone Sodium Succinate	1.25
Methylprednisone	1.25
Methylprednisone Acetate	1.25
Prednisolone	1
Prednisolone Acetate	1
Prednisolone Hemisuccinate	1
Prednisolone Sodium Succinate	1
Prednisone	1
Prednisone Acetate	1
Triamcinolone	1.25
Triamcinolone Acetonide	1.25

Extent of Exposure (Days)

- Within each study part (Part A/Part B) the number of days of total exposure to mepolizumab will be calculated based on the formula:
  Duration of Exposure = Last dose of mepolizumab – (First dose of mepolizumab) + 29
- Within each study part (Part A/Part B) the number of days of exposure to specific mepolizumab doses will be calculated as follows:
  Subjects receiving mepolizumab 40mg SC only:
  Duration of Exposure = Last dose of mepo 40mg – (First dose of mepo 40mg) + 29
  Subjects receiving mepolizumab 100mg SC only:
  Duration of Exposure = Last dose of mepo 100mg – (First dose of mepo 100mg) + 29
  Subjects receiving mepolizumab 40mg SC and mepolizumab 100mg (Part B only):
  Duration of 40mg Exposure = First dose of mepo 100mg – (First dose of mepo 40mg) + 1
  Duration of 100mg Exposure = Last dose of mepo 100mg – (First dose of mepo 100mg) + 28
- Subjects who never received a mepolizumab dose will be categorised as having zero days of exposure.
- The extent of exposure will also be summarised as the number of study treatments administered within each study part (Part A/Part B).

10.6.3. Subject Disposition

Subject Disposition
• It is an eligibility requirement that subjects must complete all study assessments up-to and including Visit 8 (and received all 3 doses of investigational product) in Part A before entering study Part B • Subjects who complete Part A will not have a disposition (study part completion/withdrawal) record created at the completion of Part A. Instead a derived disposition record will be required utilising the Part B status (RLSTUDY) flag. A disposition record will be available for Part B.

10.6.4. Safety

AEs of Special Interest
Section 8.2.1.1 provides a full list of AEs of special interest for this compound. AESIs of anaphylaxis reactions, systemic reactions, and local injection site reactions are collected via targeted eCRF. Systemic reactions with preferred terms such as injection related reaction or administration related reaction will be considered non-allergic reactions; those with other preferred terms will be considered allergic/hypersensitivity reactions. The AESIs of opportunistic infections, malignancies, serious 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 latest version of the MedDRA dictionary available at the time of database freeze for this study (See Program Safety Analysis Plan for additional details).

ECG Parameters
RR Interval
All ECG parameters required in this study will be databased, and therefore, further derivations will not be performed by Stats and Programming. The definitions of these parameters are given in this section. • If RR interval (msec) is not databased, then RR can be derived as : [1] If QTcB is machine read & QTcF is not provided, then : $$RR = \left[\left(\frac{QT}{QTcB}\right)^{2}\right] * 1000$$ [2] If QTcF is machine read and QTcB is not provided, then: $$RR = \left[\left(\frac{QT}{QTcF}\right)^{3}\right] * 1000$$ • If ECGs are manually read, the RR value should be a collected value and will not be derived.

Corrected QT Intervals

- When not databased, corrected QT intervals by Bazett's (QTcB) and Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements.
- If RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as :

$$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

- Individual maximum QTc(F) and QTc(B) values will also be summarised by treatment group for each scheduled study visit to show the number of subjects with maximum values (msec) in the following categories:
  - <= 450
  - 450 < to <= 480
  - 480 < to <= 500
  - > 500
- Additionally, individual maximum changes from baseline in QTc(F) and QTc(B) values will be summarised by treatment group for each scheduled study visit to show the number of subjects with maximum changes (msec) in the following categories:
  - < -60
  - ≥ -60 to < -30
  - ≥ -30 to < 0
  - ≥ 0 to < 30
  - ≥ 30 to < 60
  - ≥ 60

Laboratory Parameters

- If a laboratory value which is expected to have a numeric value for summary purposes, has a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field), the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.
  - Example 1: 2 Significant Digits = '< x ' becomes x – 0.01
  - Example 2: 1 Significant Digit = '> x' becomes x + 0.1
  - Example 3: 0 Significant Digits = '< x' becomes x – 1
- If a laboratory value is missing due to being below the limit of quantification (BLQ) then the value will be imputed as half the lower limit of quantification for that measure (i.e. the lowest observed value for that measure within the entire study database).

10.6.5. Efficacy

Patient Reported Outcomes/Questionnaires
ACQ-7
• The questionnaire includes 7 items; and requires a 1 week recall (for items on symptoms and rescue inhaler use). The ACQ has a multidimensional construct assessing symptoms (5 items administered by clinic staff to the child) and rescue bronchodilator use (query to child or parent), and FEV1 % predicted (1 item) completed by clinic staff. • Each question on the ACQ-7 is scored on a 7-point scale from 0 = no impairment to 6 = maximum impairment. The questions are equally weighted and the ACQ-7 score will be the mean of the 7 questions, thus giving a score between 0 (totally controlled) and 6 (severely uncontrolled) [Juniper, 2010; Juniper, 1999; Juniper, 2005]. • A subject will be deemed a responder if the subject has a ≥0.5 reduction in ACQ score from Baseline • If a subject does not complete 1 of the 7 questions at a visit, then the ACQ-7 score will be the mean of the responses to the remaining 6 questions at that visit. • If a subject does not complete more than 1 of the 7 questions at a visit, then their ACQ-7 score will be set to missing at that visit. • ACQ-7 Responder/Non-responder category will be missing if the overall ACQ-7 score is missing.
ACQ-5
• The ACQ-5 questionnaire consists of the 5 symptoms questions (Q1-Q5) of the ACQ-7 requiring a 1 week recall. • Each question on the ACQ-5 is scored on a 7-point scale from 0 = no impairment to 6 = maximum impairment. The questions are equally weighted and the ACQ-5 score will be the mean of the 5 questions, thus giving a score between 0 (totally controlled) and 6 (severely uncontrolled) [Juniper, 2010; Juniper, 1999; Juniper, 2005]. • A subject will be deemed a responder if the subject has a ≥0.5 reduction in ACQ score from Baseline • If a subject does not complete 1 of the 5 questions at a visit, then the ACQ-5 score will be the mean of the responses to the remaining 4 questions at that visit. • If a subject does not complete more than 1 of the 5 questions at a visit, then their ACQ-5 score will be set to missing at that visit. • ACQ-5 Responder/Non-responder category will be missing if the overall ACQ-5 score is missing.
C-ACT
• The C-ACT is a 7-question, 2-part questionnaire, with items one through 4 to be completed by the child (with assistance from a caregiver, as needed) and items 5 to 7 to be completed by the caregiver [Liu, 2010; Liu, 2007]. • The scores for each of the questions will be summed to derive the total score for that subject at that visit. If the response to any question is missing then the C-ACT total score is also set to missing.

Exacerbations
An exacerbation of asthma as defined as: Worsening of asthma which requires use of systemic corticosteroids[1]and/or hospitalisation and/or Emergency Department (ED) visits. • *[1]For all subjects, i.v. or oral steroid (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For subjects on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days is required.* Exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation. Each individual exacerbation will be listed.

10.7. Appendix 7: Premature Withdrawals & Handling of Missing Data

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. completion of all study visits or withdraw prematurely from the study) was detailed in the study protocol. • Withdrawn subjects will not be replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in data displays (e.g. summary tables) unless otherwise specified.
Pre-Screen, Screen and Run-in Failures	Pre-screen failures, screening failures and run-in failures will be defined as follows: • Subjects will be assigned a subject number at the time the informed consent is signed (Pre-screen Visit). Subjects who are assigned a subject number but do not have a Visit 1 (screening) procedure will be considered **pre-screen failures**. • Those subjects that complete at least one Visit 1 (Screening) procedure but do not enter the run-in period will be considered **screen failures**. • Those subjects that enter the run-in period but are not subsequently dosed will be considered **run-in failures**.

10.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided. 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. Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should not be displayed as missing. • PK concentrations reported as Not Quantified (NQ)/Below the Lower Limit of Quantification (BQL) will be handled as per standard GSK practice. Below the limit of quantification (BLQ) is not missing data and must be displayed as such and included in all listings and summaries

Element	Reporting Detail
	• If a blood eosinophil count of zero is reported, it will be imputed with half of the lowest possible blood eosinophil count, where applicable, prior to log transforming the data (Note: this imputation has typically been 0.5 * 0.01 GI/L = 0.005 GI/L for previous mepolizumab studies). • The ACQ-7 score will be considered as missing if <6 items of the questionnaire are completed at a visit. ACQ-7 Responder/Non-responder category will be missing if the overall ACQ-7 score is missing. • The ACQ-5 score will be considered as missing if <4 items of the questionnaire are completed at a visit. ACQ-5 Responder/Non-responder category will be missing if the overall ACQ-5 score is missing. • Missing values will not be imputed for any of the other endpoints.
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.
Sensitivity analysis	• No sensitivity analyses are planned for this study. However as detailed in Section 7, exploratory sensitivity analyses may be considered if there are protocol deviations that may potentially affect the PK and/or PD endpoints. If any sensitivity analyses are performed the details will be documented in the clinical study report.

10.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• The eCRF allows for the possibility of partial dates (i.e. only month and year) to be recorded for event start and end dates; that is, the day of the month may be missing. • Partial dates will be displayed as captured in subject listing displays.
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.
AEs	• Any partial dates for adverse events and exacerbations will be raised to data management. If the full date cannot be ascertained, the following assumptions will be made: ○ 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 these results in a date prior to the first dose of mepolizumab and the event could possibly have occurred during treatment from the partial information, then the first dose of mepolizumab date will be assumed to be the start date. The AE will then be considered to start on-treatment (worst case) as per Appendix 4: Treatment Phases. ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day

Element	Reporting Detail
	(dependent on the month and year) and 'Dec' will be used for the month. • The above conventions will also be applied when calculating the time to onset and duration of the event containing missing or partial start and end dates. • The recorded partial date will be displayed in listings. • Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

10.8. Appendix 8: Population Pharmacokinetic Analyses

10.8.1. Population-PK Analysis

Sparse PK samples collected will be analysed by population PK methods, using appropriate software, and based on the PK population.

Based on mepolizumab PK knowledge, concentrations below the limit of quantification (BLQ) of the assay is considered unlikely at the 100 mg and 40 mg SC dose investigated in view of the PK sampling scheme selected in the study. Thus any such results will be treated as missing in the population PK analysis.
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.
The established most recent adult population PK model parameterised in terms of macro-constants (i.e. A, B, alpha, beta) will be used to conduct the analysis of the data from this study.

$C_i(t) = A_i*\exp(-Alpha*t) + B_i*\exp(-Beta_i*t) - (A_i+B_i)*\exp(-Ka*t)$,
Where:

A denotes the coefficient of the distribution phase
B denotes the coefficient of the elimination phase
Alpha denotes the distribution phase rate constant
Beta denotes the terminal phase rate constant
pBWT denotes the power for the bodyweight covariate on a parameter
Ka_i absorption rate constant.

Bodyweight will be included as a structural covariate on parameters A, B, Alpha and Beta. In consideration of the sparse sampling used and the relatively small sample size in the study, a number of pharmacokinetic parameters will be fixed from adult values in the model as deemed necessary (e.g. absorption and inter-compartmental rate constant parameters, pBWT).

Individual AUC(0-inf), CL/F, Cmax and t1/2 will be derived as follow:

AUC(0-inf) = (A/alpha) + (B/beta) – (A+B)/Ka
CL/F = Dose/AUC(0-inf)

$T_{1/2}$ = Ln(2)/beta

Cmax will be estimated using an approximation method as described below:

The approximate one compartment solution combining absorption and distribution phases takes the form:

$C_i'(t) = B*(\exp(-Beta*t) - \exp(-Ka2*t))$

With :
Ka2 = Ka + Alpha (from the bi-exponential model)

Hence
Tmax = logn((Alpha+Ka)/Beta)/(Ka+Alpha-Beta)
Cmax(n doses) = ∑(j=1..n) B*(exp(-Beta*(Tmax+((j-1)*Tau))) – exp(-Ka2*(Tmax+((j-1)*Tau))))

The parameter estimates from the final PK model, the derived parameters and diagnostic plots assessing the performance of the population PK model will be presented.

Simulation from the final PK model will be conducted and a plot of model predicted (5^{th}, 50^{th}, and 95^{th} Percentiles) mepolizumab plasma concentrations with individual observed plasma concentrations will be presented as a means to validate the final PK Model.

10.8.2. Additional Analysis to Support Paediatric Extrapolation Strategy

10.8.2.1. Population-PK analysis

In addition, to confirm that paediatric PK data from 6-11 years old subjects can be predicted from the adult PK model, the most recent population PK model will also 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 Cramér–von Mises and Kolmogorov-Smirnov tests are accepted methods of comparing Empirical Distribution Functions for model and data (i.e. PK concentrations) to evaluate whether independent observations (observed PK concentrations from the study) are adequately described by a model.

The current PK 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.

10.8.2.2. Population-PK/PD analysis

Likewise, to confirm that paediatric blood eosinophil count data from 6-11 years old subjects can be predicted from the adult PK/PD model, the most recent population PK/PD 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 above (using the observed data from the study).

The population PK/PD 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.

If a blood eosinophil count of zero is reported, it will be imputed with half of the lowest possible blood eosinophil count, where applicable, prior to log transforming the data (Note: this imputation has typically been 0.5 * 0.01 GI/L = 0.005 GI/L for previous mepolizumab studies).

10.9. Appendix 9: Abbreviations & Trade Marks

10.9.1. Abbreviations

Abbreviation	Description
ACQ-7	Asthma Control Questionnaire-7
ADA	Anti-drug Antibody
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ASE	All Subjects Enrolled
ATC	Anatomical Therapeutic Chemical
AUC	Area under concentration time curve
AUC(0-inf)	Area under concentration time curve to infinity
C-ACT	Childhood Asthma Control Test
BLQ	Below Limit of Quantification
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
Cmax	Maximum observed concentration
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
CVT	Cardiac, Vascular and Thromboembolic
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Place
eCRF	Electronic Case Record Form
ECG	Electrocardiogram
FEV_1	Forced expiratory volume in 1 second
FVC	Forced Vital Capacity
GSK	GlaxoSmithKline
GUI	Guidance
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IG	Implementation Guide
IgE	Immunoglobulin E
IL-5	Interleukin-5
IM	Intramuscular
IP	Investigational Product
ITT	Intent-To-Treat
IV	Intravenous
kg	Kilograms
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams

Abbreviation	Description
NAb	Neutralising Antibody
NQ	Non-quantifiable
PD	Pharmacodynamic
PDe	Pharmacodynamic (Blood Eosinophils) Population
PDo	Pharmacodynamic (Outcome Assessments) Population
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
Pop-PK	Population Pharmacokinetics
PT	Preferred Term
QC	Quality Control
QT	The QT interval is measured from the beginning of the QRS complex to the end of the T wave
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RTF	Rich Text Format
SAC	Statistical Analysis Complete
SAE	Serious adverse event(s)
SAS	Statistical Analysis Software
SC	Subcutaneous
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SOC	System Organ Class
$t_{1/2}$	Terminal phase half-life
TFL	Tables, Figures & Listings
Tmax	Time of occurrence of Cmax
µL	Microlitre

10.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

10.10. Appendix 10: List of Data Displays

10.10.1. Data Display Numbering and Priority

10.10.1.1. Part A

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.22	Not applicable
Pharmacokinetic Analysis	2.1 to 2.11	2.1 to 2.15
Efficacy Analysis	2.12 to 2.24	2.16 to 2.23
Safety Analysis	3.1 to 3.53	3.1 to 3.2
Section	**Listings**	
ICH Listings	1 to 43	
Other Listings	44 to 51	

Delivery [Priority] [1]	Description
SAC1	Part A Statistical Analysis Complete 1
SAC2	Part A Statistical Analysis Complete 2 (Further analyses supportive of mepolizumab paediatric extrapolation)

NOTES:
1. Indicates priority (i.e. order) in which displays will be generated for the respective reporting effort (Part A/Part B).

10.10.1.2. Part B

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.23 to 1.28	Not applicable
Efficacy Analysis	2.25 to 2.34	2.24 to 2.25
Safety Analysis	3.54 to 3.106	3.3 to 3.4
Section	**Listings**	
ICH Listings	52 to 89	

Delivery [Priority] [1]	Description
SAC	Part B Statistical Analysis Complete

NOTES:
1. Indicates priority (i.e. order) in which displays will be generated for the respective reporting effort (Part A/Part B).

10.10.2. Part A

10.10.2.1. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable Priority**
Subject Disposition					
1.1.	Safety	SA1	Summary of Subject Populations (Part A)		SAC1
1.2.	ASE	ES6	Summary of Reasons for Screening or Run-In Failure (Part A)	Include separate pages for Pre-screening, Screening and Run-in	SAC1
1.3.	ASE	IE2	Summary of Failed Inclusion/Exclusion Criteria for Screening or Run-in Failures (Part A)		SAC1
1.4.	Safety	IE2	Summary of Failed Inclusion/Exclusion Criteria for Subjects within the Safety Population (Part A)		SAC1
1.5.	Safety	NS1	Summary of Number of Subjects Dosed by Country and Site (Part A)		SAC1
1.6.	Safety	ES1	Summary of Subject Disposition (Part A)	Should include subject disposition, reason for withdrawal. See Section 10.6.3.	SAC1
Demography					
1.7.	Safety	DM1	Summary of Demographic Characteristics (Part A)		SAC1
1.8.	ASE	DM11	Summary of Age Ranges (Part A)	EMA, keep row ≥2-11, ≥12-17 (if imputed age is above 12 yrs)	SAC1
1.9.	Safety	DM5	Summary of Race and Racial Combinations (Part A)		SAC1
1.10.	Safety	DM6	Summary of Race and Racial Combinations Details (Part A)		SAC1
Medical History					
1.11.	Safety	MH4	Summary of Past Medical Conditions (Part A)		SAC1

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable Priority**
1.12.	Safety	MH4	Summary of Current Medical Conditions (Part A)		SAC1
1.13.	Safety		Summary of Cardiovascular Assessments – Family History (Part A)	See format of Study Population Table 1.14 (200862 'final' reporting effort)	SAC1
Baseline Disease Characteristics					
1.14.	Safety	SD1	Summary of Asthma Exacerbation History (Part A)	See format of Study Population Table 1.17 (200862 'final' reporting effort)	SAC1
1.15.	Safety		Summary of Asthma History and Baseline Disease Characteristics (Part A)	See format of Study Population Table 1.16 (200862 'final' reporting effort) To include OCS maintenance use and the two eosinophil entry criteria in isolation and in combination	SAC1
1.16.	Safety		Summary of Screening and Baseline Lung Function Results (Part A)	See format of Study Population Table 1.20 (200862 'final' reporting effort)	SAC1
Prior and Concomitant Medications					
1.17.	Safety		Summary of Asthma Concomitant Medication Taken Before the Run-In by Respiratory Medication Class (Part A)	See format of Study Population Table 1.21 (200862 'final' reporting effort)	SAC1
1.18.	Safety		Summary of Asthma Concomitant Medication During the Run-In by Respiratory Medication Class (Part A)	See format of Study Population Table 1.22 (200862 'final' reporting effort)	SAC1

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable Priority**
1.19.	Safety		Summary of Asthma Concomitant Medication Taken During Treatment by Respiratory Medication Class (Part A)	See format of Study Population Table 1.23 (200862 'final' reporting effort)	SAC1
1.20.	Safety		Summary of Asthma Concomitant Medication Taken Post-Treatment by Respiratory Medication Class (Part A)	See format of Study Population Table 1.25 (200862 'final' reporting effort)	SAC1
1.21.	Safety	CM1	Summary of non-Asthma Concomitant Medication Taken During Treatment (Part A)		SAC1
Protocol Deviations					
1.22.	Safety	DV1B	Summary of Important Protocol Deviations (Part A)		SAC1

10.10.2.2. Pharmacokinetic Tables

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable [Priority]
PK (Primary Endpoint)					
2.1.	PK	DBRL1/DBRN1	Summary of Plasma Mepolizumab Pharmacokinetic Concentration-Time Data (observed and predicted)	Shell from Respiratory display standards [Only the summary of untransformed data will be included] Summary by mepolizumab dose group and mepolizumab overall.	SAC1
2.2.	PK	DBRL4/DBRN4	Summary Statistics of Individual Model Predicted and Plasma Mepolizumab Pharmacokinetic Parameters (non-transformed and log-transformed)	Include untransformed and log-transformed summary statistics. Include 95% CIs for geometric mean. Summary by mepolizumab dose group and mepolizumab overall	SAC1
2.3.	PK		Description and Evaluation of Key PK Models Tested	Provided by CPMS	SAC1
2.4.	PK		Population PK Parameter Estimates with 95% CI of Final PK Model	Provided by CPMS Summary for mepolizumab overall	SAC1
2.5.	PK		Demographics Summary (only if different from study population)	Provided by CPMS	SAC1
2.6.	PK		Samples Summary	Provided by CPMS	SAC1
PK (Secondary Endpoint)					
2.7.	PK		Population estimate and 90% CI of bodyweight-adjusted clearance in paediatric subjects together with historic value in adults around which a proposed 80-125% interval is applied.	Summarise mepolizumab overall Provided by CPMS	SAC1
PK (Exploratory Analysis)					
2.8.	PK		Goodness of Fit Test Results	Provided by CPMS	SAC2

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable [Priority]
PKPD (Exploratory Analysis)					
2.9.	PKPD		Demographics Summary (only if different from study population)	Provided by CPMS	SAC2
2.10.	PKPD		Samples Summary	Provided by CPMS	SAC2
2.11.	PKPD		Goodness of Fit Test Results	Provided by CPMS	SAC2

10.10.2.3. Pharmacokinetic Figures

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable [Priority]
PK (Primary Endpoint)					
2.1.	PK		Model Predicted Mepolizumab Individual Plasma Concentration Time Profiles with Individual Observed Plasma Concentrations and Plasma Concentration Population Prediction from Final PK Model (Linear and Semi Log Plots) by Treatment	Provided by CPMS	SAC1
2.2.	PK		Model Predicted Mepolizumab Individual Plasma Concentration Time Profiles with Individual Observed Plasma Concentrations and Plasma Concentration Population Prediction from Final PK Model (Semi Log Plots) by Subject	Provided by CPMS	SAC1
2.3.	PK		Model Goodness of Fit Plots	Provided by CPMS	SAC1
2.4.	PK		Observed Plasma Mepolizumab Concentration-Time Profiles by Anti-drug Antibody Status	Provided by CPMS	SAC1
2.5.	PK		Plasma Mepolizumab Observed Concentration-Time Profiles (Japanese versus non-Japanese Subjects)	Provided by CPMS	SAC1
2.6.	PK		PK Model Evaluation: Model Predicted (5th, 50th, and 95th Percentiles) Mepolizumab Plasma Concentrations with Individual Observed Plasma Concentrations For Final PK Model	Provided by CPMS	SAC1
PK (Exploratory Analysis)					
2.7.	PK		Plasma Mepolizumab Observed/Predicted Concentration-Time Profiles (by Treatment)	Provided by CPMS	SAC2
2.8.	PK		Model Goodness of Fit Plots	Provided by CPMS	SAC2
2.9.	PK		Plasma Mepolizumab Observed/Predicted Concentration-Time Profiles (by Subject)	Provided by CPMS	SAC2
2.10.	PK		Visual Predictive Check	Provided by CPMS	SAC2

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable [Priority]
PKPD (Exploratory Analysis)					
2.11.	PKPD		Observed/Predicted Blood Eosinophil Count-Time Profiles (by Treatment)	Provided by CPMS	SAC2
2.12.	PKPD		Model Goodness of Fit Plots	Provided by CPMS	SAC2
2.13.	PKPD		Observed/Predicted Blood Eosinophil Count-Time Profiles (by Subject)	Provided by CPMS	SAC2
2.14.	PKPD		Visual Predictive Check	Provided by CPMS	SAC2
2.15.	PKPD		Blood Eosinophil Count-Time Profiles (Japanese versus non-Japanese Subjects)	Provided by CPMS	SAC2

10.10.2.4. Efficacy Tables

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable [Priority]
Blood Eosinophil Count (Primary Endpoint)					
2.12.	PDe		Summary of Blood Eosinophil Count (Part A)	Log transformed with geometric mean, include ratio to baseline See format of Efficacy Table 2.73 (200862 'final' reporting effort) To also include 95% CIs by visit	SAC1
Asthma Control Questionnaire					
2.13.	PDo		Summary of ACQ-7 Score (Part A)	See format of Efficacy Table 2.34 (200862 'final' reporting effort) To also include 95% CIs by visit	SAC1
2.14.	PDo		Summary of 0.5 Point or More Reduction in ACQ-7 Score from Baseline (Part A)	See format of Efficacy Table 2.41 (200862 'final' reporting effort). Note: Logistic regression to not be included and Odds Ratio to not be shown	SAC1
2.15.	PDo		Summary of ACQ-5 Score (Part A)	See format of Efficacy Table 2.34 (200862 'final' reporting effort) To also include 95% CIs by visit	SAC1
2.16.	PDo		Summary of 0.5 Point or More Reduction in ACQ-5 Score from Baseline (Part A)	See format of Efficacy Table 2.41 (200862 'final' reporting effort). Note: Logistic regression to not be included and Odds Ratio to not be shown	SAC1

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable [Priority]
Childhood Asthma Control Test (C-ACT)					
2.17.	PDo		Summary of C-ACT Score (Part A)	See format of Efficacy Table 2.34 (200862 'final' reporting effort). To also include 95% CIs by visit	SAC1
FEV1					
2.18.	PDo		Summary of FEV_1 (Part A)	See format of Efficacy Table 2.27 (200862 'final' reporting effort). To also include 95% CIs by visit	SAC1
Asthma Exacerbations					
2.19.	PDo		Overview of Asthma Exacerbations (Part A)	See format of Efficacy Table 2.61 (200862 'final' reporting effort).	SAC1
2.20.	PDo		Summary of Frequency of Exacerbations (Week 0 –Week 12) (Part A)	See format of Efficacy Table 2.62 (200862 'final' reporting effort)	SAC1
2.21.	PDo		Summary of Frequency of Exacerbations (Week 0 –Week 20) (Part A)	See format of Efficacy Table 2.62 (200862 'final' reporting effort)	SAC1
2.22.	PDo		Summary of Time to First Asthma Exacerbation (Part A)	See format of Efficacy Table 2.68 (200862 'final' reporting effort)	SAC1
IgE					
2.23.	PDo		Summary of IgE (Part A)	Log transformed with geometric mean, include ratio to baseline See format of Efficacy Table 6.71 (MEA115588 'final' reporting effort)	SAC1

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable [Priority]
IL-5					
2.24.	PDo		Summary of IL-5 (Part A)	Log transformed with geometric mean, include ratio to baseline See format of Efficacy Table 6.71 (MEA115588 'final' reporting effort)	SAC1

10.10.2.5. Efficacy Figures

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable [Priority]
Blood Eosinophil Count (Primary Endpoint)					
2.16.	PDe		Figure of Absolute Blood Eosinophil Count (Mean Change from Baseline at Each Visit by Treatment Group) (Part A)	See format of Efficacy Figure 6.18 (MEA115588 'final' reporting effort)	SAC1
2.17.	PDe		Figure of Ratio of Blood Eosinophil Count to Baseline (Mean Change from Baseline at Each Visit by Treatment Group) (Part A)	See format of Efficacy Figure 6.18 (MEA115588 'final' reporting effort)	SAC1
Asthma Control Questionnaire					
2.18.	PDo		Figure of Change from Baseline in Overall ACQ-7 score (Mean Change from Baseline at Each Visit by Treatment Group) (Part A)	See format of Efficacy Figure 2.11 (200862 'final' reporting effort)	SAC1
2.19.	PDo		Figure of Change from Baseline in Overall ACQ-5 score (Mean Change from Baseline at Each Visit by Treatment Group) (Part A)	See format of Efficacy Figure 2.11 (200862 'final' reporting effort)	SAC1
Childhood Asthma Control Test (C-ACT)					
2.20.	PDo		Figure of Change from Baseline in Overall C-ACT score (Mean Change from Baseline at Each Visit by Treatment Group) (Part A)	See format of Efficacy Figure 2.11 (200862 'final' reporting effort)	SAC1
FEV_1					
2.21.	PDo		Figure of Change from Baseline in Pre-Bronchodilator FEV_1 (mL) (Mean Change from Baseline at Each Visit by Treatment Group) (Part A)	See format of Efficacy Figure 2.09 (200862 'final' reporting effort)	SAC1
Exacerbations					
2.22.	PDo		Kaplan-Meier Cumulative Incidence Curve for Time to First Exacerbation (Part A)	See format of Efficacy Figure 2.15 (200862 'final' reporting effort)	SAC1

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable [Priority]
IL-5					
2.23.	PDo		Figure of Ratio to Baseline in IL-5 Data (Mean Change from Baseline at Each Visit by Treatment Group) (Part A)	See format of Efficacy Figure 6.18 (MEA115588 'final' reporting effort)	SAC1

10.10.2.6. Safety Tables

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure					
3.1.	Safety		Summary of Number of Treatments Administered and Time On-Treatment (Part A)	See format of Study Population Table 1.28 (200862 'final' reporting effort)	SAC1
AEs					
3.2.	Safety		Overview of All Adverse Events (Part A)	See format of Safety Table 3.01 (200862 'final' reporting effort)	SAC1
3.3.	Safety	AE1	Summary of All On-Treatment Adverse Events by System Organ Class (Part A)		SAC1
3.4.	Safety	AE5	Summary of All On-Treatment Adverse Events by System Organ Class and Maximum Intensity (Part A)	Add a Total column across all severities	SAC1
3.5.	Safety	AE1	Summary of All Post-Treatment Adverse Events by System Organ Class (Part A)		SAC1
3.6.	Safety	AE5	Summary of All Post-Treatment Adverse Events by System Organ Class and Maximum Intensity (Part A)	Add a Total column across all severities	SAC1
3.7.	Safety	AE3	Summary of On-Treatment Adverse Events by Overall Frequency (Part A)		SAC1
3.8.	Safety	AE1	Summary of All On-Treatment Drug-Related Adverse Events by System Organ Class (Part A)		SAC1
3.9.	Safety	AE5	Summary of All On-Treatment Drug-Related Adverse Events by System Organ Class and Maximum Intensity (Part A)	Add a Total column across all severities	SAC1
3.10.	Safety	AE1	Summary of On-Treatment Adverse Events by Highest Anti Drug Antibody Result At Any Time Post Baseline (Part A)	Add in row with n in each ADA result category	SAC1

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.11.	Safety	AE1	Summary of Post-Treatment Adverse Events by Highest Anti Drug Antibody Result At Any Time Post Baseline (Part A)	Add in row with n in each ADA result category	SAC1
3.12.	Safety	AE15	Summary of Number of Subjects and Occurrences of Common On-Treatment Non-Serious Adverse Events by System Organ Class (Part A)	≥3% (prior to rounding to nearest percent) XML file to be produced using standard HARP macro	SAC1
Serious and Other Significant AEs					
3.13.	Safety	AE1	Summary of Fatal Serious Adverse Events by System Organ Class (Part A)		SAC1
3.14.	Safety	AE1	Summary of Non-Fatal Serious On-Treatment Adverse Events by System Organ Class (Part A)		SAC1
3.15.	Safety	AE1	Summary of Non-Fatal Serious Post-Treatment Adverse Events by System Organ Class (Part A)		SAC1
3.16.	Safety	AE1	Summary of On-Treatment Serious Adverse Events by System Organ Class (Part A)		SAC1
3.17.	Safety	AE1	Summary of Post-Treatment Serious Adverse Events by System Organ Class (Part A)		SAC1
3.18.	Safety	AE1	Summary of Drug-Related Serious Adverse Events by System Organ Class (Part A)		SAC1
3.19.	Safety	AE1	Summary of Drug-Related Serious Adverse Events by System Organ Class and Maximum Severity (Part A)	Add a Total column across all severities	SAC1
3.20.	Safety	AE3	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by Overall Frequency (Part A)		SAC1

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.21.	Safety	AE16	Summary of Number of Subjects and Occurrences of Serious Adverse Events by System Organ Class and Preferred Term (Part A)		SAC1
Adverse Events of Special Interest					
3.22.	Safety	AE3	Summary of Systemic(non-allergic or allergic/hypersensitivity) Reactions (On-Treatment) (Part A)	Footnote 'Events defined by the investigator as being a Systemic Reaction'	SAC1
3.23.	Safety		Summary Profile of Systemic (non-allergic or allergic/hypersensitivity) Reactions (On-Treatment) (Part A)	See format of Safety Table 3.23 (200862 'final' reporting effort) Footnote 'Events defined by the investigator as being a Systemic Reaction'	SAC1
3.24.	Safety		Summary Profile of Systemic Allergic Reactions (On-Treatment) (Part A)	See format of Safety Table 3.24 (200862 'final' reporting effort) Footnote 'Events defined by the investigator as being a Systemic Reaction'	SAC1
3.25.	Safety		Summary Profile of Systemic Non-Allergic Reactions (On-Treatment) (Part A)	See format of Safety Table 3.25 (200862 'final' reporting effort) Footnote 'Events defined by the investigator as being a Systemic Reaction'	SAC1
3.26.	Safety	AE3	Summary of Local Injection Site Reactions (On-Treatment) (Part A)	Footnote 'Events defined by the investigator as being a Local Injection Site Reaction'	SAC1

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.27.	Safety		Summary of Local Injection Site Reactions by Relation to IP (On-Treatment) (Part A)	See format of Safety Table 3.28 (200862 'final' reporting effort) Footnote 'Events defined by the investigator as being a Local Injection Site Reaction'	SAC1
3.28.	Safety		Summary Profile of Local Injection Site Reactions (On-Treatment) (Part A)	See format of Safety Table 3.29 (200862 'final' reporting effort) Footnote 'Events defined by the investigator as being a Local Injection Site Reaction'	SAC1
3.29.	Safety	AE1	Summary of AEs meeting Anaphylaxis Criteria (On-Treatment) (Part A)	Present Anaphylactic Criterion 1,2 and 3 rather than SOC as shown in AE1 Footnote 'Events identified by the investigator as meeting the criteria for anaphylaxis'	SAC1
3.30.	Safety		Summary Profile of AEs meeting Anaphylaxis Criteria (On-Treatment) (Part A)	See format of Safety Table 3.31 (200862 'final' reporting effort) Footnote 'Events identified by the investigator as meeting the criteria for anaphylaxis'	SAC1
3.31.	Safety	AE1	Summary of Serious Cardiac, Vascular and Thromboembolic Adverse Events (On-Treatment) (Part A)	Footnote 'Serious events in the Cardiac Disorders and Vascular Disorders MedDRA System Organ Classes, thromboembolic events identified via SMQs and sub-SMQs'	SAC1

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.32.	Safety		Summary Profile of Serious Cardiac, Vascular and Thromboembolic Adverse Events (On-Treatment) (Part A)	See format of Safety Table 3.33 (200862 'final' reporting effort) Footnote 'Serious events in the Cardiac Disorders and Vascular Disorders MedDRA System Organ Classes, thromboembolic events identified via SMQs and sub-SMQs'	SAC1
3.33.	Safety	AE3	Summary of Serious Ischemic AEs (On-Treatment) (Part A)	Footnote 'Serious Ischemic events, a subset of serious cardiac, vascular and thromboembolic events, identified via SMQs and sub-SMQs'	SAC1
3.34.	Safety		Summary Profile of Serious Ischemic AEs (On-Treatment) (Part A)	See format of Safety Table 3.35 (200862 'final' reporting effort) Footnote 'Serious Ischemic events, a subset of serious cardiac, vascular and thromboembolic events, identified via SMQs and sub-SMQs'	SAC1
3.35.	Safety	AE3	Summary of Malignancies (On-Treatment) (Part A)	Footnote 'Events identified from sub-SMQs under the Malignancy SMQ'	SAC1
3.36.	Safety		Summary Profile of Malignancies (On-Treatment) (Part A)	See format of Safety Table 3.37 (200862 'final' reporting effort) Footnote 'Events identified from sub-SMQs under the Malignancy SMQ'	SAC1
3.37.	Safety	AE3	Summary of Opportunistic Infections (On-Treatment) (Part A)	Footnote 'Events matching terms based on a published list considered as opportunistic infections in the setting of biologic therapy [Winthrop, 2015]'	SAC1

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.38.	Safety		Summary Profile of Opportunistic Infections (On-Treatment) (Part A)	See format of Safety Table 3.39 (200862 'final' reporting effort) Footnote 'Events matching terms based on a published list considered as opportunistic infections in the setting of biologic therapy [Winthrop, 2015]'	SAC1
3.39.	Safety		Summary of Serious AEs and AEs of Special Interest (Part A)	See format of Safety Table 3.40 (200862 'final' reporting effort) Do not include Relative Risk or % Risk Difference columns	SAC1
Cardiovascular Events					
3.40.	Safety		Summary of All Cardiovascular Events Reported by the Investigator (Part A)	See format of Safety Table 3.11 (200862 'final' reporting effort)	SAC1
Immunogenicity					
3.41.	Safety		Summary of ADA Assay Results (Part A)	See format of Safety Table 3.41 (200862 'final' reporting effort)	SAC1
3.42.	Safety		Summary of NAb Assay Results (Part A)	See format of Safety Table 3.42 (200862 'final' reporting effort)	SAC1
3.43.	Safety		Summary of Treatment Emergent ADA Assay Results (Part A)	See format of Safety Table 3.41 (200862 'final' reporting effort)	SAC1
Laboratory Data					
3.44.	Safety	LB1	Summary of Change From Baseline in Chemistry Data (Part A)	Include Baseline values	SAC1
3.45.	Safety	LB3	Summary of Chemistry Results (Change from Baseline Relative to the Normal Range) (Part A)		SAC1
3.46.	Safety	LB1	Summary of Change From Baseline in Haematology Data (Part A)	Include Baseline values	SAC1

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.47.	Safety	LB3	Summary of Haematology Results (Change from Baseline Relative to the Normal Range) (Part A)		SAC1
Hepatobiliary (Liver)					
3.48.	Safety	LIVER10	Summary of Subjects Meeting Emergent Hepatobiliary Laboratory Abnormality Criteria (Part A)		SAC1
Electrocardiogram (ECG)					
3.49.	Safety	EG1	Summary of ECG Findings (Part A)		SAC1
3.50.	Safety	EG2	Summary of Change from Baseline ECG Values by Visit (Part A)	Include Baseline values	SAC1
3.51.	Safety		Summary of Actual and Change From Baseline QTc(F) Values by Category (msec) (Part A)	See format of Safety Table 7.50 (MEA115588 'final' reporting effort) See Section 10.6.4 for details Note: For Any Time Post-Baseline, the highest post-baseline QTc value and the change from baseline for this highest post-baseline QTc value is categorised	SAC1
3.52.	Safety		Summary of Actual and Change From Baseline QTc(B) Values by Category (msec) (Part A)	See format of Safety Table 7.50 (MEA115588 'final' reporting effort) See Section 10.6.4 for details Note: For Any Time Post-Baseline, the highest post-baseline QTc value and the change from baseline for this highest post-baseline QTc value is categorised	SAC1
Vital Signs					
3.53.	Safety	VS1	Summary of Change from Baseline in Vital Signs (Part A)	Include Baseline values	SAC1

10.10.2.7. Safety Figures

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory					
3.1.	Safety	LIVER9	Scatter Plot of Maximum vs. Baseline for ALT (Part A)		SAC1
3.2.	Safety	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin (Part A)		SAC1

10.10.2.8. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	ASE	ES7	Listing of Reasons for Screening or Run-In Failure (Part A)		SAC1
2.	Safety	IE3	Listing of Subjects within Inclusion/Exclusion Criteria Deviations (Part A)		SAC1
3.	Safety	ES2	Listing of Reasons for Premature Study Withdrawal (Part A)		SAC1
Demography					
4.	Safety	DM2	Listing of Demographic Characteristics (Part A)		SAC1
5.	Safety	DM9	Listing of Race (Part A)		SAC1
Concomitant Medication					
6.	Safety	CM6	Relationship Between ATC Level 1, Ingredient and Verbatim Text (Part A)	Include all asthma and non-asthma concomitant medications (including those given for exacerbation and rescue use)	SAC1
Protocol Deviations					
7.	Safety	DV2	Listing of Important Protocol Deviations (Part A)		SAC1
Blood Eosinophils					
8.	PDe		Listing of Blood Eosinophil Data (10^9/L) (Part A)	See format of Efficacy Listing 18 (200862 'final' reporting effort)	SAC1

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exacerbations					
9.	PDo		Listing of Exacerbations (Part A)	See format of Efficacy Listing 17 (200862 'final' reporting effort) Include Pre, on-treatment and Post-treatment events within Part A (See Section 10.4.2)	SAC1
IL-5					
10.	PDo		Listing of IL-5 Data (Part A)	See format of Efficacy Listing 18 (200862 'final' reporting effort)	SAC1
Exposure					
11.	Safety	EX3	Listing of Study Treatment Data (Part A)		SAC1
Adverse Events					
12.	Safety	AE8	Listing of All Adverse Events (Part A)		SAC1
13.	Safety	AE7	Listings of Subject Numbers for Individual Adverse Events (Part A)		SAC1
14.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text (Part A)		SAC1
15.	Safety	AE8	Listing of all Fatal Adverse Events (Part A)		SAC1
16.	Safety	AE8	Listing of Non-Fatal Serious Adverse Events (Part A)		SAC1
17.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event (Part A)		SAC1
18.	Safety	AE8	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by Overall Frequency (Part A)		SAC1

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
19.	Safety		Listing of Adverse Events Defined by the Investigator as a Systemic (non-allergic or allergic/hypersensitivity) Injection Reaction (Part A)	See format of Safety Listing 26 (200862 'final' reporting effort)	SAC1
20.	Safety		Listing of Adverse Events Defined by the Investigator as a Local Injection Site Reaction (Part A)	See format of Safety Listing 27 (200862 'final' reporting effort)	SAC1
21.	Safety		Listing of AEs meeting Anaphylaxis Criteria (Part A)	See format of Safety Listing 28 (200862 'final' reporting effort)	SAC1
22.	Safety		Listing of Serious Cardiac, Vascular and Thromboembolic (CVT) AEs (Part A)	See format of Safety Listing 29 (200862 'final' reporting effort)	SAC1
23.	Safety		Listing of Serious Ischemic AEs (Part A)	See format of Safety Listing 30 (200862 'final' reporting effort)	SAC1
24.	Safety		Listing of Malignancies (Part A)	See format of Safety Listing 31 (200862 'final' reporting effort)	SAC1
25.	Safety		Listing of Opportunistic Infections (Part A)	See format of Safety Listing 32 (200862 'final' reporting effort)	SAC1
Cardiovascular Events					
26.	Safety		Listing of Investigator Reported Cardiovascular Events: Arrhythmias (Part A)	See format of Safety Listing 33 (200862 'final' reporting effort)	SAC1
27.	Safety		Listing of Investigator Reported Cardiovascular Events: Congestive Heart Failure (Part A)	See format of Safety Listing 34 (200862 'final' reporting effort)	SAC1
28.	Safety		Listing of Investigator Reported Cardiovascular Events: Cerebrovascular Events/Stroke (Part A)	See format of Safety Listing 35 (200862 'final' reporting effort)	SAC1
29.	Safety		Listing of Investigator Reported Cardiovascular Events: Deep venous Thrombosis/ Pulmonary Embolism (Part A)	See format of Safety Listing 36 (200862 'final' reporting effort)	SAC1

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
30.	Safety		Listing of Investigator Reported Cardiovascular Events: Myocardial Infarction/Unstable Angina (Part A)	See format of Safety Listing 37 (200862 'final' reporting effort)	SAC1
31.	Safety		Listing of Investigator Reported Cardiovascular Events: Peripheral Arterial Thrombosis Embolism (Part A)	See format of Safety Listing 38 (200862 'final' reporting effort)	SAC1
32.	Safety		Listing of Investigator Reported Cardiovascular Events: Pulmonary Hypertension (Part A)	See format of Safety Listing 39 (200862 'final' reporting effort)	SAC1
33.	Safety		Listing of Investigator Reported Cardiovascular Events: Revascularisation (Part A)	See format of Safety Listing 40 (200862 'final' reporting effort)	SAC1
34.	Safety		Listing of Investigator Reported Cardiovascular Events: Valvulopathy (Part A)	See format of Safety Listing 41 (200862 'final' reporting effort)	SAC1
35.	Safety		Listing of Investigator Reported Cardiovascular Events: All Cause Deaths (Part A)	See format of Safety Listing 42 (200862 'final' reporting effort)	SAC1
Immunogenicity					
36.	Safety		Listing of Immunogenicity Results (Part A)	See format of Safety Listing 43 (200862 'final' reporting effort)	SAC1
Laboratory Data					
37.	Safety		Listing of Urinalysis (Part A)	See format of Safety Listing 44 (200862 'final' reporting effort)	SAC1
Liver Event					
38.	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting (Part A)		SAC1
39.	Safety	LB5	Chemistry Results for Subjects Meeting Liver Monitoring/Stopping Event Criteria (Part A)	Subset for subjects in above Liver Monitoring/Stopping Event listing	SAC1
40.	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events (Part A)		SAC1

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
41.	Safety	SU2	Listing of Substance Use for Subjects with Liver Stopping Events (Part A)		SAC1
42.	Safety	LIVER13	Listing of Subjects Meeting Hepatobiliary Laboratory Criteria Post-Baseline (Part A)		SAC1
Electrocardiogram (ECG)					
43.	Safety	EG6	Listing of ECG Findings for Abnormal Interpretations (Part A)	See format of Safety Listing 7.32 (MEA115588 'final' reporting effort)	SAC1

10.10.2.9. Non-ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK					
44.	PK		Listing of Mepolizumab Plasma Pharmacokinetic Concentration Data (Observed and Predicted)	See format of Safety Listing 10.01 (MEA115588 'final' reporting effort)	SAC1
45.	PK		Listing of Individual Model-Predicted and Derived Plasma Mepolizumab Pharmacokinetic Parameters	See format of Safety Listing 10.02 (MEA115588 'final' reporting effort)	SAC1
46.	PK		Listing of Data and Subjects Excluded from PK Analysis	Provided by CPMS	SAC1
47.	PK	N/A	Final PK Model Listings (Primary Endpoint)	Provided by CPMS	SAC1
48.	PK	N/A	Output from the Validation of the Final PK Model	Provided by CPMS	SAC1
PK (Exploratory Analysis)					
49.	PK	N/A	Final PK Model Listings (Exploratory Endpoint)	Provided by CPMS	SAC2
PKPD (Exploratory Analysis)					
50.	PKPD		Listing of Data and Subjects Excluded from PKPD Analysis (only if different from PK analysis)	Provided by CPMS	SAC2
51.	PKPD	N/A	Final PKPD Model Listings (Exploratory Endpoint)	Provided by CPMS	SAC2

10.10.3. Part B

10.10.3.1. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable Priority**
Subject Disposition					
1.23.	Safety	SA1	Summary of Subject Populations (Part B)		SAC
1.24.	Safety	ES1	Summary of Subject Disposition (Part B)	Should include subject disposition, reason for withdrawal.	SAC
Prior and Concomitant Medications					
1.25.	Safety		Summary of Asthma Concomitant Medication Taken During Treatment by Respiratory Medication Class (Part B)	See format of Study Population Table 1.23 (200862 'final' reporting effort)	SAC
1.26.	Safety		Summary of Asthma Concomitant Medication Taken Post-Treatment by Respiratory Medication Class (Part B)	See format of Study Population Table 1.25 (200862 'final' reporting effort)	SAC
1.27.	Safety	CM1	Summary of non-Asthma Concomitant Medication Taken During Treatment (Part B)		SAC
Protocol Deviations					
1.28.	Safety	DV1B	Summary of Important Protocol Deviations (Part B)		SAC

10.10.3.2. Efficacy Tables

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable [Priority]
Blood Eosinophil Count					
2.25.	PDe		Summary of Blood Eosinophil Count (Part B)	Log transformed with geometric mean, include ratio to baseline See format of Efficacy Table 2.73 (200862 'final' reporting effort) To also include 95% CIs by visit	SAC
Asthma Control Questionnaire					
2.26.	PDo		Summary of ACQ-7 Score (Part B)	See format of Efficacy Table 2.34 (200862 'final' reporting effort) To also include 95% CIs by visit	SAC
2.27.	PDo		Summary of 0.5 Point or More Reduction in ACQ-7 Score from Baseline (Part B)	See format of Efficacy Table 2.41 (200862 'final' reporting effort). Note: Logistic regression to not be included and Odds Ratio to not be shown	SAC
2.28.	PDo		Summary of ACQ-5 Score (Part B)	See format of Efficacy Table 2.34 (200862 'final' reporting effort) To also include 95% CIs by visit	SAC
2.29.	PDo		Summary of 0.5 Point or More Reduction in ACQ-5 Score from Baseline (Part B)	See format of Efficacy Table 2.41 (200862 'final' reporting effort). Note: Logistic regression to not be included and Odds Ratio to not be shown	SAC

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable [Priority]
Childhood Asthma Control Test (C-ACT)					
2.30.	PDo		Summary of C-ACT Score (Part B)	See format of Efficacy Table 2.34 (200862 'final' reporting effort) To also include 95% CIs by visit	SAC
FEV1					
2.31.	PDo		Summary of FEV_1 (Part B)	See format of Efficacy Table 2.27 (200862 'final' reporting effort) To also include 95% CIs by visit	SAC
Asthma Exacerbations					
2.32.	PDo		Overview of Asthma Exacerbations (Part B)	See format of Efficacy Table 2.61 (200862 'final' reporting effort).	SAC
2.33.	PDo		Summary of Frequency of Exacerbations (Week 20 –Week 72) (Part B)	See format of Efficacy Table 2.62 (200862 'final' reporting effort)	SAC
2.34.	PDo		Summary of Time to First Asthma Exacerbation (Part B)	See format of Efficacy Table 2.68 (200862 'final' reporting effort)	SAC

10.10.3.3. Efficacy Figures

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable [Priority]
Blood Eosinophil Count					
2.24.	PDe		Figure of Absolute Blood Eosinophil Count (Mean Change from Baseline at Each Visit by Treatment Group) (Part B)	See format of Efficacy Figure 6.18 (MEA115588 'final' reporting effort)	SAC
2.25.	PDe		Figure of Ratio of Blood Eosinophil Count to Baseline (Mean Change from Baseline at Each Visit by Treatment Group) (Part B)	See format of Efficacy Figure 6.18 (MEA115588 'final' reporting effort)	SAC

10.10.3.4. Safety Tables

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure					
3.54.	Safety		Summary of Number of Treatments Administered and Time On-Treatment (Part B)	See format of Study Population Table 1.28 (200862 'final' reporting effort)	SAC
AEs					
3.55.	Safety		Overview of All Adverse Events (Part B)	See format of Safety Table 3.01 (200862 'final' reporting effort)	SAC
3.56.	Safety	AE1	Summary of All On-Treatment Adverse Events by System Organ Class (Part B)		SAC
3.57.	Safety	AE5	Summary of All On-Treatment Adverse Events by System Organ Class and Maximum Intensity (Part B)	Add a Total column across all severities	SAC
3.58.	Safety	AE1	Summary of All Post-Treatment Adverse Events by System Organ Class (Part B)		SAC
3.59.	Safety	AE5	Summary of All Post-Treatment Adverse Events by System Organ Class and Maximum Intensity (Part B)	Add a Total column across all severities	SAC
3.60.	Safety	AE3	Summary of On-Treatment Adverse Events by Overall Frequency (Part B)		SAC
3.61.	Safety	AE1	Summary of All On-Treatment Drug-Related Adverse Events by System Organ Class (Part B)		SAC
3.62.	Safety	AE5	Summary of All On-Treatment Drug-Related Adverse Events by System Organ Class and Maximum Intensity (Part B)	Add a Total column across all severities	SAC
3.63.	Safety	AE1	Summary of On-Treatment Adverse Events by Highest Anti Drug Antibody Result At Any Time Post Baseline (Part B)	Add in row with n in each ADA result category	SAC

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.64.	Safety	AE1	Summary of Post-Treatment Adverse Events by Highest Anti Drug Antibody Result At Any Time Post Baseline (Part B)	Add in row with n in each ADA result category	SAC
3.65.	Safety	AE15	Summary of Number of Subjects and Occurrences of Common On-Treatment Non-Serious Adverse Events by System Organ Class (Part B)	≥3% (prior to rounding to nearest percent) XML file to be produced using standard HARP macro	SAC
Serious and Other Significant AEs					
3.66.	Safety	AE1	Summary of Fatal Serious Adverse Events by System Organ Class (Part B)		SAC
3.67.	Safety	AE1	Summary of Non-Fatal Serious On-Treatment Adverse Events by System Organ Class (Part B)		SAC
3.68.	Safety	AE1	Summary of Non-Fatal Serious Post-Treatment Adverse Events by System Organ Class (Part B)		SAC
3.69.	Safety	AE1	Summary of On-Treatment Serious Adverse Events by System Organ Class (Part B)		SAC
3.70.	Safety	AE1	Summary of Post-Treatment Serious Adverse Events by System Organ Class (Part B)		SAC
3.71.	Safety	AE1	Summary of Drug-Related Serious Adverse Events by System Organ Class (Part B)		SAC
3.72.	Safety	AE1	Summary of Drug-Related Serious Adverse Events by System Organ Class and Maximum Severity (Part B)	Add a Total column across all severities	SAC
3.73.	Safety	AE3	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by Overall Frequency (Part B)		SAC

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.74.	Safety	AE16	Summary of Number of Subjects and Occurrences of Serious Adverse Events by System Organ Class and Preferred Term (Part B)		SAC
Adverse Events of Special Interest					
3.75.	Safety	AE3	Summary of Systemic(non-allergic or allergic/hypersensitivity) Reactions (On-Treatment) (Part B)	Footnote 'Events defined by the investigator as being a Systemic Reaction'	SAC
3.76.	Safety		Summary Profile of Systemic (non-allergic or allergic/hypersensitivity) Reactions (On-Treatment) (Part B)	See format of Safety Table 3.23 (200862 'final' reporting effort) Footnote 'Events defined by the investigator as being a Systemic Reaction'	SAC
3.77.	Safety		Summary Profile of Systemic Allergic Reactions (On-Treatment) (Part B)	See format of Safety Table 3.24 (200862 'final' reporting effort) Footnote 'Events defined by the investigator as being a Systemic Reaction'	SAC
3.78.	Safety		Summary Profile of Systemic Non-Allergic Reactions (On-Treatment) (Part B)	See format of Safety Table 3.25 (200862 'final' reporting effort) Footnote 'Events defined by the investigator as being a Systemic Reaction'	SAC
3.79.	Safety	AE3	Summary of Local Injection Site Reactions (On-Treatment) (Part B)	Footnote 'Events defined by the investigator as being a Local Injection Site Reaction'	SAC

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.80.	Safety		Summary of Local Injection Site Reactions by Relation to IP (On-Treatment) (Part B)	See format of Safety Table 3.28 (200862 'final' reporting effort) Footnote 'Events defined by the investigator as being a Local Injection Site Reaction'	SAC
3.81.	Safety		Summary Profile of Local Injection Site Reactions (On-Treatment) (Part B)	See format of Safety Table 3.29 (200862 'final' reporting effort) Footnote 'Events defined by the investigator as being a Local Injection Site Reaction'	SAC
3.82.	Safety	AE1	Summary of AEs meeting Anaphylaxis Criteria (On-Treatment) (Part B)	Present Anaphylactic Criterion 1,2 and 3 rather than SOC as shown in AE1 Footnote 'Events identified by the investigator as meeting the criteria for anaphylaxis'	SAC
3.83.	Safety		Summary Profile of AEs meeting Anaphylaxis Criteria (On-Treatment) (Part B)	See format of Safety Table 3.31 (200862 'final' reporting effort) Footnote 'Events identified by the investigator as meeting the criteria for anaphylaxis'	SAC
3.84.	Safety	AE1	Summary of Serious Cardiac, Vascular and Thromboembolic Adverse Events (On-Treatment) (Part B)	Footnote 'Serious events in the Cardiac Disorders and Vascular Disorders MedDRA System Organ Classes, thromboembolic events identified via SMQs and sub-SMQs'	SAC

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.85.	Safety		Summary Profile of Serious Cardiac, Vascular and Thromboembolic Adverse Events (On-Treatment) (Part B)	See format of Safety Table 3.33 (200862 'final' reporting effort) Footnote 'Serious events in the Cardiac Disorders and Vascular Disorders MedDRA System Organ Classes, thromboembolic events identified via SMQs and sub-SMQs'	SAC
3.86.	Safety	AE3	Summary of Serious Ischemic AEs (On-Treatment) (Part B)	Footnote 'Serious Ischemic events, a subset of serious cardiac, vascular and thromboembolic events, identified via SMQs and sub-SMQs'	SAC
3.87.	Safety		Summary Profile of Serious Ischemic AEs (On-Treatment) (Part B)	See format of Safety Table 3.35 (200862 'final' reporting effort) Footnote 'Serious Ischemic events, a subset of serious cardiac, vascular and thromboembolic events, identified via SMQs and sub-SMQs'	SAC
3.88.	Safety	AE3	Summary of Malignancies (On-Treatment) (Part B)	Footnote 'Events identified from sub-SMQs under the Malignancy SMQ'	SAC
3.89.	Safety		Summary Profile of Malignancies (On-Treatment) (Part B)	See format of Safety Table 3.37 (200862 'final' reporting effort) Footnote 'Events identified from sub-SMQs under the Malignancy SMQ'	SAC
3.90.	Safety	AE3	Summary of Opportunistic Infections (On-Treatment) (Part B)	Footnote 'Events matching terms based on a published list considered as opportunistic infections in the setting of biologic therapy [Winthrop, 2015]'	SAC

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.91.	Safety		Summary Profile of Opportunistic Infections (On-Treatment) (Part B)	See format of Safety Table 3.39 (200862 'final' reporting effort) Footnote 'Events matching terms based on a published list considered as opportunistic infections in the setting of biologic therapy [Winthrop, 2015]'	SAC
3.92.	Safety		Summary of Serious AEs and AEs of Special Interest (Part B)	See format of Safety Table 3.40 (200862 'final' reporting effort) Do not include Relative Risk or % Risk Difference columns	SAC
Cardiovascular Events					
3.93.	Safety		Summary of All Cardiovascular Events Reported by the Investigator (Part B)	See format of Safety Table 3.11 (200862 'final' reporting effort)	SAC
Immunogenicity					
3.94.	Safety		Summary of ADA Assay Results (Part B)	See format of Safety Table 3.41 (200862 'final' reporting effort)	SAC
3.95.	Safety		Summary of NAb Assay Results (Part B)	See format of Safety Table 3.42 (200862 'final' reporting effort)	SAC
3.96.	Safety		Summary of Treatment Emergent ADA Assay Results (Part B)	See format of Safety Table 3.41 (200862 'final' reporting effort)	SAC
Laboratory Data					
3.97.	Safety	LB1	Summary of Change From Baseline in Chemistry Data (Part B)	Include Baseline values	SAC
3.98.	Safety	LB3	Summary of Chemistry Results (Change from Baseline Relative to the Normal Range) (Part B)		SAC
3.99.	Safety	LB1	Summary of Change From Baseline in Haematology Data (Part B)	Include Baseline values	SAC

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.100.	Safety	LB3	Summary of Haematology Results (Change from Baseline Relative to the Normal Range) (Part B)		SAC
Hepatobiliary (Liver)					
3.101.	Safety	LIVER10	Summary of Subjects Meeting Emergent Hepatobiliary Laboratory Abnormality Criteria (Part A)		SAC
Electrocardiogram (ECG)					
3.102.	Safety	EG1	Summary of ECG Findings (Part B)		SAC
3.103.	Safety	EG2	Summary of Change from Baseline ECG Values by Visit (Part B)	Include Baseline values	SAC
3.104.	Safety		Summary of Actual and Change From Baseline QTc(F) Values by Category (msec) (Part B)	See format of Safety Table 7.50 (MEA115588 'final' reporting effort) See Section 10.6.4 for details Note: For Any Time Post-Baseline, the highest post-baseline QTc value and the change from baseline for this highest post-baseline QTc value is categorised	SAC
3.105.	Safety		Summary of Actual and Change From Baseline QTc(B) Values by Category (msec) (Part B)	See format of Safety Table 7.50 (MEA115588 'final' reporting effort) See Section 10.6.4 for details Note: For Any Time Post-Baseline, the highest post-baseline QTc value and the change from baseline for this highest post-baseline QTc value is categorised	SAC
Vital Signs					
3.106.	Safety	VS1	Summary of Change from Baseline in Vital Signs (Part B)	Include Baseline values	SAC

10.10.3.5. Safety Figures

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory					
3.3.	Safety	LIVER9	Scatter Plot of Maximum vs. Baseline for ALT (Part B)		SAC
3.4.	Safety	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin (Part B)		SAC

10.10.3.6. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
52.	Safety	ES2	Listing of Reasons for Premature Study Withdrawal (Part B)		SAC
Concomitant Medication					
53.	Safety	CM6	Relationship Between ATC Level 1, Ingredient and Verbatim Text (Part B)	Include all asthma and non-asthma concomitant medications (including those given for exacerbation and rescue use)	SAC
Protocol Deviations					
54.	Safety	DV2	Listing of Important Protocol Deviations (Part B)		SAC
Blood Eosinophils					
55.	PDe		Listing of Blood Eosinophil Data (10^9/L) (Part B)	See format of Efficacy Listing 18 (200862 'final' reporting effort)	SAC
Exacerbations					
56.	PDo		Listing of Exacerbations (Part B)	See format of Efficacy Listing 17 (200862 'final' reporting effort) Include Pre, on-treatment and Post-treatment events within Part A (See Section 10.4.2)	SAC
Exposure					
57.	Safety	EX3	Listing of Study Treatment Data (Part B)		SAC
Adverse Events					
58.	Safety	AE8	Listing of All Adverse Events (Part B)		SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
59.	Safety	AE7	Listings of Subject Numbers for Individual Adverse Events (Part B)		SAC
60.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text (Part B)		SAC
61.	Safety	AE8	Listing of all Fatal Adverse Events (Part B)		SAC
62.	Safety	AE8	Listing of Non-Fatal Serious Adverse Events (Part B)		SAC
63.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event (Part B)		SAC
64.	Safety	AE8	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by Overall Frequency (Part B)		SAC
65.	Safety		Listing of Adverse Events Defined by the Investigator as a Systemic (non-allergic or allergic/hypersensitivity) Injection Reaction (Part B)	See format of Safety Listing 26 (200862 'final' reporting effort)	SAC
66.	Safety		Listing of Adverse Events Defined by the Investigator as a Local Injection Site Reaction (Part B)	See format of Safety Listing 27 (200862 'final' reporting effort)	SAC
67.	Safety		Listing of AEs meeting Anaphylaxis Criteria (Part B)	See format of Safety Listing 28 (200862 'final' reporting effort)	SAC
68.	Safety		Listing of Serious Cardiac, Vascular and Thromboembolic (CVT) AEs (Part B)	See format of Safety Listing 29 (200862 'final' reporting effort)	SAC
69.	Safety		Listing of Serious Ischemic AEs (Part B)	See format of Safety Listing 30 (200862 'final' reporting effort)	SAC
70.	Safety		Listing of Malignancies (Part B)	See format of Safety Listing 31 (200862 'final' reporting effort)	SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
71.	Safety		Listing of Opportunistic Infections (Part B)	See format of Safety Listing 32 (200862 'final' reporting effort)	SAC
Cardiovascular Events					
72.	Safety		Listing of Investigator Reported Cardiovascular Events: Arrhythmias (Part B)	See format of Safety Listing 33 (200862 'final' reporting effort)	SAC
73.	Safety		Listing of Investigator Reported Cardiovascular Events: Congestive Heart Failure (Part B)	See format of Safety Listing 34 (200862 'final' reporting effort)	SAC
74.	Safety		Listing of Investigator Reported Cardiovascular Events: Cerebrovascular Events/Stroke (Part B)	See format of Safety Listing 35 (200862 'final' reporting effort)	SAC
75.	Safety		Listing of Investigator Reported Cardiovascular Events: Deep venous Thrombosis/ Pulmonary Embolism (Part B)	See format of Safety Listing 36 (200862 'final' reporting effort)	SAC
76.	Safety		Listing of Investigator Reported Cardiovascular Events: Myocardial Infarction/Unstable Angina (Part B)	See format of Safety Listing 37 (200862 'final' reporting effort)	SAC
77.	Safety		Listing of Investigator Reported Cardiovascular Events: Peripheral Arterial Thrombosis Embolism (Part B)	See format of Safety Listing 38 (200862 'final' reporting effort)	SAC
78.	Safety		Listing of Investigator Reported Cardiovascular Events: Pulmonary Hypertension (Part B)	See format of Safety Listing 39 (200862 'final' reporting effort)	SAC
79.	Safety		Listing of Investigator Reported Cardiovascular Events: Revascularisation (Part B)	See format of Safety Listing 40 (200862 'final' reporting effort)	SAC
80.	Safety		Listing of Investigator Reported Cardiovascular Events: Valvulopathy (Part B)	See format of Safety Listing 41 (200862 'final' reporting effort)	SAC
81.	Safety		Listing of Investigator Reported Cardiovascular Events: All Cause Deaths (Part B)	See format of Safety Listing 42 (200862 'final' reporting effort)	SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Immunogenicity					
82.	Safety		Listing of Immunogenicity Results (Part B)	See format of Safety Listing 43 (200862 'final' reporting effort)	SAC
Laboratory Data					
83.	Safety		Listing of Urinalysis (Part B)	See format of Safety Listing 44 (200862 'final' reporting effort)	SAC
Liver Event					
84.	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting (Part B)		SAC
85.	Safety	LB5	Chemistry Results for Subjects Meeting Liver Monitoring/Stopping Event Criteria (Part B)	Subset for subjects in above Liver Monitoring/Stopping Event listing	SAC
86.	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events (Part B)		SAC
87.	Safety	SU2	Listing of Substance Use for Subjects with Liver Stopping Events (Part B)		SAC
88.	Safety	LIVER13	Listing of Subjects Meeting Hepatobiliary Laboratory Criteria Post-Baseline (Part B)		SAC
Electrocardiogram (ECG)					
89.	Safety	EG6	Listing of ECG Findings for Abnormal Interpretations (Part B)	See format of Safety Listing 7.32 (MEA115588 'final' reporting effort)	SAC

10.11. Appendix 11: Example Mock Shells for Data Displays

See Supplementary RAP material