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

Title	:	Reporting and Analysis Plan for Study 201810, A multi-center, randomized, double-blind, placebo controlled, parallel group study to compare cessation versus continuation of long-term mepolizumab treatment in patients with severe eosinophilic asthma
Compound Number	:	SB-240563
Effective Date	:	20-MAR-2019

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 201810.
- The critical components RAP was completed on the 2nd December 2015. This document represents the final RAP which will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 201810:

Revision Chronology of Protocol:		
GSK Document Number	**Date**	**Version**
2015N232375_00	20-May-2015	Original
2015N232375_01	23-Jun-2015	Republished Original Protocol
2015N232375_02	06-Nov-2015	Amendment No. 1
2015N232375_03	07-Jul-2016	Amendment No. 2

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

This RAP is based on the protocol amendment 02 (Dated: 07-Jul-2016) of study 201810 (GSK Document No: 2015N232375_03) and eCRF Version 1.0.

There were no changes or deviations to the originally planned statistical analysis specified in protocol amendment 02 (Dated: 07-Jul-2016).

2.2. Study Objective(s)

2.2.1. Primary Objective

- To evaluate whether patients with severe eosinophilic asthma who have received long-term treatment with mepolizumab (at least 3 years) need to maintain treatment with mepolizumab to continue to receive benefit.

2.2.2. Secondary Objective

- To assess the safety and tolerability of mepolizumab continuation compared to placebo following long-term treatment with mepolizumab in patients with severe eosinophilic asthma.

2.3. Study Endpoint(s)

2.3.1. Primary Endpoint

- Time to first clinically significant exacerbation

  Clinically significant exacerbations will be defined as worsening of asthma which requires use of systemic corticosteroids[1] and/or hospitalisation and/or ED visits.

  [1]For all subjects, i.v. or oral corticosteroid (e.g., prednisone) for at least 3 days or a single intramuscular (IM) corticosteroid dose is required. For subjects on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days is required.

2.3.2. Secondary Endpoints

- Ratio to baseline in blood eosinophil count at weeks 12, 24, 36 and 52
- Time to a decrease in asthma control, defined as an increase from baseline in Asthma Control Questionnaire-5 (ACQ-5) score of $\geq$ 0.5 units
- Time to first exacerbation requiring hospitalization or ED visit

2.3.3. Other Endpoints

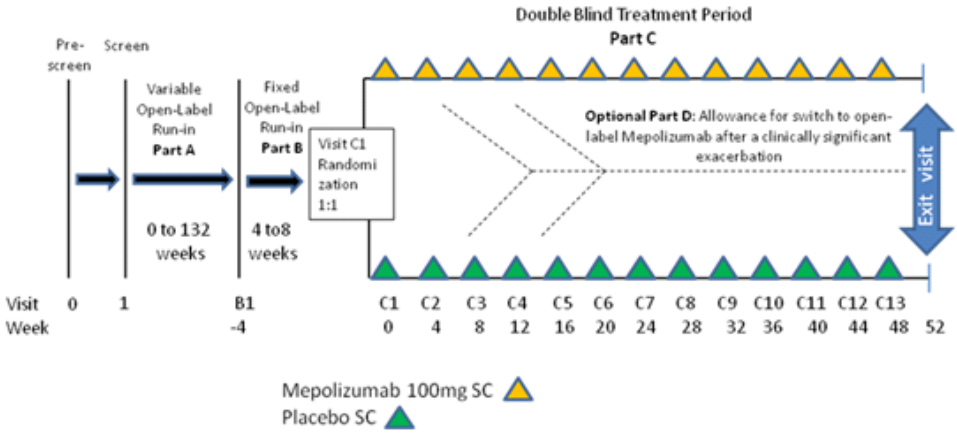
- Time to first exacerbation requiring hospitalization
- Mean change from baseline in clinic pre-bronchodilator FEV_1 at weeks 12, 24, 36, 52
- Mean change from baseline in clinic post-bronchodilator FEV_1 at weeks 12, 24, 36, 52
- Mean change from baseline in daily salbutamol/albuterol use (occasions/day)
- Mean change from baseline in daily asthma symptom scores
- Mean change from baseline in awakening at night due to asthma symptoms requiring rescue medication use
- Mean change from baseline in morning (AM) Peak Expiratory Flow (PEF)
- Time to worsening of asthma (subjects meeting at least 2 of the following 4 criteria for worsening of asthma for at least 2 consecutive days)
  - **AM PEF:** Decrease in AM PEF ≥30% compared with baseline
  - **Rescue Medication Use:** An increase of ≥50% in rescue medication compared with the average use for the previous week
  - **Night time awakenings requiring rescue medication:** Awakening due to asthma symptoms requiring rescue medication
  - **Symptoms:** An asthma symptom score of 5
- Mean change from baseline in ACQ-5 score

- Proportion of patients experiencing a decrease in asthma control, defined as an increase from baseline in ACQ-5 score of ≥ 0.5 units
- Proportion of subjects with a clinically meaningful worsening of health-related quality of life measurements (SGRQ) at weeks 12, 24, 36 and 52 (defined as subjects who have a clinically relevant increase from baseline of ≥4 units in SGRQ score).
- Mean change from baseline in SGRQ Total score at week 12, 24, 36 and 52
- Subject/Clinician global impression of asthma severity rating at weeks 12, 24, 36 and 52
- Subject/Clinician rating of response to therapy at weeks 12, 24, 36 and 52
- Number of days in hospital due to asthma
- Unscheduled healthcare contacts/resource utilization
- Days off of regular work/school

2.3.4. Safety Endpoints

- Adverse Events and Serious Adverse Events
- Clinical Laboratory parameters
- 12-lead ECG parameters
- Vital Signs

2.4. Study Design

Overview of Study Design and Key Features	
	
Design Features	• A 52-week, 2-arm, randomized, double-blind, placebo-controlled, parallel-group, multicenter study evaluating mepolizumab 100 mg and placebo administered subcutaneously (SC) every 4 weeks in subjects with severe eosinophilic asthma who have been treated with mepolizumab continuously in addition to standard of care therapy for at least 3 years. • Prior to randomization subjects are required to have reached a total of 3 years continuous exposure to mepolizumab treatment. If a subject has over 3 years continuous exposure to mepolizumab treatment at Screening they will immediately enter Part B of the study. Subjects with less than 3 years at Screening will be dosed within Part A until they achieve 3 years of continuous exposure to mepolizumab. • Subjects who completed the Follow Up/Exit Visit or EW Visit from either open-label studies MEA115666 or 201312 and who have no treatment gaps of more than 12 weeks (84 days) between any two doses of mepolizumab in MEA115666 or 201312, will be eligible to participate in this study.
Dosing	Study design contains multiple parts (as shown within the study schematic above): • Part A: Open-label mepolizumab (100 mg SC) every 4 weeks for 0-132 weeks to allow subjects to achieve 3 years of continuous exposure to mepolizumab • Part B: Open-label mepolizumab (100 mg SC) every 4 weeks for 4-8 weeks • Part C: Double-blind treatment SC every 4 weeks for up to 52 weeks (subjects may switch to Part D following experiencing an asthma exacerbation) • Part D: Optional switch to open-label mepolizumab (100 mg SC) every 4 weeks for up to 52 weeks following experiencing an asthma exacerbation during Part C (for the remainder of the treatment period until an Exit Visit 52 weeks after Visit C1) Additionally, subjects within Parts C and D had the option to permanently discontinue their assigned treatment and remain within the study off-treatment until conclusion.
Time & Events	• Refer to Appendix 2: Schedule of Activities
Treatment Assignment	• Approximately 300 subjects from studies MEA115666 and 201312 will be randomized 1:1 to double-blind study treatment (150 per arm) at visit C1. • GSK RandAll NG will be used to generate randomization schedules. • A web based interactive system performed centralized randomization separately for each country using GSK RAMOS NG for treatment allocation.
Interim Analysis	• No interim analysis of data is planned for this study.

2.5. Statistical Hypotheses

The study is designed to test the superiority of continued mepolizumab 100 mg SC treatment vs. mepolizumab discontinuation (placebo) within Part C of the study. Significance tests will be performed at the two-sided 5% alpha level (one-sided 2.5%).

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analysis of data is planned for this study.

3.2. Final Analyses

All decisions regarding final analysis, specified in this RAP document, will be made prior to Database Freeze (unblinding) of the study data.

The reporting of the study will be divided into three distinct periods, with displays reflecting data collected within each period separately:

- Period 1: Parts A/B – variable and fixed run-in periods combined, with subjects receiving open-label mepolizumab treatment
- Period 2: Part C – double-blind treatment period, with subjects receiving mepolizumab or placebo
- Period 3: Part D – optional treatment switch period, with subjects returning to open-label mepolizumab treatment

A complete analysis in accordance with all study objectives and endpoints across all periods (Parts A/B, Part C, Part D) will be performed following the completion of the last study visit.

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

1. All participants have exited the study as defined in the protocol
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.
3. All criteria for unblinding the randomization codes have been met.
4. Randomization codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Distinct analysis populations have been defined to support the reporting of each period separately, as shown below:

Population	Definition / Criteria	Analyses Evaluated
All Subjects Enrolled (ASE)	• Comprised of all subjects enrolled and for whom a record exists on the study database.	• Screen failures • Listings across study parts
As Treated (AT) [Part A/B]	• Comprised of all subjects with at least one dose of open-label mepolizumab within Part A/B	• Data collected within the variable open-label run-in (Part A) and fixed run-in (Part B)
Intent-to-Treat (ITT) [Part C[1]]	• Comprised of all randomized subjects who receive at least one dose of double-blind study medication within Part C.	• Data collected within the double-blind period (Part C)
Per Protocol (PP) [Part C[1]]	• Comprised of all subjects in the ITT population who have not been identified as full protocol deviators with respect to criteria that are considered to potentially impact the primary efficacy analysis within Part C. • The decision to exclude a subject from the PP Population or exclude part of their data from the PP Population analyses will be made prior to breaking the blind. • Protocol deviations that would exclude subjects from the PP population are defined in Section 4.1 (Protocol Deviations) and Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population.	• Supplementary analysis of the primary endpoint in a supporting population to evaluate efficacy within Part C.
As Treated (AT) [Part D[1]]	• Comprised of all subjects with at least one dose of open-label mepolizumab within Part D	• Data collected within the open-label treatment switch period (Part D)

Refer to Appendix 11: List of Data Displays which details the population used for each display.
1 - All analyses of Part C and Part D data will be analysed according to the treatment each subject received for more than 50% of injections within Part C (see Section 5.1).

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 [Version 2, Dated: 15-Nov-2017].

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the Per Protocol analysis are captured and categorised on 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 summarised and listed.

Important deviations which result in exclusion from the analysis population will also be summarised and listed (Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).

A separate summary and listing of all inclusion/exclusion/randomization criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion/randomization pages of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment Display Descriptors

The study treatment each subject receives may differ within each reporting period:

- Period 1: Parts A/B – variable and fixed run-in periods combined, with subjects receiving open-label mepolizumab treatment
- Period 2: Part C – double-blind treatment period, with subjects receiving mepolizumab or placebo
- Period 3: Part D – optional treatment switch period, with subjects returning to open-label mepolizumab treatment

The treatment group descriptions within outputs will depend on the period of the study:

Treatment Group Descriptions (Parts A/B)			
RandAll NG[1]		Data Displays for Reporting	
Code	Description	Description	Order in TFL
N/A	N/A	Mepolizumab 100mg SC	1
Treatment Group Descriptions (Part C)			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TFL
1	Placebo	Placebo	1
2	Mepolizumab 100mg SC	Mepolizumab 100mg SC	2
Treatment Group Descriptions (Part D)			
RandAll NG[1]		Data Displays for Reporting	
Code	Description	Description	Order in TFL
N/A	N/A	Mepolizumab 100mg SC (Prev. Placebo)	1
N/A	N/A	Mepolizumab 100mg SC (Prev. Mepo)	2

NOTES:

1. Parts A/B and Part D are open-label treatment periods where all subjects received mepolizumab 100mg SC and therefore treatment group descriptions/assignments are not required for RandAll NG

Within displays summarising Part C and Part D, data will be presented according to the treatment each subject received for more than 50% of injections within Part C.

5.2. Baseline Definitions and Derivations

5.2.1. Baseline Definitions

5.2.1.1. Parts A/B Baseline Definition

- The Part A and B baseline will be defined for all subjects who are within the As Treated (AT) [Part A/B] population.
- For all endpoints the Part A/B baseline values for each assessment will be the latest available assessment prior to first dose of open-label mepolizumab, including data from unscheduled visits.
- Measurements on the same date as the first administration of open-label mepolizumab will be considered within the baseline derivation if measurement time is not captured. Where the measurement time is captured this should be compared against the time of first receiving open-label mepolizumab.
- In order to reduce the burden of repeated procedures at the transition from precursor studies (MEA115666/201312) to 201810, some assessments collected at the last clinic visit of the precursor studies (MEA115666/201312) will be utilized as the Screening Visit (Visit 1) assessment for this study (201810). The following data collected at the last clinic visit of the precursor studies will be utilized for reporting and considered within the above baseline derivation (see Section 5.2.3 for further details):
    - 12-lead ECG
    - Laboratory assessments (Haematology and Clinical Chemistry)
    - Immunogenicity

5.2.1.2. Part C Baseline Definition

- The Part C baseline will be defined for all subjects who are within the ITT (Part C) population.
- For endpoints collected outside of the eDiary and Asthma Control Questionnaire (ACQ-5) collected in the eDiary the Part C baseline values for each assessment will be the latest available assessment prior to first dose of double-blind treatment (however no earlier than the first dose of open-label mepolizumab), including data from unscheduled visits.
- Measurements on the same date as the first administration of double-blind treatment will be considered within the baseline derivation if measurement time is not captured. Where the measurement time is captured this should be compared against the time of first receiving double-blind treatment.
- For data collected via the eDiary device (i.e. morning peak flow, usage of rescue medication [i.e. salbutamol/albuterol], asthma symptom score and frequency of awakening due to asthma symptoms), the Part C baseline for analyses of averaged 4-weekly data will be calculated as an average using values over 7 days (immediately

prior and including the first dose of double-blind treatment), see Section 11.3.5 for further details.

- The current smoking status at Visit C1 will be derived from the responses obtained at Screening and Visit C1 (where changes in smoking status are collected, See Section 11.6.2).

5.2.1.3. Part D Baseline Definition

- The Part D baseline will be defined for all subjects who are within the As Treated (AT) [Part D] population.
- For all endpoints (collected outside of the eDiary) the Part D baseline values for each assessment will be the latest available assessment prior to first dose of open-label mepolizumab within Part D (however no earlier than the first administration of double-blind treatment), including data from unscheduled visits.
- Measurements on the same date as the first administration of open-label mepolizumab within Part D will be considered within the baseline derivation if measurement time is not captured. Where the measurement time is captured this should be compared against the time of first receiving open-label mepolizumab within Part D.

5.2.2. Derivations and Handling of Missing Baseline Data

- Changes from baseline will be defined within each appropriate period (Parts A/B, Part C, Part D), comparing back to the baseline (last available measurement prior to first dose of treatment within each period).

Definition	Reporting Details
Change from Baseline	= Visit Value – Baseline
Ratio to Baseline	= Visit Value / Baseline

- Unless otherwise specified, the baseline definitions specified in Section 5.2.1 Baseline Definitions will be used for derivations of endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.2.3. Screening Assessments (Copying from MEA115666 or 201312)

Subjects will enter this study (201810) after completion of either study MEA115666 or 201312. In order to reduce the burden of repeated procedures at the transition from precursor studies (MEA115666/201312) to 201810 some assessments (where available) will be copied forward by Biostatistics within the analysis datasets from each subject's last clinic visit within the previous study (typically the subject's Early Withdrawal Visit or Follow Up Visit) and will be utilized as the Screening Visit (Visit 1) assessment for this study (201810).

Detailed scenarios for the forward copying of assessments are described below. Under Scenario 1 and Scenario 2, assessments in **bold** (where available) will be copied from each subject's last clinic visit within MEA115666 or 201312. The remaining assessments will be performed at Screening (Visit 1) of the 201810 study and therefore no copying from studies MEA115666 or 201312 is required.

Scenario 1: 201810 Screening (Visit 1) date is equal to the subject's last clinic visit date of study MEA115666 or 201312;

	Precursor Study	
	MEA115666	**201312**
ECG	**Copy forward**	**Copy forward**
Laboratory (including Haematology, Chemistry and Liver Event test panels)	**Copy forward**	**Copy forward**
Immunogenicity	**Copy forward**	**Copy forward**

Scenario 2: 201810 Screening (Visit 1) date is after the subject's last clinic visit date of study MEA115666 or 201312;

	Precursor Study	
	MEA115666	**201312**
ECG	Re-performed in 201810	Re-performed in 201810
Laboratory (including Haematology, Chemistry and Liver Event test panels)	Re-performed in 201810	Re-performed in 201810
Immunogenicity	**Copy forward**	**Copy forward**

5.3. Multicentre Studies

- In this multicentre global study, subjects will be presented pooled across investigative sites and countries.
- For the purposes of covariate adjustment in the statistical analysis centres will be grouped into regions. The following regions are defined with consideration for standard of care medical practice, number of subjects enrolled and regulatory considerations:

Region	Countries
European Union	France, Germany, Netherlands, Poland, Romania, Spain
US/Canada	Canada, United States
Japan/Korea	Japan, Republic of Korea
Rest of World	Argentina, Australia, Russia, Ukraine

5.4. Examination of Covariates and Subgroups

5.4.1. Handling of Covariates

- The following is a list of covariates that will be used in all model-based statistical analyses. For analyses where a baseline value (of the analysis variable) is available this will also be included as a covariate in the analyses.

Covariate[1]	Subgroups
Region	Europe, Rest of World (See Section 5.3 for further details)
Exacerbations in the year prior to randomization [Visit C1] (to be included as an ordinal variable)	0, 1, ≥2
Use of baseline maintenance oral corticosteroids at randomization [Visit C1]	Yes (Requires OCS use), No (Without OCS use)

[1] Additional covariates of clinical interest may also be considered

- Categories may be combined if a subgroup contains an insufficient number of subjects to allow meaningful inference to be drawn from the model.

5.4.2. Examination of Subgroups

- Analyses will be performed to investigate the influence of the following Part C baseline variables on the effect of study treatment within the analysis of the primary endpoint:

Subgroup[1]	Categories
Age at Visit C1	12-17,18-64, ≥65 years
Sex	Male, Female
Weight at Visit C1	<75kg, ≥75kg
Region	Europe, Rest of World (See Section 5.3 for further details)
Exacerbations in year prior to randomization [Visit C1]	0, 1, ≥2
Use of baseline maintenance oral corticosteroids at randomization [Visit C1]	Yes (Requires OCS use), No (Without OCS use)
Part C Baseline blood eosinophils:	<0.05, 0.05-<0.15, ≥0.15 GI/L
Part C Baseline anti-drug antibody (ADA) status	Positive, Negative

[1] Additional subgroups of clinical interest may also be considered
See Section 7.1 for further details regarding the analysis of the primary endpoint.

- Treatment differences in each subgroup will be estimated in separate analysis models similar to those used in the main analysis of each endpoint, including only subjects contained within the corresponding subgroup.
- The estimated hazard ratio (mepolizumab/placebo) in each subgroup will be reported along with the corresponding 95% confidence interval (CI).
- No formal hypothesis testing in sub-groups of the populations will be performed.
- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup.
- The following list of subgroups will be used in descriptive summaries of adverse event safety data:

Subgroup[1]	Categories
Age at start of Study Part[2]	12-17,18-64, ≥65 years
Highest ADA Result Any Time On-Treatment During Study Part[3]	Positive, Negative

[1] Additional subgroups of clinical interest may also be considered
[2] Age defined at the baseline/start of Parts A/B, Part C and Part D, respectively.
[3] Highest ADA Result Any Time On-Treatment During Parts A/B, Part C and Part D, respectively.

5.4.3. Exploratory Multivariable Modelling

- The potential effect of Part C baseline covariates on treatment efficacy will be investigated using variable selection procedures (e.g. backwards elimination) to determine which Part C baseline parameters are most influential on the estimated treatment effect (mepolizumab/placebo).
- The Part C baseline variables listed in Section 5.4.2 will be considered for inclusion in the multivariate modelling.
- Within the multivariate modelling age at Visit C1, weight at Visit C1, exacerbations in the year prior to randomization [Visit C1] (as an ordinal variable) and Part C baseline blood eosinophils will each be treated as continuous. When presenting tabulations, each variable will be categorised as shown in Section 5.4.2.

5.5. Multiple Comparisons and Multiplicity

The primary comparison of interest is during Part C of the study in the comparison between continued mepolizumab treatment and mepolizumab discontinuation (subjects receiving placebo treatment) when assessing the primary endpoint in the ITT population.

Analyses of secondary and other efficacy endpoints will not be subject to any multiplicity adjustment.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

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

Section	Component
11.3	Appendix 3: Assessment Windows
11.4	Appendix 4: Study Periods and Treatment Phases
11.5	Appendix 5: Data Display Standards & Handling Conventions
11.6	Appendix 6: Derived and Transformed Data
11.7	Appendix 7: Reporting Standards for Missing Data
11.8	Appendix 8: Values of Potential Clinical Importance
11.9	Appendix 9: Guidelines for Exacerbation Verification Process

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the following analysis populations for each reporting period, unless otherwise specified:

Period	Population
Parts A/B	As Treated (AT) [Part A/B]
Part C	Intent-to-Treat (ITT) [Part C[1]]
Part D	As Treated (AT) [Part D[1]]

1 - All analyses of Part C and Part D data will be analysed according to the treatment each subject received for more than 50% of injections within Part C (see Section 5.1).

Study population analyses including analyses of subject's disposition, demographic and baseline characteristics, concomitant medications, protocol deviations, and exposure will be presented based on GSK Core Data Standards separately for each period (Parts A/B, Part C and Part D). Details of the planned displays are presented in Appendix 11: List of Data Displays.

6.2. Subject Disposition

A summary of the number of subjects included in each period (Parts A/B, Part C and Part D) and population will be produced.

The proportion of screen failures, reason for screen failure, proportion of run-in failures and reason for run-in failure will be presented. Additionally, the proportion who failed each eligibility/randomization criteria and number of randomised subjects who did not receive double-blind treatment will be presented.

The proportion of subjects who withdrew from the study, reasons for withdrawal, proportion of subjects who discontinued study treatment and reasons for discontinuing treatment will be presented. A Kaplan-Meier plot presenting the percentage of subjects withdrawing from investigational product over time in Part C will be produced.

An additional summary of subject attendance at each Part C and Part D clinic visit and a by visit summary of the number of subjects who switched to open-label mepolizumab treatment within Part D will be provided.

6.3. Demographics

Demographic characteristics (age, sex, ethnicity, height, weight and body mass index) will be summarised and listed for subjects enrolled into Part C. The proportion of subjects in each race and racial combination category will also be presented.

The proportion of subjects at each site and within each country and region will be presented.

6.4. Medical Conditions

Each subject's past and current medical history will be collected at Visit 1 (Screening). The proportion of subjects who report medical conditions in each class will be presented, for past and current conditions separately.

6.5. Cardiovascular Assessments at Screening

A summary of the cardiovascular assessments at Visit 1 (Screening) will be presented. The proportion of subjects who report a family history of medical conditions that may indicate predisposition towards cardiovascular conditions will be summarised.

6.6. Smoking Status

At Visit C1 (randomization) the proportion of subjects who report each smoking status (never smoked, current smoker, former smoker) will be presented after accounting for subject's change in status from Screening (See Section 11.6.2).

6.7. Baseline Disease Characteristics

Asthma history at Randomisation (Visit C1) including duration of asthma (derived from age of onset), Asthma Disease Characteristics (ATS Criteria), prior intubations related to asthma and OCS use will be summarised. Exacerbations in the 12 months prior to Randomisation (Visit C1) and causes of exacerbations will also be summarised. See Section 11.6.2 for further details of derivations.

The following clinic lung function results at Randomisation (Visit C1), as derived in Section 11.6.3, will be summarised:

- Pre- and post-bronchodilator FEV_1 (mL)
- Pre- and post-bronchodilator percent predicted FEV_1 (%)
- Pre- and post-bronchodilator Forced Vital Capacity (FVC) (mL)
- Pre- and post-bronchodilator FEV_1/FVC
- Reversibility (in mL and in %)

6.8. Concomitant Medications

The proportion of subjects reporting each concomitant medication will be presented according to GSK Drug dictionary coding. Multi-ingredient medications will be presented according to their combination ATC classification rather than the classifications of the ingredients. Summaries will be split into asthma and non-asthma concomitant medications taken during double-blind treatment in Part C. Asthma medication outputs will not display ATC grouping.

Classification of a medication as during double-blind treatment in Part C will be made relative to the study treatment start and stop dates and the medication start and stop dates (as described in Section 11.4.5).

6.9. Protocol Deviations

Important protocol deviations and deviations resulting in exclusion from the protocol Per-Protocol population (see Section 11.1) will be summarised and listed for each period (Parts A/B, Part C and Part D). More details are in Appendix 11: List of Data Displays.

6.10. Continuous Exposure to Mepolizumab Prior to Randomization (Visit C1)

For each subject the period of continuous mepolizumab exposure prior to randomization (first dose of double-blind treatment at Visit C1) will be summarised considering mepolizumab treatment from the following precursor studies where the same individuals participated: MEA115666, MEA115588, MEA115575, MEA115661, 201312 in addition to any mepolizumab treatment administered within 201810 Parts A/B.

See Section 11.6.2 for the definition of continuous exposure to mepolizumab prior to randomization (Visit C1).

6.11. Extent of Exposure

The exposure to study treatment (mepolizumab/placebo) will be reported separately from each period (Parts A/B, Part C and Part D). The number of treatments administered and the number of days on-treatment will be summarised and listed.

See Section 11.6.2 for the definition of the duration of exposure to study treatment.

7. EFFICACY ANALYSES

Efficacy data will be presented for Part C. In addition, a descriptive summary of blood eosinophils from Part D will be produced. Presentations of results will conform to GSK's Integrated Data Standards Library (IDSL) standards.

The efficacy analyses will be based on the following analysis populations for each study period, unless otherwise specified:

Period	Population
Part C	Intent-to-Treat (ITT) [Part C[1]]
Part D	As Treated (AT) [Part D[1]]

1 - All analyses of Part C and Part D data will be analysed according to the treatment each subject received for more than 50% of injections within Part C (see Section 5.1).

7.1. Primary Efficacy Analyses

7.1.1. Endpoint / Variables

The primary efficacy analyses endpoint is the time to first clinically significant exacerbation within Part C relative to the date of first dose of double-blind treatment [see Section 11.6.1, Part C study day].

Clinically significant exacerbations will be 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 corticosteroid (e.g., prednisone) for at least 3 days or a single intramuscular (IM) corticosteroid dose is required. For subjects on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days is required.*

Exacerbations will only be included within the primary efficacy analyses if supported by objective assessments of asthma deterioration, as reviewed by the Exacerbation Verification Process (see Section 7.1.5.2).

For consistency, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation (see Section 11.6.3). Handling of missing or partial dates in reported exacerbations is detailed within Section 11.7.2.1.

7.1.2. Summary Measure

The hazard ratio (Mepolizumab 100mg SC / Placebo) will be the summary measure used for the treatment comparison.

7.1.3. Population of Interest

The population of interest is represented by the randomization inclusion/exclusion criteria of the study and therefore the primary efficacy analyses will be based on the Intent-to-Treat (ITT) [Part C] population, unless otherwise specified.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

A hypothetical estimand strategy will be applied in the handling of the intercurrent event of discontinuation of double-blind treatment. The treatment effect therefore refers to the outcome if all patients had continued to take double-blind treatment.

Only the On-treatment (Part C) period will be used in the analysis and subjects will be analysed according to the treatment each subject received for more than 50% of injections within Part C (see Section 5.1).

All subjects will be considered to be at risk from their first dose of double-blind treatment at visit C1. Subjects who complete Part C will be considered to be at risk up to their Week 52 (Exit Visit/C14) visit date. Subjects who discontinued double-blind treatment prior to experiencing an exacerbation (event) will be censored at the time of treatment discontinuation [see On-treatment (Part C) definition within Section 11.4.2].

7.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.1.5.1. Statistical Methodology Specification

Endpoint / Variables
• Time to first clinically significant exacerbation (ADaM Dataset: ADTTE)
Model Specification
• The endpoint will be compared between treatment groups using a Cox proportional hazards model. Fixed Categorical Covariates: Treatment, Region, Baseline maintenance OCS use [Visit C1] Fixed Continuous Covariates: Exacerbations in the year prior to randomization [Visit C1] (as an ordinal variable) See Section 5.4.1 for further details around model covariates.
Model Checking & Diagnostics

• The TIES=EXACT option will be applied for the handling of ties in failure times.
• In the event that this model fails to converge, the list of covariates may be adjusted and/or reduced.
• Distributional assumptions underlying the model used for analysis will be examined by:
  ○ assessing if a sufficient number of events occurred within covariate categories.
• The proportional hazards assumptions will be examined by:
  ○ obtaining plots of the Kaplan-Meier curves and of the log of the cumulative hazard function (log of the negative log of the estimated survivor function) against the log of the survival time
• If there are any major important departures from the distributional or proportional hazard assumptions transformations of covariates may be considered or alternative models may be explored as supportive analysis.

Model Results Presentation
• Summaries and graphs will be produced presenting the probability of an event over time by treatment group using Kaplan-Meier estimates and the corresponding 95% confidence intervals.

• The hazard ratio (Mepolizumab/Placebo) from the Cox proportional hazards model will be reported with the corresponding 95% CI and p-value.
Sensitivity and Supportive Analyses
• A supportive analysis of the Per Protocol (PP) population will also be performed.
Subgroup Analyses
• Subgroup analyses of the primary endpoint will be performed for the Intent-To-Treat (ITT) population and all subgroups listed within Section 5.4.2.

7.1.5.2. Exacerbation Verification Process

In order to provide an objective assessment of the circumstances linked to the clinical decision that defines asthma exacerbations, in study Part C and Part D each exacerbation recorded in the eCRF by the Investigator or designee will be verified using data from the eDiary to confirm that the exacerbation was associated with changes in peak flow, rescue medication use, nocturnal awakening due to asthma symptoms requiring rescue medication use or symptoms. In the case that an exacerbation is regarded as not associated with deterioration in at least one of these objective eDiary parameters, the investigator will be asked to provide an explanation to support the decision for defining the event as a clinically significant exacerbation. In those circumstances where the event cannot be supported by any objective assessment, the case will not be included as a clinically significant exacerbation but will be included as an investigator defined exacerbation. This verification process will be overseen by GSK clinical staff to ensure consistency. This is the same process as employed in previous Phase III mepolizumab severe asthma studies (MEA112997, MEA115588, MEA115575). This verification process is described in detail within Section 11.9.

7.2. Secondary Efficacy Analyses

7.2.1. Population of Interest

The population of interest is represented by the randomization inclusion/exclusion criteria of the study and therefore the secondary efficacy analyses will be based on the Intent-to-Treat (ITT) [Part C] population, unless otherwise specified.

7.2.2. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK data standards and statistical principles.

7.2.2.1. Statistical Methodology Specification

Endpoint / Variables
• Ratio to baseline in blood eosinophil count at weeks 12, 24, 36 and 52 (ADaM Dataset: ADLB)
• See Section 5.2 for further details regarding baseline and change from baseline derivations. • See Section 11.6.3 for additional details regarding handling blood eosinophil data.
Summary Measure
• Mean treatment difference at weeks 12, 24, 36 and 52 (Exit Visit/C14)
Strategy for Intercurrent (Post-Randomization) Events
• A hypothetical estimand strategy will be applied in the handling of the intercurrent event of discontinuation of double-blind treatment. The treatment effect therefore refers to the outcome if all patients had continued to take double-blind treatment. • Only the On-treatment (Part C) period will be used in the analysis and subjects will be analysed according to the treatment received for more than 50% of injections within Part C (see Section 5.1). • All subjects will be considered on-treatment from their first dose of double-blind treatment at visit C1. Subjects who complete Part C will be considered on-treatment up to their Week 52 (Exit Visit/C14) visit date. Subjects who discontinued double-blind treatment will be considered on-treatment until the time of treatment discontinuation. ○ Blood Eosinophils: see On-treatment (Part C) definition within Section 11.4.3
Model Specification
• Endpoint will be analysed using a mixed model repeated measures (MMRM) model • A log transformation will be applied to blood eosinophil count data prior to analysis. • Terms fitted in the MMRM model will include: Fixed Categorical Covariates: Treatment, Region, Baseline maintenance OCS use [Visit C1], Visit, Visit * Treatment Interaction Fixed Continuous Covariates: Baseline, Exacerbations in the year prior to randomization [Visit C1] (as an ordinal variable), Visit * Baseline Repeated: Visit See Section 5.4.1 for further details around model covariates.
Model Checking & Diagnostics
• The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used (DDMF=KR). • An unstructured covariance structure for the R matrix will be used by specifying 'TYPE=UN' on the REPEATED line. • In the event that this model fails to converge, the list of covariates may be adjusted and/or reduced. • Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking

the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. • If there are important departures from the distributional assumptions, transformations of covariates may be considered or alternative models may be explored as supportive analysis.
Model Results Presentation
• The estimated means for each treatment group will be calculated from the model using the observed marginal distributions of the sample covariates (OM option in LSMEANS statement). • Adjusted absolute means and mean changes from baseline will be presented for each treatment by visit with corresponding standard errors of means on the $\log_e$ scale. The estimated treatment ratios (Mepolizumab/Placebo) will also be presented at each visit with the corresponding 95% confidence intervals and p-values. • Plots of LS means ratio to baseline in blood eosinophil count and 95% confidence intervals from the model will be generated for each treatment by visit.

Endpoint / Variables
• Time to a decrease in asthma control, defined as an increase from baseline in Asthma Control Questionnaire-5 (ACQ-5) score of ≥ 0.5 units (ADaM Dataset: ADTTE) • Time to first exacerbation requiring hospitalization or ED visit (ADaM Dataset: ADTTE)
• Time to first event within Part C will be derived relative to the date of first dose of double-blind treatment [see Section 11.6.1, Part C study day]. • See Section 5.2 for further details regarding baseline and change from baseline derivations. • See Section 11.6.3 for details of the ACQ-5 questionnaire and Section 11.3.5 regarding visit windowing. • For consistency, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation (see Section 11.6.3). • See Section 11.7.2.1 for details on handling missing/partial dates.
Summary Measure
• The hazard ratio (Mepolizumab 100mg SC / Placebo) will be the summary measure used for the treatment comparison.
Strategy for Intercurrent (Post-Randomization) Events
• A hypothetical estimand strategy will be applied in the handling of the intercurrent event of discontinuation of double-blind treatment. The treatment effect therefore refers to the outcome if all patients had continued to take double-blind treatment. • Only the On-treatment (Part C) period will be used in the analysis and subjects will be analysed according to the treatment received for more than 50% of injections within Part C (see Section 5.1). • All subjects will be considered to be at risk from their first dose of double-blind treatment at visit C1. Subjects who complete Part C will be considered to be at risk up to their Week 52 (Exit Visit/C14) visit date. Subjects who discontinued double-blind treatment prior to experiencing an event will be censored at the time of treatment discontinuation. ○ Questionnaires: see On-treatment (Part C) definition within Section 11.4.3 ○ Exacerbations: see On-treatment (Part C) definition within Section 11.4.2
Model Specification
• See Primary Efficacy Statistical Analysis, Section 7.1.5.1
Model Checking & Diagnostics
• See Primary Efficacy Statistical Analysis, Section 7.1.5.1
Model Results Presentation
• See Primary Efficacy Statistical Analysis, Section 7.1.5.1

7.3. Exploratory Efficacy Analyses

7.3.1. Population of Interest

The population of interest is represented by the randomization inclusion/exclusion criteria of the study and therefore the exploratory efficacy analyses will be based on the Intent-to-Treat (ITT) [Part C] population, unless otherwise specified.

7.3.2. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK data standards and statistical principles.

7.3.2.1. Statistical Methodology Specification

Endpoint / Variables

• Time to first exacerbation requiring hospitalization (ADaM Dataset: ADTTE)
• Time to worsening of asthma (subjects meeting at least 2 of the following 4 criteria for worsening of asthma for at least 2 consecutive days) (ADaM Dataset: ADTTE):
  ○ AM PEF: Decrease in AM PEF ≥30% compared with Part C baseline
  ○ Rescue Medication Use: An increase of ≥50% in rescue medication compared with the average use for the previous week
  ○ Night time awakenings requiring rescue medication: Awakening due to asthma symptoms requiring rescue medication
  ○ Symptoms: An asthma symptom score of 5

• Time to first event within Part C will be derived relative to the date of first dose of double-blind treatment [see Section 11.6.1, Part C study day]. • For consistency, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation (see Section 11.6.3). • See Section 5.2 for further details regarding baseline and change from baseline derivations. • See Section 11.6.3 for details regarding eDiary data and Section 11.3.5 regarding visit windowing. • In the analysis of Time to worsening of asthma only non-missing measurements indicative of asthma worsening (per above endpoint definition) will be considered as an event. Intermediate missing responses in a subject's eDiary data will be assumed to be missing at random, and will not be considered to indicate a worsening of their asthma. • See Section 11.7.2 for further details on handling missing/partial data.
Summary Measure
• The hazard ratio (Mepolizumab 100mg SC / Placebo) will be the summary measure used for the treatment comparison.
Strategy for Intercurrent (Post-Randomization) Events

• A hypothetical estimand strategy will be applied in the handling of the intercurrent event of discontinuation of double-blind treatment. The treatment effect therefore refers to the outcome if all patients had continued to take double-blind treatment.
• Only the On-treatment (Part C) period will be used in the analysis and subjects will be analysed according to the treatment received for more than 50% of injections within Part C (see Section 5.1).
• All subjects will be considered to be at risk from their first dose of double-blind treatment at visit C1. Subjects who complete Part C will be considered to be at risk up to their Week 52 (Exit Visit/C14) visit date. Subjects who discontinued double-blind treatment prior to experiencing an event will be censored at the time of treatment discontinuation.
  ○ Exacerbations: see On-treatment (Part C) definition within Section 11.4.2
  ○ eDiary data: see On-treatment (Part C) definition within Section 11.4.3.

Model Specification
• See Primary Efficacy Statistical Analysis, Section 7.1.5.1
Model Checking & Diagnostics
• See Primary Efficacy Statistical Analysis, Section 7.1.5.1
Model Results Presentation
• See Primary Efficacy Statistical Analysis, Section 7.1.5.1

Endpoint / Variables
• Mean change from baseline in clinic pre-bronchodilator FEV1 at weeks 12, 24, 36, 52 • Mean change from baseline in clinic post-bronchodilator FEV1 at weeks 12, 24, 36, 52 (ADaM Dataset: ADPFT) • Mean change from baseline in ACQ-5 score (ADaM Dataset: ADACQ5) • Mean change from baseline in SGRQ Total score at week 12, 24, 36 and 52 • Mean change from baseline in SGRQ Symptom Domain score at week 12, 24, 36 and 52 • Mean change from baseline in SGRQ Activity Domain score at week 12, 24, 36 and 52 • Mean change from baseline in SGRQ Impacts Domain score at week 12, 24, 36 and 52 (ADaM Dataset: ADSGRQ)
• See Section 5.2 for further details regarding baseline and change from baseline derivations. • See Section 11.6.3 for additional details regarding spirometry, the ACQ-5 and SGRQ questionnaires. • See Section 11.3.5 regarding visit windowing of the ACQ-5 questionnaire.
Summary Measure
• Spirometry and SGRQ: Mean treatment difference at weeks 12, 24, 36 and 52 (Exit Visit/C14) • ACQ-5: Mean treatment difference at weeks 12, 24, 36 and 52
Strategy for Intercurrent (Post-Randomization) Events
• A hypothetical estimand strategy will be applied in the handling of the intercurrent event of discontinuation of double-blind treatment. The treatment effect therefore refers to the outcome if all patients had continued to take double-blind treatment. • Only the On-treatment (Part C) period will be used in the analysis and subjects will be analysed according to the treatment received for more than 50% of injections within Part C (see Section 5.1). • All subjects will be considered on-treatment from their first dose of double-blind treatment at visit C1. Subjects who complete Part C will be considered on-treatment up to their Week 52 (Exit Visit/C14) visit date. Subjects who discontinued double-blind treatment will be considered on-treatment until the time of treatment discontinuation.   ○ Spirometry and Questionnaires: see On-treatment (Part C) definition within Section 11.4.3
Model Specification
• See Secondary Efficacy Statistical Analysis, Section 7.2.2.1.
Model Checking & Diagnostics
• See Secondary Efficacy Statistical Analysis, Section 7.2.2.1.
Model Results Presentation
• The estimated means for each treatment group will be calculated from the model using the observed marginal distributions of the sample covariates (OM option in LSMEANS statement). • Adjusted absolute means and mean changes from baseline will be presented for each treatment by visit with corresponding standard errors of means. The estimated treatment difference (Mepolizumab – Placebo) will also be presented at each visit with the corresponding 95% confidence intervals and p-values. • Plots of LS means change from baseline and 95% confidence intervals from the model will be generated for each treatment by visit.

Endpoint / Variables
• Proportion of patients experiencing a decrease in asthma control, defined as an increase from baseline in ACQ-5 score of ≥ 0.5 units (ADaM Dataset: ADACQ5) • Proportion of subjects with a clinically meaningful worsening of health-related quality of life measurements (SGRQ) at weeks 12, 24, 36 and 52 (defined as subjects who have a clinically relevant increase from baseline of ≥4 units in SGRQ total score) (ADaM Dataset: ADSGRQ)
• See Section 5.2 for further details regarding baseline and change from baseline derivations. • See Section 11.6.3 for additional details regarding the ACQ-5 and SGRQ questionnaires. • See Section 11.3.5 regarding visit windowing of the ACQ-5 questionnaire.
Summary Measure
• ACQ-5: Odds Ratio (Mepolizumab 100mg SC / Placebo) at weeks 12, 24, 36 and 52 • SGRQ: Odds Ratio (Mepolizumab 100mg SC / Placebo) at weeks 12, 24, 36 and 52 (Exit Visit/C14)
Strategy for Intercurrent (Post-Randomization) Events
• A composite estimand strategy will be applied in the handling of the intercurrent event of discontinuation of double-blind treatment. • Subjects will be categorized during the On-treatment (Part C) period according to their questionnaire (ACQ-5 / SGRQ) response. Following treatment discontinuation (end of On-treatment [Part C] phase) subjects will be shown as missing and on analysis included in the least favorable category of increase from baseline of ≥ 0.5 units or ≥4 units for the ACQ-5 and SGRQ endpoints, respectively. • Subjects will be analysed according to the treatment received for more than 50% of injections within Part C (see Section 5.1). • All subjects will be considered on-treatment from their first dose of double-blind treatment at visit C1. Subjects who complete Part C will be considered on-treatment up to their Week 52 (Exit Visit/C14) visit date. Subjects who discontinued double-blind treatment will be considered on-treatment until the time of treatment discontinuation.   ○ Questionnaires: see On-treatment (Part C) definition within Section 11.4.3
Model Specification
• Logistic regression will be used to compare the proportion of patients achieving a 0.5 units / 4 point or greater increase from baseline in ACQ-5 / SGRQ Total Score between treatment groups at each analysis visit (separate models will be used for each analysis visit). • Subjects with a missing response at a particular visit will be included in the least favorable category as having a 0.5 units / 4 point or greater increase from baseline in ACQ-5 / SGRQ Total Score in the logistic regression model for the analysis of that visit. • Terms fitted in each logistic regression model will include: Fixed Categorical Covariates: Treatment, Region, Baseline maintenance OCS use [Visit C1] Fixed Continuous Covariates: Baseline Score, Exacerbations in the year prior to randomization [Visit C1] (as an ordinal variable) See Section 5.4.1 for further details around model covariates.
Model Checking & Diagnostics
• In the event that this model fails to converge, the list of covariates may be adjusted and/or reduced. • Distributional assumptions underlying the model used for analysis will be examined by: ○ assessing if a sufficient number of events occurred within covariate categories. • If there are any major important departures from the distributional assumptions transformations of covariates may be considered or alternative models may be explored as supportive analysis.
Model Results Presentation
• The number and percentage of subjects achieving a 0.5 units / 4 point or greater increase in ACQ-5 / SGRQ Total Score compared to baseline will be presented by treatment group for each visit. • The estimated odds ratio (Mepolizumab/Placebo) at each visit for the treatment variable in the logistic regression model will be reported with the corresponding 95% CI and p-value.

Endpoint / Variables
• Subject/Clinician global impression of asthma severity rating at weeks 12, 24, 36 and 52 (ADaM Dataset: ADGLOBRT) • Subject/Clinician rating of response to therapy at weeks 12, 24, 36 and 52 (ADaM Dataset: ADEVRESP)
• See Section 5.2 for further details regarding baseline derivations. • See Section 11.6.3 for additional details regarding the Subject/Clinician global impression of asthma severity rating and the Subject/Clinician rating of response to therapy questionnaires.
Summary Measure
• Subject/Clinician global impression of asthma severity rating: Odds Ratio (Mepolizumab 100mg SC / Placebo) at weeks 12, 24, 36 and 52 (Exit Visit/C14) • Subject/Clinician rating of response to therapy: Odds Ratio (Mepolizumab 100mg SC / Placebo) at weeks 12, 24, 36 and 52 (Exit Visit/C14)
Strategy for Intercurrent (Post-Randomization) Events
• A composite estimand strategy will be applied in the handling of the intercurrent event of discontinuation of double-blind treatment. • Subjects will be categorized during the On-treatment (Part C) period according to their response. Following treatment discontinuation (end of On-treatment [Part C] phase) subjects will be shown as missing and on analysis included in the least favorable category of the respective outcome. • Subjects will be analysed according to the treatment received for more than 50% of injections within Part C (see Section 5.1). • All subjects will be considered on-treatment from their first dose of double-blind treatment at visit C1. Subjects who complete Part C will be considered on-treatment up to their Week 52 (Exit Visit/C14) visit date. Subjects who discontinued double-blind treatment will be considered on-treatment until the time of treatment discontinuation. ○ Questionnaires: see On-treatment (Part C) definition within Section 11.4.3
Model Specification
• Ordinal logistic regression (proportional odds model) will be used to compare the proportion of patients in each response category between treatment groups at each analysis visit (separate models will be used for each analysis visit). • Subjects with a missing response at a particular visit will be included in the least favorable category of the respective outcome in the ordinal logistic regression model for the analysis of that visit. • Terms fitted in each ordinal logistic regression model will include: Fixed Categorical Covariates: Treatment, Baseline (Global impression of asthma severity rating only), Region, Baseline maintenance OCS use [Visit C1] Fixed Continuous Covariates: Exacerbations in the year prior to randomization [Visit C1] (as an ordinal variable) See Section 5.4.1 for further details around model covariates.
Model Checking & Diagnostics
• In the event that this model fails to converge, the list of covariates may be adjusted and/or reduced. • Distributional assumptions underlying the model used for analysis will be examined by: ○ assessing if a sufficient number of events occurred within covariate categories. • If there are any major important departures from the distributional assumptions transformations of covariates may be considered or alternative models may be explored as supportive analysis.
Model Results Presentation
• The number and percentage of subjects in each response category and with a missing response will be presented by treatment group for each visit. • The estimated odds ratio (Mepolizumab/Placebo) at each visit for the treatment variable in the ordinal logistic regression model will be reported with the corresponding 95% CI and p-value.

7.3.3. Change from Baseline in eDiary Parameters

Daily eDiary data for the following parameters will be aggregated whilst on-treatment over 4-weekly periods (see Section 11.3.5) within study Part C, respectively:

- Occasions/day of rescue medication (salbutamol/albuterol) usage over the previous 24-hours
- Asthma symptom score over the previous 24-hours (using a 6-point scale)
- Frequency of awakening due to asthma symptoms requiring rescue medication use
- Morning peak expiratory flow [PEF] (L/min), before rescue medication usage

The mean daily data whilst on-treatment, excluding days with missing data, will be calculated for each 4-weekly period (Weeks 0-4, 4-8, …, 48-52) within study Part C, respectively. Data for each 4-week period and change from baseline for each 4-week period will be summarised by treatment group.

7.3.4. Unscheduled Healthcare Contacts/Resource Utilization

Number of days in hospital due to asthma, unscheduled healthcare resource use and number of days off work/school whilst on-treatment will be summarised separately for subjects who complete 12, 24, 36 and 52 weeks of Part C double-blind treatment.

Number of days in hospital due to asthma whilst on-treatment will be summarised by treatment group. See Section 11.6.3 for details regarding collection of days in hospital.

Unscheduled healthcare resource use due to a clinically significant exacerbation whilst on-treatment will be summarised by treatment group. In addition, total unscheduled asthma related healthcare resource use whilst on-treatment (combining healthcare contacts due to a clinically significant exacerbation and not associated with an asthma exacerbation) will be summarised by treatment group. See Section 11.6.3 for details regarding collection of healthcare resource use.

Number of days off work/school whilst on-treatment will be summarised by treatment group.

8. SAFETY ANALYSES

Safety data will be presented separately from each period (Parts A/B, Part C and Part D) in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

The safety analyses will be based on the following analysis populations for each study period, unless otherwise specified:

Period	Population
Parts A/B	As Treated (AT) [Part A/B]
Part C	Intent-to-Treat (ITT) [Part C[1]]
Part D	As Treated (AT) [Part D[1]]

1 - All analyses of Part C and Part D data will be analysed according to the treatment each subject received for more than 50% of injections within Part C (see Section 5.1).

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards.

AEs occurring during the on-treatment phase will be summarised separately for each period (Parts A/B, Part C and Part D). Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

The number and percentage of subjects experiencing at least one AE will be summarised. Exposure adjusted rates of AEs during Part C will also be presented to account for the length of subject exposure within the double-blind treatment period. For the definition of exposure adjusted AEs, see Section 11.6.4.

The details of the planned displays are provided in Appendix 11: List of Data Displays.

8.1.1. Adverse Events of Special Interest Analyses

Adverse events of special interest (AESIs) for closer monitoring are listed in Section 11.6.4.

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

8.1.2. Cardiovascular Events and Deaths (All Causes)

Cardiovascular events and deaths (all causes) will be captured on targeted 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
- Death (all causes)

8.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Haematology laboratory tests, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 11: List of Data Displays.

8.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs, vital signs and immunogenicity will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 11: List of Data Displays.

8.3.1. 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 (see Section 11.6.4).

A table will be produced summarising the number and percentage of subjects with negative and confirmed positive on-treatment ADA samples by treatment group and visit. The table will also summarise the highest assay result obtained whilst on-treatment for each subject. A similar table will also be produced summarising results for the neutralising antibody assay 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 at the first dose of study treatment in each period (Parts A/B, Part C and Part D) will also be presented.

All immunogenicity results (i.e. ADA screening and confirmatory assay results, titre values, neutralising antibody results) will be listed.

The details of the planned Immunogenicity displays are presented in Appendix 11: List of Data Displays.

9. BIOMARKER ANALYSES

Blood (serum) samples were collected during Part C of the study and may be used for the purposes of measuring biomarkers to identify factors that may influence the development of asthma and/or medically related conditions, as well as the biological and clinical responses to mepolizumab.

A separate plan will be produced detailing any additional analysis of collected biomarker data.

10. REFERENCES

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11. APPENDICES

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

11.1.1. Exclusions from Per Protocol Population

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/randomization criteria, conduct of the trial, patient management or patient assessment) will be listed and summarised.

Subjects with protocol deviations considered to potentially have an effect on efficacy will be removed from the Per Protocol (PP) population. Determination of the Per Protocol population will be performed whilst blinded to treatment, before the database is frozen. The reason for the exclusion of any subject will be documented.

A further review of the Per Protocol population will be performed following unblinding regarding protocol deviation criteria impacted by blinded study treatment (e.g. exclusion criteria number 5 below). Similarly the reason for the exclusion of any subject will be documented.

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

Number	Exclusion Description
01	Randomization Inclusion Criterion #1 – Any subject without documented evidence of at least 3 years (156 weeks) of treatment with mepolizumab, with no treatment gaps of greater than 12 weeks (84 days) between any two doses at the time of randomization. See Section 11.6.2 for further details regarding the definition of continuous mepolizumab treatment.
02	Randomization Inclusion Criterion #3 – Any subject with changes in the dose or regimen of ICS, and/or additional controller medication during the fixed run-in period (Part B). N.B. This excludes the use of OCS for the treatment of an asthma exacerbation.
03	Any subject with changes in the dose or regimen of ICS, and/or additional controller medication during double-blind treatment (Part C). N.B. This excludes the use of OCS for the treatment of an asthma exacerbation.
04	Breaking of the treatment blind at any point during Part C of the study.
05	Receiving the incorrect study treatment at any point during Part C of the study (not the treatment to which the subject was randomized) [1].
06	Use of any prohibited medication during Parts B or C of the study [2].
07	Randomization Exclusion Criterion #6 – Current smokers at Visit C1.
08	Randomization Exclusion Criterion #7 – Subjects with an asthma exacerbation that has not resolved completely within 7 days of Visit C1.

- [1] This incorrect study treatment criteria will be re-assessed following unblinding, where an additional review of subject data will be performed. The reason for the exclusion of any subject will be documented.
- [2] See Protocol Section 7.9.2 for the list of prohibited medications within this study.

11.2. Appendix 2: Schedule of Activities

11.2.1. Protocol Defined Schedule of Events

Table 1 Time and Events Table: Screening/Variable Open-Label Run-In Weeks 0 - 52 - Part A

PART A **Procedures**	**Pre-Screen[1]**	**Exit/EW Visit MEA115666 or 201312/ Screen[1]**	**Variable Open-Label Treatment Part A[2] (window is ± 1 week)**													EW Visit[5]
Visit	**0**	**1**	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**	**A10**	**A11**	**A12**	**A13**	
Week of Variable Run-In		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Written Informed Consent	X															
Demography		X														
Medical History		X														
Assess cardiac risk factors		X														
Smoking status		X														
Inclusion/Exclusion Criteria		X														
Safety Assessments[3]																
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination		X												X		X
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG		X						X						X		X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[3]																
Haematology		X						X						X		X
Chemistry (incl. LFT)		X						X						X		X
Pregnancy Test[4]		U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Immunogenicity		X												X		X
HbsAg and hepatitis C antibody		X														
Efficacy Assessments[3]																
Exacerbation review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

PART A **Procedures**	**Pre-Screen[1]**	**Exit/EW Visit MEA115666 or 201312/ Screen[1]**	**Variable Open-Label Treatment Part A[2] (window is ± 1 week)**													EW Visit[5]
Visit	**0**	**1**	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**	**A10**	**A11**	**A12**	**A13**	
Week of Variable Run-In		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Asthma Control Questionnaire-5		X			X			X			X			X		X
Spirometry		X						X						X		X
Worksheets/Diary/IP/ eCRF																
Administer open-label mepolizumab		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense albuterol/salbutamol		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect albuterol/salbutamol			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense paper diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect/review paper diary			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	X															X
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. The Pre-Screen Visit and Screening Visit may occur on the same day.
2. Visits should be conducted every 4 weeks until the subject has reached 3 years of mepolizumab exposure.
3. Please see the SRM for details on which screening procedures to perform for subjects entering from 201312 and MEA115666. ALL procedures should be completed prior to dosing with open-label mepolizumab.
4. Urine pregnancy tests (U) should be conducted for women of child bearing potential.
5. EW = Early Withdrawal. Should be conducted 4 ± 1 weeks from the subject's last dose

Table 2 Time and Events Table: Screening/Variable Open-Label Run-In Weeks 56 - 132- Part A

PART A Procedures	Variable Open-Label Treatment Part A[1] (window is ± 1 week)													EW Visit[3]
Visit	**A14/A27**	**A15/A28**	**A16/A29**	**A17/A30**	**A18/A31**	**A19/A32**	**A20/A33**	**A21**	**A22**	**A23**	**A24**	**A25**	**A26**	
Week of Variable Run-In	**56/108**	**60/112**	**64/116**	**68/120**	**72/124**	**76/128**	**80/132**	**84**	**88**	**92**	**96**	**100**	**104**	
Safety Assessments														
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination												X		X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG					X							X		X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments														
Haematology					X							X		X
Chemistry (incl. LFT)					X							X		X
Pregnancy Test[2]	U	U	U	U	U	U	U	U	U	U	U	U	U	X
Immunogenicity												X		X
Efficacy Assessments														
Exacerbation review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Asthma Control Questionnaire-5		X			X			X				X		X
Spirometry					X							X		X
Worksheets/Diary/IP/eCRF														
Administer open-label mepolizumab	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense albuterol/salbutamol	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect albuterol/salbutamol	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense paper diary	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect/review paper diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT														X
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Visits should be conducted every 4 weeks until the subject has reached 3 years of mepolizumab exposure.
2. Urine pregnancy tests (U) should be conducted for women of child bearing potential.
3. EW = Early Withdrawal. Should be conducted 4 ± 1 weeks from the subject's last dose

Table 3 Time and Events Table: Fixed Run-In & Double-Blind Treatment Period – Parts B and C

PARTS B&C Procedures	Fixed Run-in Part B		EW from Part B[7]	Randomization	Double-Blind Treatment Part C (window is ± 1 week)													IPDISC/EW Visit [7]
Visit	**B1**	**B2[1]**	**Part B EW**	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**	**C13**	**Exit Visit**	
Week of Study	**-4 ± 1**	**-4 ± 1[1]**		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Smoking status				X														
Randomization Criteria				X														
Safety Assessments[2]																		
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X		X	X													X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X		X							X							X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[2]																		
Haematology	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry (incl. LFT)	X		X	X						X							X	X
Biomarkers				X	X	X	X	X	X	X							X	X
Pregnancy Test [3]	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Immunogenicity			X														X	X
Efficacy Assessments[2]																		
Subject/Clinician Global Impression Rating				X			X			X			X				X	X
Subject/Clinician Rating of Response to Therapy							X			X			X				X	X
SGRQ				X			X			X			X				X	X

PARTS B&C Procedures	Fixed Run-in Part B		EW from Part B[7]	Randomization	Double-Blind Treatment Part C (window is ± 1 week)												IPDISC/EW Visit [7]
Visit	**B1**	**B2[1]**	**Part B EW**	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**	**C13**	**Exit Visit**	
Week of Study	**-4 ± 1**	**-4 ± 1[1]**		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Exacerbation review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry (pre- and post-albuterol/salbutamol)			X[8]	X			X			X			X				X	X
Healthcare resource utilization					X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review eDiary[4] (symptoms, rescue use, nocturnal awakenings, PEF, ACQ-5, missed days of work/school)	◄																	►
Worksheets/Diary/IP/ eCRF[2]																		
Administer open-label mepolizumab[4]	X	X																
Administer double blind study treatment				X[5]	X	X	X	X	X	X	X	X	X	X	X	X		
Dispense albuterol/salbutamol	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Collect albuterol/salbutamol	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense paper diary	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		
Dispense eDiary	X																	
Collect eDiary			X														X	X[6]
Collect/review paper diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT			X	X													X	X

PARTS B&C Procedures	Fixed Run-in Part B		EW from Part B[7]	Randomization	Double-Blind Treatment Part C (window is ± 1 week)												IPDISC/EW Visit [7]
Visit	**B1**	**B2**[1]	**Part B EW**	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**	**C13**	**Exit Visit**	
Week of Study	**-4 ± 1**	**-4 ± 1**[1]		**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Visit B2 is only intended for subjects who experience an exacerbation in the run-in Part B which is not resolved within 7 days of Visit C1 or subjects who fail eDiary Compliance Criteria (Protocol Section 6.3).
2. All assessments to be completed prior to dosing.
3. Urine pregnancy tests (U) should be conducted every 4 weeks for women of child bearing potential.
4. Subjects eDiary entries should be reviewed by the site weekly during Part C
5. An unblinding card will be dispensed after Randomization at Visit C1.
6. The eDiary is only collected at an Early Withdrawal visit and not at IPDISC in Part C.
7. IPDISC/EW visit should be conducted 4 ± 1 weeks from the subject's last dose
8. Only *pre*-bronchodilator spirometry required at this visit.

Table 4 Time and Events Table: Optional Open-Label Switch to Mepolizumab – Part D

PART D **Procedures**	**OPTIONAL Open-Label Switch to mepolizumab Part D[1] (window is ± 1 week)**														**IPDISC/EW Visit [8]**
Visit	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D13**	**Exit Visit**	
Week of Study[2]	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Safety Assessments[3]															
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination														X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG							X							X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[3]															
Haematology[4]				X			X			X				X	X
Chemistry (incl. LFT)							X							X	X
Pregnancy Test [5]	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Immunogenicity														X	X
Efficacy Assessments[3]															
Exacerbation review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry				X			X			X				X	X
Worksheets/Diary/IP/ eCRF[3]															
Administer open-label mepolizumab	X	X	X	X	X	X	X	X	X	X	X	X	X		
Dispense albuterol/salbutamol	X	X	X	X	X	X	X	X	X	X	X	X	X		
Collect albuterol/salbutamol	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense paper diary	X	X	X	X	X	X	X	X	X	X	X	X	X		
Review eDiary[6] (symptoms, rescue use, nocturnal awakenings, PEF, ACQ-5, missed days of work/school)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect eDiary														X	X[7]

PART D **Procedures**	**OPTIONAL Open-Label Switch to mepolizumab Part D[1] (window is ± 1 week)**														**IPDISC/EW Visit [8]**
Visit	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D13**	**Exit Visit**	
Week of Study[2]	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	
Collect/review paper diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT														X	X
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. The combined treatment period (Part C) and any switch to open-label mepolizumab (Part D) should not exceed a total duration of 52 weeks.
2. Subjects may enter the Open-label Switch Part D at any point during Part C provided they meet switch criteria, starting with the week of study that the switch is made and continuing until week 52, discontinuation of IP or early withdrawal.
3. All assessments to be completed prior to dosing
4. Haematology samples will be collected for each of the subject's first 3 visits of Part D, and then according to designated Visits in Table 4
5. Urine pregnancy tests (U) should be conducted every 4 weeks for women of child bearing potential.
6. The eDiary should be reviewed at each visit. Weekly review is not required in Part D.
7. The eDiary is only collected at an Early Withdrawal or Exit visit.
8. IPDISC/EW visit should be conducted 4 ± 1 weeks from the subject's last dose

11.3. Appendix 3: Assessment Windows and Visit Slotting

11.3.1. Analysis Visit Labels

When summarising data within Parts A/B of the study nominal clinic visit will be presented (in weeks) relative to the date of first dose of open-label treatment (Parts A/B). For example:

Screening = Week 0
Visit A1 = Week 4
Visit A2 = Week 8
etc.

When summarising data within Part C of the study nominal clinic visit will be presented (in weeks) relative to the date of first dose of double-blind treatment (Part C). For example:

Visit C1 = Week 0
Visit C2 = Week 4
Visit C3 = Week 8
etc.

When summarising data within Part D of the study nominal clinic visit will be presented (in weeks) relative to the clinic visit where each subject received the first dose of open-label treatment within Part D. For example, if a subject switched to open-label mepolizumab at Visit D4:

Visit D4 = Week 0
Visit D5 = Week 4
Visit D6 = Week 8
etc.

See Section 11.6.1 for the presentation of study days with each reporting period.

11.3.2. Visit Based Assessments

In some circumstances certain Visit 1 (Screening) assessments will not be performed and assessments will be copied forward from each subject's last clinic visit from the precursor studies MEA115666/201312. Refer to Section 5.2.3 for more details.

All other visits are scheduled to take place as specified in Appendix 2: Schedule of Activities. No assessment windows are defined for visit based assessments, hence 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 the subject will still be analysed under that visit.

See Section 11.3.3 and Section 11.3.4 for details regarding the slotting of data collected at an Early Withdrawal/Treatment Discontinuation Visit and unscheduled data to clinic visits for analysis.

11.3.3. Early Withdrawal / Treatment (IP) Discontinuation Visits

If a subject completes an Early Withdrawal or Treatment Discontinuation Visit at a visit where endpoint data were not scheduled to be collected, the data will be summarised and analysed (as appropriate) together with other data recorded as scheduled at the nominal visits according to the Time and Events schedule (Appendix 2: Schedule of Activities).

Parts A/B

Subjects who discontinue open-label mepolizumab/withdraw from study participation during Part A/B were expected to return to the clinic for an Early Withdrawal (EW) visit and to return any study materials approximately 4 weeks following their last dose of open-label mepolizumab. No additional follow-up is needed.

If a subject completes a Parts A/B Early Withdrawal Visit at a scheduled visit at which endpoint data were not scheduled to be collected, data will be slotted to the nearest adjacent visit within Part A/B where the endpoint data was scheduled to be collected according to the Time and Events schedule (Appendix 2: Schedule of Activities) unless data are already recorded at that visit.

Part C or Part D

Subjects who withdrew prematurely from treatment or from the study during Part C or Part D may have data recorded under either a nominal visit at which it was scheduled for collection, a nominal visit at which it was not scheduled for collection, or an early withdrawal/IP discontinuation visit.

Subjects switching from treatment within Part C to Part D following an asthma exacerbation are required to complete an IP discontinuation/switch visit with a full set of assessments at each subject's first Part D visit, prior to first dose with open-label mepolizumab per Appendix 2: Schedule of Activities. Such IP discontinuation/switch visits will be handled as a Treatment Discontinuation Visit as discussed below and data will attempt to be slotted to the nearest adjacent visit within Part C where the endpoint data was scheduled to be collected according to the Time and Events schedule (Appendix 2: Schedule of Activities) unless data are already recorded at that visit

If a subject was withdrawn from the study for any reason the Investigator must make every effort to have the subject to return to the clinic for an EW Visit approximately 4 weeks following the last dose to perform EW Visit assessments and to return all study-related materials. Assessments are described in Appendix 2: Schedule of Activities.

Subjects in study Part C or Part D who have permanently discontinued double-blind or open-label IP were not required to withdraw from the study. Subjects who have permanently discontinued IP and have not withdrawn consent may have continued in the study off-treatment.

Subjects wishing to remain in the study will have completed an IP Discontinuation Visit (approximately 4 weeks after the last dose at the same time as the next scheduled visit) and continued to attend the clinic visits at the protocol designated time intervals and completed eDiary daily and weekly entries for important efficacy and safety assessments.

If the subject was unable to visit the clinic to complete any study assessments which require physical presence of the subject, visits could have continued to occur by telephone contact to review exacerbations, adverse events and concomitant medications.

Subjects who have previously discontinued IP and have already completed their IP Discontinuation Visit (approximately 4 weeks following the last dose) but then decided at a later date that they no longer wish to participate in the study, will be asked to return to the clinic to complete an EW Visit approximately 4 weeks following the last clinic visit to complete any EW assessments and to return any remaining study materials. No additional safety follow-up visit is required.

If a subject completes an Early Withdrawal or Treatment Discontinuation Visit in Part C or Part D at a scheduled visit at which endpoint data were not scheduled to be collected, data will be slotted to the nearest adjacent visit within the appropriate reporting period (Part C or Part D) where the endpoint data was scheduled to be collected according to the Time and Events schedule (Appendix 2: Schedule of Activities) unless data are already recorded at that visit.

11.3.4. Unscheduled Visits

If a subject has an unscheduled assessment then this data will be slotted to the closest adjacent scheduled visit within the appropriate reporting period (Parts A/B, Part C or Part D) where the endpoint data was scheduled to be collected according to the Time and Events schedule (Appendix 2: Schedule of Activities) unless data are already recorded 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 included in any by visit summary tables; it will however be included in relevant summaries of any time on-treatment data and listings.

11.3.5. Definitions of Assessment Windows for Analyses

The following assessments will be collected on a daily basis using an eDiary device: morning peak flow, usage of rescue medication (i.e. salbutamol/albutamol), asthma symptom score, frequency of awakening due to asthma symptoms requiring use of rescue medication and time missed from work/school. Part C data will be summarised in 4-weekly periods relative to the first Part C dose, as shown in the below table.

Domain	Parameter	Analysis Window[1,2]		Analysis Timepoint
		Beginning Timepoint	Ending Timepoint	
eDiary Data	morning peak flow, usage of rescue medication (i.e. salbutamol/albuterol), asthma symptom score, frequency of awakening due to asthma symptoms and time missed from work/school	6 days prior to day of first dose	Date of first dose	Baseline
		Day after day of first dose	28 days after day of first dose	Week 0-4
		29 days after day of first dose	56 days after day of first dose	Week 4-8
		57 days after day of first dose	84 days after day of first dose	Week 8-12
		85 days after day of first dose	112 days after day of first dose	Week 12-16
		113 days after day of first dose	140 days after day of first dose	Week 16-20
		141 days after day of first dose	168 days after day of first dose	Week 20-24
		169 days after day of first dose	196 days after day of first dose	Week 24-28
		197 days after day of first dose	224 days after day of first dose	Week 28-32
		225 days after day of first dose	252 days after day of first dose	Week 32-36
		253 days after day of first dose	280 days after day of first dose	Week 36-40
		281 days after day of first dose	308 days after day of first dose	Week 40-44
		309 days after day of first dose	336 days after day of first dose	Week 44-48
		337 days after day of first dose	Week 52 visit date (or 364 days after day of first dose, if earlier)	Week 48-52

- [1] Only non-missing eDiary measurements will be summarised in 4-weekly windows, see Section 11.7.2 for further details.
- [2] Day of first dose within this table referring to first dose of double-blind IP at visit C1.
  For subjects analysis windowing to be restricted to 364 days following first dose of double-blind IP at visit C1.

Within Part A ACQ-5 assessments will be performed at scheduled clinic visits (according to Appendix 2: Schedule of Activities) and captured within the subject's eCRF. The ACQ-5 assessments within study Part B, Part C and Part D will be collected on a weekly basis using an eDiary device. Part C data will be summarised weekly relative to the first Part C dose, as shown in the below table.

Domain	Parameter	Target [1]	Analysis Window[2]		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
eDiary Data	ACQ-5		≥8 days prior to day of first dose		Run-in Period (Not to be summarised)
		Day 1	7 days prior to day of first dose	Date of first dose	Baseline
		Day 8	Day after date of first dose	11 days after date of first dose	Week 1
		Day 15	12 days after date of first dose	18 days after date of first dose	Week 2
		Day 22	19 days after date of first dose	25 days after date of first dose	Week 3
		Day 29	26 days after date of first dose	32 days after date of first dose	Week 4
		Day 36	33 days after date of first dose	39 days after date of first dose	Week 5
		Day 43	40 days after date of first dose	46 days after date of first dose	Week 6
		Day 50	47 days after date of first dose	53 days after date of first dose	Week 7
		Day 57	54 days after date of first dose	60 days after date of first dose	Week 8
		Day 64	61 days after date of first dose	67 days after date of first dose	Week 9
		Day 71	68 days after date of first dose	74 days after date of first dose	Week 10
		Day 78	75 days after date of first dose	81 days after date of first dose	Week 11
		Day 85	82 days after date of first dose	88 days after date of first dose	Week 12
		Day 92	89 days after date of first dose	95 days after date of first dose	Week 13
		Day 99	96 days after date of first dose	102 days after date of first dose	Week 14
		Day 106	103 days after date of first dose	109 days after date of first dose	Week 15
		Day 113	110 days after date of first dose	116 days after date of first dose	Week 16
		Day 120	117 days after date of first dose	123 days after date of first dose	Week 17
		Day 127	124 days after date of first dose	130 days after date of first dose	Week 18
		Day 134	131 days after	137 days after	Week 19

Domain	Parameter	Target [1]	Analysis Window[2]		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
			date of first dose	date of first dose	
		Day 141	138 days after date of first dose	144 days after date of first dose	Week 20
		Day 148	145 days after date of first dose	151 days after date of first dose	Week 21
		Day 155	152 days after date of first dose	158 days after date of first dose	Week 22
		Day 162	159 days after date of first dose	165 days after date of first dose	Week 23
		Day 169	166 days after date of first dose	172 days after date of first dose	Week 24
		Day 176	173 days after date of first dose	179 days after date of first dose	Week 25
		Day 183	180 days after date of first dose	186 days after date of first dose	Week 26
		Day 190	187 days after date of first dose	193 days after date of first dose	Week 27
		Day 197	194 days after date of first dose	200 days after date of first dose	Week 28
		Day 204	201 days after date of first dose	207 days after date of first dose	Week 29
		Day 211	208 days after date of first dose	214 days after date of first dose	Week 30
		Day 218	215 days after date of first dose	221 days after date of first dose	Week 31
		Day 225	222 days after date of first dose	228 days after date of first dose	Week 32
		Day 232	229 days after date of first dose	235 days after date of first dose	Week 33
		Day 239	236 days after date of first dose	242 days after date of first dose	Week 34
		Day 246	243 days after date of first dose	249 days after date of first dose	Week 35
		Day 253	250 days after date of first dose	256 days after date of first dose	Week 36
		Day 260	257 days after date of first dose	263 days after date of first dose	Week 37
		Day 267	264 days after date of first dose	270 days after date of first dose	Week 38
		Day 274	271 days after date of first dose	277 days after date of first dose	Week 39
		Day 281	278 days after date of first dose	284 days after date of first dose	Week 40
		Day 288	285 days after date of first dose	291 days after date of first dose	Week 41
		Day 295	292 days after date of first dose	298 days after date of first dose	Week 42
		Day 302	299 days after	305 days after	Week 43

Domain	Parameter	Target [1]	Analysis Window[2]		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
			date of first dose	date of first dose	
		Day 309	306 days after date of first dose	312 days after date of first dose	Week 44
		Day 316	313 days after date of first dose	319 days after date of first dose	Week 45
		Day 323	320 days after date of first dose	326 days after date of first dose	Week 46
		Day 330	327 days after date of first dose	333 days after date of first dose	Week 47
		Day 337	334 days after date of first dose	340 days after date of first dose	Week 48
		Day 344	341 days after date of first dose	347 days after date of first dose	Week 49
		Day 351	348 days after date of first dose	354 days after date of first dose	Week 50
		Day 358	355 days after date of first dose	361 days after date of first dose	Week 51
		Day 365	362 days after date of first dose onwards		Week 52

- [1] If multiple scores are available within analysis window see Section 11.6.1.
- [2] Day of first dose within this table referring to first dose of double-blind IP at visit C1.
  For subjects analysis windowing to be restricted to 364 days following first dose of double-blind IP at visit C1.

11.4. Appendix 4: Study Periods and Treatment Phases

11.4.1. Study Periods

The reporting of the study will be divided into three distinct periods, with displays reflecting data collected within each period separately:

- Period 1: Parts A/B – variable and fixed run-in periods combined, receiving open-label mepolizumab treatment
- Period 2: Part C – double-blind treatment period, receiving mepolizumab or placebo
- Period 3: Part D – optional treatment switch period, returning to open-label mepolizumab treatment

Data will be collected across all periods within a single study database and will be attributed to an individual period according to the time of occurrence/assessment relative to the attendance of subjects at specific visits as follows:

Study Period	Period Start	Period End
Period 1: Parts A/B	Date of Pre-screening visit	Subjects who are randomized and receive double-blind treatment: Day prior to Period 2 (Part C) start Subjects who are not randomized: Date of study conclusion (screen/run-in failure)
Period 2: Parts C	Date of first dose within Part C (Visit C1)	Subjects completing study Part C: Date of study conclusion Subjects discontinuing study treatment/withdrawing early from within Part C: Latest date of 1) Part C Early Withdrawal visit and 2) study conclusion Subjects who switch to study Part D: Day prior to Period 3 (Part D) start
Period 3: Parts D	Date of first dose within Part D	Subjects completing study Part D: Date of study conclusion Subjects discontinuing study treatment/withdrawing early from within Part D: Latest date of 1) Part D Early Withdrawal visit and 2) study conclusion

11.4.2. Treatment Phases (Exacerbations and Healthcare Resource Use)

Exacerbations and healthcare resource use will be classified into treatment phases according to the time of occurrence/assessment relative to the dates of the study treatment and/or the participation of subjects within specific study parts (as dictated by attendance at specific visits) as shown in the table below:

Treatment Phase	Definition
Pre-treatment	Onset Date & time < First dose of open-label mepolizumab
On-treatment (Parts A/B)	Subjects who are randomized and receive double-blind treatment: First dose of open-label mepolizumab ≤ Onset Date & time < First dose of double-blind treatment Subjects who are not randomized: First dose of open-label mepolizumab ≤ Onset Date & time ≤ Earliest of (1) Last dose of open-label mepolizumab + 28 days or (2) Early Withdrawal visit date [1]
Post-treatment (Parts A/B)	Subjects who are not randomized: Onset Date & time > Earliest of (1) Last dose of open-label mepolizumab + 28 days or (2) Early Withdrawal visit date [1]
On-treatment (Part C)	Subjects completing study Part C: First dose of double-blind treatment ≤ Onset Date & time ≤ C14 (Exit Visit) visit date Subjects discontinuing study treatment/withdrawing early from within Part C: First dose of double-blind treatment ≤ Onset Date & time ≤ Earliest of (1) Last dose of double-blind treatment + 28 days or (2) Early Withdrawal / IP Discontinuation visit date Subjects who switch to study Part D: First dose of double-blind treatment ≤ Onset Date & time < First dose of open-label mepolizumab within Part D
Post-treatment (Part C)	Subjects completing study Part C: Onset Date & time > C14 (Exit Visit) visit date Subjects discontinuing study treatment/withdrawing early from within Part C: Onset Date & time > Earliest of (1) Last dose of double-blind treatment + 28 days or (2) Early Withdrawal / IP Discontinuation visit date
On-treatment (Part D)	Subjects completing study Part D: First dose of open-label mepolizumab within Part D ≤ Onset Date & time ≤ D14 (Exit Visit) visit date Subjects discontinuing study treatment/withdrawing early from within Part D: First dose of open-label mepolizumab within Part D ≤ Onset Date & time ≤ Earliest of (1) Last dose of open-label mepolizumab within Part D + 28 days or (2) Early Withdrawal / IP Discontinuation visit date
Post-treatment (Part D)	Subjects completing study Part D: Onset Date & time > D14 (Exit Visit) visit date Subjects discontinuing study treatment/withdrawing early from within Part D: Onset Date & time > Earliest of (1) Last dose of open-label mepolizumab within Part D + 28 days or (2) Early Withdrawal / IP Discontinuation visit date

[1] Note subjects who are deemed not eligible for randomization at visit C1 will perform their Early Withdrawal visit and associated assessments at this visit.
Time of study treatment dosing and start/stop time of assessment should be considered, if collected.
Where the assessment occurs on the date of study treatment and time is not available, assessment assumed to have occurred following dosing.
Refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates in exacerbations.

11.4.3. Treatment Phases (Visit Based Efficacy and Safety Data)

Visit based efficacy data, safety data and eDiary data will be classified into treatment phases according to the time of occurrence/assessment relative to the dates of the study treatment and/or the participation of subjects within specific study parts (as dictated by attendance at specific visits) as shown in the table below:

Treatment Phase	Definition
Pre-treatment	Date & time ≤ First dose of open-label mepolizumab
On-treatment (Parts A/B)	Subjects who are randomized and receive double-blind treatment: First dose of open-label mepolizumab < Date & time ≤ First dose of double-blind treatment Subjects who are not randomized: First dose of open-label mepolizumab < Date & time ≤ Earliest of (1) Last dose of open-label mepolizumab + 28 days or (2) Early Withdrawal visit date [1]
Post-treatment (Parts A/B)	Subjects who are not randomized: Date & time > Earliest of (1) Last dose of open-label mepolizumab + 28 days or (2) Early Withdrawal visit date [1]
On-treatment (Part C)	Subjects completing study Part C: First dose of double-blind treatment < Date & time ≤ C14 (Exit Visit) visit date Subjects discontinuing study treatment/withdrawing early from within Part C: First dose of double-blind treatment < Date & time ≤ Earliest of (1) Last dose of double-blind treatment + 28 days or (2) Early Withdrawal / IP Discontinuation visit date Subjects who switch to study Part D: First dose of double-blind treatment < Date & time ≤ First dose of open-label mepolizumab within Part D
Post-treatment (Part C)	Subjects completing study Part C: Date & time > C14 (Exit Visit) visit date Subjects discontinuing study treatment/withdrawing early from within Part C: Date & time > Earliest of (1) Last dose of double-blind treatment + 28 days or (2) Early Withdrawal / IP Discontinuation visit date
On-treatment (Part D)	Subjects completing study Part D: First dose of open-label mepolizumab within Part D < Date & time ≤ D14 (Exit Visit) visit date Subjects discontinuing study treatment/withdrawing early from within Part D: First dose of open-label mepolizumab within Part D < Date & time ≤ Earliest of (1) Last dose of open-label mepolizumab within Part D + 28 days or (2) Early Withdrawal / IP Discontinuation visit date
Post-treatment (Part D)	Subjects completing study Part D: Date & time > D14 (Exit Visit) visit date Subjects discontinuing study treatment/withdrawing early from within Part D: Date & time > Earliest of (1) Last dose of open-label mepolizumab within Part D + 28 days or (2) Early Withdrawal / IP Discontinuation visit date

[1] Note subjects who are deemed not eligible for randomization at visit C1 will perform their Early Withdrawal visit and associated assessments at this visit.
Time of study treatment dosing and start/stop time of assessment should be considered, if collected.
Where the assessment occurs on the date of study treatment and time is not available, assessment assumed to have been performed prior to dosing.

Data classified in this manner will include questionnaires, lung function, laboratory assessments, liver events, immunogenicity, ECGs, vital signs and diary data.

11.4.4. Treatment Phases (Adverse Events and Cardiovascular Events)

Adverse events and cardiovascular events will be classified into treatment phases according to the time of occurrence relative to the dates of study treatment within specific study parts as shown in the table below:

Treatment Phase	Definition
Pre-treatment	Onset Date & time < First dose of open-label mepolizumab If mepolizumab treatment is never started, then all will be classified as pre-treatment.
On-treatment (Parts A/B)	Subjects who are randomized and receive double-blind treatment: First dose of open-label mepolizumab ≤ Onset Date & time < First dose of double-blind treatment Subjects who are not randomized: First dose of open-label mepolizumab ≤ Onset Date & time ≤ Last dose of open-label mepolizumab + 28 days
Post-treatment (Parts A/B)	Subjects who are not randomized: Onset Date & time > Last dose of open-label mepolizumab + 28 days
On-treatment (Part C)	Subjects who switch to study Part D: First dose of double-blind treatment ≤ Onset Date & time < First dose of open-label mepolizumab within Part D All other Part C Subjects: First dose of double-blind treatment ≤ Onset Date & time ≤ Last dose of double-blind treatment + 28 days
Post-treatment (Part C)	Subjects who do not switch to study Part D: Onset Date & time > Last dose of double-blind treatment + 28 days
On-treatment (Part D)	First dose of open-label mepolizumab within Part D ≤ Onset Date & time ≤ Last dose of open-label mepolizumab within Part D + 28 days
Post-treatment (Part D)	Onset Date & time > Last dose of open-label mepolizumab within Part D + 28 days

Time of study treatment dosing and start/stop time of event should be considered, if collected.
Where the event onset occurs on the date of study treatment and time is not available, event assumed to have occurred following dosing.
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 dose of treatment).
Refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates in adverse events and cardiovascular events.

11.4.4.1. Adverse Event Data Derivations

Treatment State	Definition
Onset Time Since 1st Dose*	If Treatment Start Date > AE Onset Date = AE Onset Date - Treatment Start Date If Treatment Start Date ≤ AE Onset Date = AE Onset Date - Treatment Start Date +1 Missing otherwise.
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	Adverse events are considered as drug-related if relationship is marked 'YES' on Inform/eCRF OR value is missing.
Severity	If adverse event severity is missing, severity is to be populated as 'UNKNOWN'
* Note: will be derived as time since 1st dose of within the respective study period (Part A/B, Part C or Part D) If less than 24 hours, will be derived in days, hours and minutes (where AE start datetime available). If greater than 24 hours or AE start datetime not available, will be derived in days	

11.4.5. Treatment Phases (Concomitant Medications)

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.

Concomitant medications will be classified into treatment phases according to start and stop dates for each medication relative to the dates of the study treatment within specific study parts as shown in the table below:

Treatment/Study Phase	Definition
Taken Before the Run-in	If Con-med Start Date < First dose of open-label mepolizumab or (Con-med Start Date is missing)
Taken During the Run-in (Parts A/B)	Subjects who are randomized and receive double-blind treatment: • If (Con-med Start Date < First dose of open-label mepolizumab or Con-med Start Date is missing) and (Con-med Stop Date ≥ First dose of open-label mepolizumab, or Con-med Stop date is missing) or • If First dose of open-label mepolizumab ≤ Con-med Start Date < First dose of double-blind treatment Subjects who are not randomized: • If (Con-med Start Date < First dose of open-label mepolizumab or Con-med Start Date is missing) and (Con-med Stop Date ≥ First dose of open-label mepolizumab, or Con-med Stop date is missing) or • If First dose of open-label mepolizumab ≤ Con-med Start Date ≤ Last dose of open-label mepolizumab + 28 days
Taken Post Treatment (Parts A/B)	Subjects who are not randomized: • Con-med Stop Date > Last dose of open-label treatment + 28 days, or • Con-med Stop Date is missing
Taken During Treatment (Part C)	Subjects who switch to study Part D: • If (Con-med Start Date < First dose of double-blind treatment or Con-med Start Date is missing) and (Con-med Stop Date ≥ First dose of double-blind treatment, or Con-med Stop date is missing) or • If First dose of double-blind treatment ≤ Con-med Start Date < First dose of open-label mepolizumab within Part D All other Part C Subjects: • If (Con-med Start Date < First dose of double-blind treatment or Con-med Start Date is missing) and (Con-med Stop Date ≥ First dose of double-blind treatment, or Con-med Stop date is missing) or • If First dose of double-blind treatment ≤ Con-med Start Date ≤ Last dose of double-blind treatment + 28 days
Taken Post Treatment (Part C)	Subjects who do not switch to study Part D: • Con-med Stop Date > Last dose of double-blind treatment + 28 days, or • Con-med Stop Date is missing
Taken During Treatment (Part D)	• If (Con-med Start Date < First dose of open-label mepolizumab within Part D or Con-med Start Date is missing) and (Con-med Stop Date ≥ First dose of open-label mepolizumab within Part D, or Con-med Stop date is missing) or • If First dose of open-label mepolizumab within Part D ≤ Con-med Start Date ≤

Treatment/Study Phase	Definition
	Last dose of open-label mepolizumab within Part D + 28 days
Taken Post Treatment (Part D)	• Con-med Stop Date > Last dose of open-label mepolizumab within Part D + 28 days, or • Con-med Stop Date is missing
Taken at Visit C1 (Randomization)	• If (Con-med Start Date < First dose of double-blind treatment or Con-med Start Date is missing) and (Con-med Stop Date ≥ First dose of double-blind treatment, or Con-med Stop date is missing)
Time Since 1st Dose (Days)*	If Treatment Start Date > Con-med Start Date = Con-med Start Date - Treatment Start Date If Treatment Start Date ≤ Con-med Start Date = Con-med Start Date - Treatment Start Date + 1 If Treatment Start Date or Con-med Start Date is missing = missing.
Duration (Days)	Con-med Stop Date –Con-med Start Date + 1

Refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates in concomitant medications.

* Note: will be derived as time since 1st dose of within the respective study period (Part A/B, Part C or Part D)

11.5. Appendix 5: Data Display Standards & Handling Conventions

11.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Area	: sb240563/mid201810
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.1.3 & ADaM IG Version 1.0) • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets (GSK Drug/MedDRA) will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files will be generated for the final reporting effort.	

11.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• All subject level listings will be located in the modular appendices as ICH listings of the GSK Clinical Study Report.

Formats
• Data within Part C will be reported according to the treatment each subject received for more than 50% of injections within Part C unless otherwise stated (see Section 5.1). • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision (decimal places) from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Nominal visits (planned time relative to dosing) will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).

• Unscheduled or unplanned readings will be presented within the subject's listings. • Scheduled visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings, summaries and statistical analyses.	
Unscheduled Visits	
• When possible, unscheduled assessments will be slotted to the closest adjacent scheduled visit where the endpoint data was scheduled to be collected and not already recorded at that 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 on-treatment' summaries and will also be presented in any relevant listings. See Section 11.3.4 for further details.	
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, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

11.6. Appendix 6: Derived and Transformed Data

11.6.1. General

Multiple Measurements at One Analysis Time Point
• Multiple ECG measurements may be performed (e.g. in triplicate) at a single clinic visit. See Section 11.6.4 for further details on handling these multiple measurements at a single visit. • If there are two values within a time window (as possible per Section 11.3.5) 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. • Participants having both High and Low values for Normal Ranges within summaries of any time on-treatment for safety parameters will be counted in both the High and Low categories of "Any time on-treatment" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day
• Study Day will be derived relative to the treatment start dates in each of the three reporting periods: 1) Study day (Parts A/B) will be calculated as the number of days from date of first dose of open-label treatment (Parts A/B): • Ref Date = Missing → Study day (Parts A/B) = Missing • Ref Date < Date of first dose of open-label treatment → Study day (Parts A/B) = Ref Date – Date of first dose of open-label treatment • Date of first open-label treatment ≤ Ref Data < Date of first double-blind treatment → Study day (Parts A/B) = Ref Date – (Date of first dose of open-label treatment) + 1 Subjects considered as screen failures (i.e. not receiving treatment within Parts A/B) will have study day (Parts A/B) populated as missing. 2) Study day (Part C) will be calculated as the number of days from date of first dose of double-blind treatment (Part C): • Ref Date = Missing → Study Day (Part C) = Missing • <u>Subjects who switch to study Part D:</u> Date of first double-blind treatment ≤ Ref Data < Date of first open-label Part D treatment → Study Day (Part C) = Ref Date – (Date of first dose of double-blind treatment) + 1 • <u>All other Part C Subjects:</u> Date of first double-blind treatment ≤ Ref Data → Study Day (Part C) = Ref Date – (Date of first dose of double-blind treatment) + 1 3) Study day (Part D) will be calculated as the number of days from date of first dose of open-label treatment within Part D: • Ref Date = Missing → Study day (Part D) = Missing • Date of first open-label Part D treatment ≤ Ref Data → Study day (Part D) = Ref Date – (First open-label mepolizumab dose within Part D) + 1

11.6.2. Study Population

Demographics
Age
• Only year of birth was collected for subjects; actual birth date was not collected. • Each subject's full birth date is available and will be utilised from each subject's first enrolled mepolizumab study: MEA112997, MEA115588 or MEA115575 • Each subject's age will be calculated as an integer value based on their imputed date of birth relative to the date of each subject's screening visit. • For those subjects randomized to double-blind treatment each subject's age will be also calculated based on their imputed date of birth relative to the date of the visit C1.
Body Mass Index (BMI)
• Calculated as Weight (kg) / Height $(m)^2$
Smoking Status
• At Visit C1 an update in each subject's smoking status since Screening (Visit 1) will be collected. • Where no change in smoking status is reported, the respective subject's smoking status information will be utilised within the analysis datasets at Visit C1 unchanged from Screening (Visit 1). • Where a change in smoking status is observed such that the subject started smoking, the subject will be presented as a 'Current Smoker' at Visit C1. • Where a change in smoking status is observed such that the subject stopped smoking, the subject will be presented as a 'Former Smoker' at Visit C1.
Baseline Characteristics
Disease Duration
• Prior to enrolment into study MEA115666, subjects previously enrolled into study MEA112997 • Similarly, prior to enrolment into study 201312, subjects previously enrolled into studies MEA115575 or MEA115588 followed by study MEA115661 • Each subject reported disease duration relative to the age of onset at the screening visit of the pre-cursor studies MEA112997 / MEA115588 / MEA115575. • Each subject's duration of asthma at Visit C1 will be derived as the total of (1) the disease duration up to the screening visit of study MEA112997 / MEA115588 / MEA115575 and (2) the duration from the screening visit of study MEA112997 / MEA115588 / MEA115575 to Visit C1.
Baseline OCS daily dose [Visit C1]
• 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 (Visit C1). 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. • If two corticosteroid records are seen to overlap on the day of first double-blind treatment, these overlapping records will be summed in order to obtain a total prednisone/prednisolone equivalent dose received.

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
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

Exposure

Continuous Mepolizumab Exposure Prior to Randomization (Visit C1)

- For each subject the period of continuous mepolizumab exposure prior to randomization (first dose of double-blind treatment at Visit C1) will be summarised considering mepolizumab treatment from the following precursor studies where the same individuals participated: MEA115666, MEA115588, MEA115575, MEA115661, 201312 in addition any mepolizumab treatment administered within 201810 Parts A/B. Study MEA112997 will not be considered in the assessment of continuous mepolizumab exposure prior to randomization since each subject experienced a prolonged gap in treatment of at least 12 months between studies MEA112997 and MEA115666.
- Number of days of continuous mepolizumab exposure prior to randomization will be calculated based on the formula:

  Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 29

  Note: where the first double-blind treatment at Visit C1 < treatment stop date + 29, the duration of

exposure will be truncated at the first double-blind treatment at Visit C1.

- The earliest date of initiating mepolizumab treatment will be considered when deriving each subject's total prior exposure, however if a gap of >84 days between any two doses of mepolizumab is experienced (corresponding to more than 2 consecutive missed doses), this exposure period can no longer be considered 'continuous'. If such an instance occurs the subject's period of continuous mepolizumab treatment will be derived from the first dose of mepolizumab following this gap in treatment.
- If a subject experiences a gap of >12 weeks (84 days) between any two doses of mepolizumab within studies MEA115666 or 201312 this will exclude the subject from entry into 201810 (Inclusion Criterion #2).

Extent of Exposure

- Exposure data will be reported separately from each period (Parts A/B, Part C and Part D).
- Number of days of exposure to study drug will be calculated based on the formula:

  Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 29

  Note: where subjects transition between periods (e.g. from Parts A/B to Part C, or equivalently from Part C to Part D) and the first treatment within the next period < treatment stop date + 29, the duration of exposure within the preceding period will be truncated at the first treatment within the subsequent period.
- The extent of exposure will also be summarised as the number of study treatments administered.

11.6.3. Efficacy

Exacerbations

- Within each subject, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation and programmatically collapsed into a single exacerbation. Exacerbations for which the collapsing has already been performed will be included in the summaries and analyses. Exacerbations will be displayed in listings as captured within the eCRF. Exacerbations which are programmatically collapsed into a single exacerbation will be highlighted.
- The programmatically collapsed exacerbation records will be constructed as follows:
  - Start date (ASTDT) is the start date of the first exacerbation in the series
  - End date (AENDT) is the end date of the last exacerbation in the series
  - Outcome (CEOUT) is the worst outcome in the series (worst to best is Fatal, Not Resolved, Resolved)
  - Cause (EBCAUSE) is the cause associated with the first exacerbation in the series
  - Clinical significance of exacerbation (ACAT) are set to 'Clinically significant' if any value for the respective variable in the series equals 'Clinically significant' (see Section 7.1.5.2)
  - Withdrawal due to exacerbation (EBWD), OCS taken for exacerbation (OCSEXB), corticosteroids taken for exacerbation (CTSEXB), hospitalization due to exacerbation (HSPEXB), emergency visit due to exacerbation (EREXB), and intubation for exacerbation (INTUBEXB) are set to 'Y' if any value for the respective variable in the series equals 'Y'
  - Number of telephone calls (TPCNUM), home day visits (HMDYVSN), home night visits (HMNTVSN), home day+night visits (HMDYNTV), office visits (OFCVSN), urgent care/outpatient visits (UCOUTVSN), emergency room visits (ERVSN), days in intensive care (ICSDYNUM), days in general ward (GWDYNUM) and days hospitalized (HSPDYNUM) are the sum of all of the values in the series for each respective variable

Blood Eosinophils

- Blood eosinophils 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 will be 0.5 * 0.01 10^9/L = 0.005 10^9/L as in previous mepolizumab studies).

Patient Reported Outcomes/Questionnaires

Asthma Control Questionnaire (ACQ)-5

- The ACQ-5 questionnaire consists of 5 symptom related questions (Q1-Q5) and requires a 1 week recall.
- In Part A subjects self-complete the ACQ-5 at specified clinic visits (see Section 11.2) on paper with their responses transcribed into the eCRF. In Parts B, C or D subjects self-complete the ACQ-5 on their eDiary once weekly.
- The five questions enquire about the frequency and/or severity of symptoms over the previous week (nocturnal awakening on waking in the morning, activity limitation, and shortness of breath, wheeze).
- 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, 1999; Juniper, 2005].
- 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.
- A subject will be deemed to have experienced a decrease in asthma control (non-responder) if the subject has a ≥0.5 increase in ACQ-5 score from Baseline. ACQ-5 Responder/Non-responder category will be missing if the ACQ-5 score is missing.

St George's Respiratory Questionnaire (SGRQ)

- The SGRQ comprises 50 questions designed to measure Quality of Life in patients with diseases of airway obstruction, measuring symptoms, impact, and activity with a recall period of 4 weeks.
- Scores are expressed as the percentage of overall impairment with 100 equal to the worst possible health and 0 the best.
- Scoring of each domain of the SGRQ (Symptoms, Activity, Impacts) and the Total score are described in the St George's Respiratory Questionnaire Manual (Version 2.3).
- A subject will be deemed to have experienced a clinically meaningful worsening of health-related quality of life (non-responder) if the subject has a ≥4 increase in SGRQ score from Baseline. SGRQ Responder/Non-responder category will be missing if the Total SGRQ score is missing.

Global Impression of Disease Severity Rating

- The investigator (or designee) and subject will complete a Global Impression of Disease Severity question at Randomization and visits described in Table 3.
- This single global question will ask subjects and clinicians to rate the subject's asthma severity on a four-point scale (mild, moderate, severe, very severe)

Rating of Response to Therapy

- The investigator (or designee) and subject will be asked to rate the subject's response to therapy at specified visits (Table 3).
- This is an overall evaluation of response to treatment, as compared to Visit C1.
- This questionnaire/assessment will be conducted separately by the investigator (or designee) and the subject using a seven-point rating scale as follows:
  - 1 = significantly improved
  - 2 = moderately improved
  - 3 = mildly improved
  - 4 = no change

5 = mildly worse
6 = moderately worse
7 = significantly worse

Spirometry (Lung Function)

- Spirometry will be performed to assess FEV_1 and FVC using the sites own equipment at specified clinic visits (see Section 11.2) on paper with their responses transcribed into the eCRF. Subjects should withhold rescue albuterol/salbutamol for ≥ 6 hours and LABAs or ICS/LABA fixed dose combinations for ≥ 12 hours prior to spirometry, if possible.
- At all spirometry assessments conducted within Parts B and C, both pre- and post-bronchodilator spirometry will be obtained. All spirometry assessments in Parts A and D will be pre-bronchodilator only.

Percent Predicted FEV_1

- FEV_1 % of predicted normal will be derived using the Global Lung Function Initiative 2012 look-up tables which are based on the Quanjer equations [Quanjer, 2012] according to the Race/Ethnicity designations specified below:

Collected Race[1]	**Quanjer Designation**
African American/African Heritage	African-American calculation will be applied
American Indian or Alaskan Native	Other calculation will be applied
Asian-Central/South Asian Heritage	South East Asian calculation will be applied
Asian-East Asian Heritage	North East Asian calculation will be applied
Asian-Japanese Heritage	Other calculation will be applied
Asian- South-east Heritage	South East Asian calculation will be applied
Native Hawaiian or Other Pacific Islander	Other calculation will be applied
White-Arabic/North African Heritage	Caucasian calculation will be applied
White-White/Caucasian/European Heritage	Caucasian calculation will be applied

NOTE: If multiple races are selected for a single subject then the "Other" calculation will be applied.

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 at a given clinic visit from the same spirometry assessment.

Reversibility

- Bronchodilator responsiveness (reversibility) will be calculated as the absolute difference (mL) and percentage difference (%) in pre- and post-bronchodilator FEV_1 values at a given clinic visit from the same spirometry assessment.

Electronic Diary (eDiary)

- The subject will record the following parameters daily in the eDiary from Visit B1 until the completion of Part C or Part D:
  - Morning peak flow (best of three), before rescue medication usage (L/min).
  - Asthma symptom score over the previous 24-hours using a 6-point scale
  - Occasions of rescue medication usage over the previous 24-hours
  - Frequency of awakening due to asthma symptoms requiring rescue medication use
- Subjects who work for pay or go to school on a regular basis will record in the eDiary any full and part days of missed work or school due to asthma.
- Whilst in Part B, C or D subjects self-complete the ACQ-5 on their eDiary once weekly (see above for details of this questionnaire).

Healthcare Resource Utilization
• All unscheduled asthma-related visits to a physician's office, visits to urgent care, visits to the emergency department, and hospitalizations associated with the subject's asthma will be recorded in the eCRF. • Healthcare resource use will be collected as unscheduled asthma-related healthcare resource use (1) associated with an asthma exacerbation, and (2) not associated with an asthma exacerbation. Additionally, healthcare resource use will be combined in order to summarise total unscheduled asthma-related healthcare resource use. • For consistency, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation (see above for details of further details on collapsing exacerbations) • The number of days in hospital is collected separately for the number of days in (1) intensive care and (2) in general ward This information is additionally collected separately for (1) associated with an asthma exacerbation, and (2) not associated with an asthma exacerbation. Therefore: o Number of days in hospital = Number of days in intensive care + days in general ward o Total days in hospital due to asthma = Number of days in hospital associated with an exacerbation + Number of days in hospital not-associated with an exacerbation

11.6.4. Safety

Adverse Events

Adverse Events of Special Interest

- Adverse events of special interest (AESIs) of systemic reactions (including systemic reactions meeting Sampson's criteria for anaphylaxis) and local injection site reactions are collected via targeted eCRF pages within the study. Events captured on the eCRF as systemic reactions will be further categorized as allergic/hypersensitivity reactions or non-allergic reactions. 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. For further details of how relevant preferred terms are identified are detailed within the Program Safety Analysis Plan (PSAP).

Exposure Adjusted Adverse Events

- The number of events per 1000 subject-years of exposure will be calculated as:

$$\frac{1000 * Number\ of\ Adverse\ Events}{(Total\ Duration\ of\ Exposure\ in\ Days)/365.25}$$

Laboratory Parameters

Haematology and Clinical Chemistry

- 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
- Regarding blood eosinophil laboratory data see Section 11.6.3.
- See Section 11.8 for further details regarding laboratory results of potential clinical concern.

ECG Parameters

- Multiple ECG measurements may be performed (e.g. in triplicate) at a single clinic visit.
- If multiple ECGs are performed at a single visit, ECG parameters (such as QTcB or QTcF) will be based on the average value of each measurement ECG.
- If multiple ECGs are performed at a single visit, ECG interpretations will be based on the worst-case interpretation across the ECGs performed, considering the following to be of increasing severity:
  - No Result, Unable to Evaluate, Normal, Abnormal, Abnormal – Possibly Significant

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) on-treatment 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 ≤ 60
  - >60

Immunogenicity

- Clinical samples are tested in a sequence of binding anti-drug antibody (ADA) and neutralising antibody assays:
  - 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.
  - 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.
  - 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.
  - 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 mepolizumb ADA (screening/confirmation/titration) assay version 2011N122789_03 is performed at a Alliance Pharma (method 120711M01.V02). The mepolizumb Nab assay version 2011N129752_03 is being performed within GSK.

11.7. Appendix 7: Reporting Standards for Missing Data

11.7.1. Premature Withdrawals

Element	Reporting Detail
General	• A subject will be considered to have completed randomized study treatment if he/she receives study treatment at Visit C13 (Week 48). • A subject will be considered to have completed study treatment if he/she receives study treatment at Visit C13 or D13 (Week 48). • A subject will be considered to have completed the study if they continue to participate in the study until the Part C/Part D Exit Visit assessments have been completed (regardless of whether the subject completed the study treatment schedule). • Subjects who discontinue study treatment or withdraw early will not be replaced in the study. • The number of subjects who discontinue randomized study treatment or withdraw early will be summarised and listed. • All available data from participants who were withdrawn from the study will be listed and all available data up to and including the date of early withdrawal will be included in summary tables and figures, unless otherwise specified. • Withdrawal visits will be slotted to an analysis clinic visit as per Section 11.3.2 for summary tables/figures and data will be listed under the collected early withdrawal visit.
Pre-Screen Failures, Screen Failures and Run-in Failures	For the purposes of this study pre-screen failures, screen failures and run-in failures will be defined as follows: • Subjects will be assigned a study number at the time of signing the informed consent (Pre-screen Visit). Subjects who do not progress to the Screening Visit will be deemed a pre-screen failure. • Those subjects that complete at least one additional Visit 1 (Screening) procedure but do not enter the run-in period will be designated as screen failures. • Those subjects that enter Part A/Part B (run-in period), but are not randomized, will be designated as run-in failures.

11.7.2. Handling of Missing Data

Element	Reporting Detail

General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument:
	  ○ These data will be indicated by the use of a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the listing.
	  ○ Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as reported.
	• Results which are found to be below the limit of quantification (BLQ) are not missing data and will be included in all displays. See Section 11.6 for the handling of this data.
	• 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 10^9/L = 0.005 10^9/L for previous mepolizumab studies).
	• The ACQ-5 score will be considered as missing if 2 or more items of the questionnaire are not completed at a visit. ACQ-5 Responder/Non-responder category will be missing if the ACQ-5 score is missing.

Element	Reporting Detail
	• Scoring of each domain of the SGRQ (Symptoms, Activity, Impacts) and the Total score are described in the St George's Respiratory Questionnaire Manual (Version 2.3), including possible missing scores following missed items. SGRQ Responder/Non-responder category will be missing if the Total SGRQ score is missing. • Missing values will not be imputed for any of the other endpoints. • When handling eDiary parameters (see Section 11.6.3) missing responses in each patient's daily diary will be assumed to be missing at random. As a result only non-missing eDiary measurements will be summarised in 4-weekly windows (see Section 11.3.5) and only non-missing eDiary measurements will be considered in the exploratory endpoint of Time to worsening of asthma which is defined according to the four measured eDiary parameters (see Section 7.3.2.1).
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

11.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• The eCRF allows for the possibility of missing or partial dates (i.e., only month and year is captured) to be recorded for event start and end dates. • The recorded missing or partial date will be displayed in listings as captured.

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' (first of the month) will be used for the day and 'Jan' will be used for the month. However, if this results in a date prior to the start of double-blind treatment and the event could possibly have occurred during double-blind treatment from the partial information, then the start date of double-blind treatment date will be assumed to be the start date, as per Appendix 4: Study Periods and Treatment Phases.
	  ○ If the partial date is a stop date, a '28/29/30/31' (last day of the month) will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.

Adverse Events, Exacerbations and Healthcare Resource Use	• Any partial dates for adverse events, cardiovascular 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' (first of the month) will be used for the day and 'Jan' will be used for the month. However, if this results in a date prior to the start of treatment and the event could possibly have occurred during treatment from the partial information, then the study treatment start date will be assumed to be the start date, as per Appendix 4: Study Periods and Treatment Phases.
	  ○ If the partial date is a stop date, a '28/29/30/31' (last day of the month) will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.
	• The above listed imputations will also be applied when calculating the time to onset and the duration of the event containing missing or partial start and end dates.
	• Completely missing start or end dates (i.e. no year specified) will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

11.8. Appendix 8: Values of Potential Clinical Importance

11.8.1. Laboratory Values

Chemistry Values of Potential Clinical Concern

Laboratory Parameter	Age	Sex	Units	Clinical Concern Low Flag (< x)	Clinical Concern High Flag (> x)
Calcium	≥3	Both	mmol/L	1.50	3.24
Glucose	≥1	Both	mmol/L	2.2	27.8
Potassium	≥3	Both	mmol/L	2.8	6.5
Sodium	≥0	Both	mmol/L	120	160
ALT (SGPT)	3-12	Both	U/L		>143 U/L (and Total Bilirubin > 43 µmol/L)
ALT (SGPT)	≥13	Both	U/L		>239 U/L (and Total Bilirubin > 43 µmol/L)

Haematology Values of Potential Clinical Concern

Laboratory Parameter	Age	Sex	Units	Clinical Concern Low Flag (< x)	Clinical Concern High Flag (> x)
Hematocrit	≥12	Both	Ratio of 1	0.201	0.599
Haemoglobin	≥12	Both	g/L	71	199
Platelet Count	≥1	Both	$x10^9$/ L	31	1499
While Blood Cell Count (WBC) / Leukocytes	≥12	Both	$x10^9$/ L	1.1	

11.9. Appendix 9: Guidelines for Exacerbation Verification Process

Purpose

The purpose of this appendix is to describe the methodology to be used to determine if exacerbations recorded by the investigators (or designees) in InForm are based on objective assessments of asthma deterioration. These evaluations will be made in a blinded manner. All exacerbations recorded in InForm will be compared with data collected in the eDiary and if necessary other pages in InForm. This process will determine whether the exacerbation forms part of the primary endpoint analysis (clinically significant exacerbations).

It is expected that all exacerbations reported as such meet the basic protocol definition:

Worsening of asthma which requires use of systemic corticosteroids[1] and/or hospitalisation and/or Emergency Department (ED) visits.

[1]*For all subjects, IV or oral steroid (e.g., prednisone) for at least 3 days or a single IM corticosteroid dose is required. For subjects on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days is required.*

Responsibilities

The in-stream review will be performed by the medical monitor (or delegate) on the study. This review will be performed at approximately 3 month intervals during the study, and will be performed on all resolved exacerbations reported up to that point. The review will be done on complete data.

Prior to the review performed by the medical monitor (or delegate), the data will have undergone a clinical review to ensure it meets basic protocol criteria for an exacerbation (stated above).

Guidelines

The intention-to-treat principle will be used in identifying events to be evaluated. As a result, all cases will be reviewed whether or not the subject received randomized treatment and whether or not he/she continued to receive the randomized treatment for the planned duration of the study. Evaluations will be performed blinded to study treatment assignments.

Evaluation Process

Clinically Significant Asthma Exacerbations

In order to provide an objective assessment of the circumstances linked to the clinical decision that defines asthma exacerbations, the investigator must take into account changes on one or more of the following parameters recorded in the subject's eDiary:

- decrease in morning peak flow
- increase in the use of rescue medication
- increase in the frequency of nocturnal awakening due to asthma symptoms requiring rescue medication use
- increase in overall asthma symptom score

This clinical verification process is designed to verify that the exacerbations recorded by the investigator are associated with objective evidence, such as the eDiary parameters described above.

The following steps will be followed for verification of asthma exacerbations:

1. Clinical Review will initially be performed by the CIL (Clinical Investigation Leader) to evaluate each exacerbation to determine whether the event meets the protocol definition (shown above). Follow up will be done with the Investigator in the event that data needs to be queried. This initial clinical review will be performed for all study Parts (pre-screen, A, B, C and D).
2. For exacerbations that start within study Parts B, C or D the medical monitor (or delegate) will review each exacerbation in InForm and verify the exacerbation against eDiary data (extracted from the ERT Portal), to confirm the exacerbation was associated with one of the following:
    a. Decreases in peak flow:
        i. as flagged by an alert in the eDiary (Decrease in morning PEF ≥30% on at least two of three successive days, compared with baseline) or;
        ii. any other decrease judged by the medical monitor (or delegate) to be clinically significant
    b. Increase in rescue medication use:
        i. as flagged by an alert in the eDiary (An increase of ≥50% in rescue medication on at least two of three successive days, compared with the average use for the previous week) or;
        ii. any other increase judged by the medical monitor (or delegate) to be clinically significant (e.g. ≥4 puffs in 2 or more consecutive days)
    c. Increase in nocturnal awakenings due to asthma symptoms requiring use of rescue medication
        i. as flagged by an alert in the eDiary (Awakening due to asthma symptoms requiring rescue medication use for at least two of three successive nights) or;
        ii. any other increase judged by the medical monitor (or delegate) to be clinically significant

d. Changes in Asthma Symptoms (increase in overall asthma symptom score):
    i. as flagged by an alert in the eDiary (A symptom score of 5 for at least two of three successive days) or;
    ii. any other change judged by the medical monitor (or delegate) to be clinically significant (e.g. ≥4 during 2 or more consecutive days when baseline is 0)

No eDiary is provided to the subject prior to visit B1; therefore this and latter process steps will not be performed on exacerbations which start within the pre-screen period or Part A of the study.

3. The medical monitor (or delegate) will review data in the eDiary 10 days prior to the event start date and 5 days post the event start date. In exceptional circumstances data from outside this window may be considered adequate evidence.
4. If sufficient evidence was available within the eDiary data the medical monitor (or delegate) will confirm that the exacerbation is "*clinically significant*" within the CRF and will tick the relevant check-box (i.e. peak flow; rescue med use; nocturnal awakenings; asthma symptoms) based on the objective evidence available.
5. For each exacerbation for which objective evidence is not available in the eDiary data the medical monitor (or delegate) will follow up with the investigator to determine if there is alternative objective data (not in the eDiary) to support it being a "*clinically significant*" exacerbation.
6. A final decision will be made by the medical monitor on whether exacerbations with no supporting eDiary data but possibly other objective data can be included as part of the primary endpoint analysis of "*clinically significant"* exacerbations.
7. If an exacerbation with no eDiary data to support it is deemed as having another source of objective evidence, the medical monitor (or delegate) will confirm that the exacerbation is "*clinically significant*" within the CRF and will update the comments section of the InForm adjudication page to clearly specify what evidence is supporting the decision.
8. In the event that the investigator is unable to provide objective evidence to support the exacerbation, then the event will be confirmed as an "*Investigator- defined*" exacerbation within the CRF. Frequencies of "*Investigator- defined*" exacerbations will be summarised within the analysis of efficacy .

Documentation of Discussions with Investigator

In the event that the medical monitor (or delegate) has a discussion with the investigator about an exacerbation that does not have eDiary data to support it, the contact (telephone/email) should be documented with the following:

- Date of conversation
- Details of Discussion
- Decision
- Action Item

This documentation will be filed and archived as part of the central study file.

11.10. Appendix 10: Abbreviations & Trademarks

11.10.1. Abbreviations

Abbreviation	Description
ACQ	Asthma Control Questionnaire
ADA	Anti-drug Antibody
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
AM	Morning (ante meridiem)
ASE	All Subjects Enrolled
AT	As Treated
ATC	Anatomical Therapeutic Chemical
BLQ	Below Limit of Quantification
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CIL	Clinical Investigation Leader
CS	Corticosteroid
CSR	Clinical Study Report
CTR	Clinical Trial Register
CVT	Cardiac, Vascular and Thromboembolic
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
ED	Emergency Department
eDiary	Electronic Diary
EW	Early Withdrawal
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
FEV_1	Forced expiratory volume in 1 second
FVC	Forced Vital Capacity
GSK	GlaxoSmithKline
HbsAg	Hepatitis B Surface Antigen
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
IDSL	Integrated Data Standards Library
IG	Implementation Guide
IM	Intramuscular
IP	Investigational Product
IPDISC	Investigational Product Discontinuation
IRT	Interactive Response Technology
ITT	Intent-To-Treat
IV	Intravenous
kg	Kilograms
LABA	Long-acting beta-agonist

Abbreviation	Description
LFT	Liver Function Test
LLQ	Lower Limit of Quantification
MMRM	Mixed Model Repeated Measures
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliters
Nab	Neutralising Antibody
OCS	Oral Corticosteroids
PCI	Potential Clinical Importance
PDMP	Protocol Deviation Management Plan
PEF	Peak Expiratory Flow
PP	Per Protocol
PSAP	Program Safety Analysis Plan
PT	Preferred Term
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAMOS NG	Randomization & Medication Ordering System Next Generation
RAP	Reporting & Analysis Plan
RTF	Rich Text Format
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SC	Subcutaneous
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SGRQ	St. George's Respiratory Questionnaire
SMQ	Standard MedDRA Query
SOC	System Organ Class
SRM	Study Reference Manual
TFL	Tables, Figures & Listings
TMF	Trial Master File
TST	Therapeutic Standards Team
WBC	White Blood Cell

11.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

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SAS

11.11. Appendix 11: List of Data Displays

11.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Parts A/B		
Section	**Tables**	**Figures**
Study Population	1.1 to 1.12	N/A
Efficacy	N/A	N/A
Safety	3.1 to 3.52	N/A
Part C		
Section	**Tables**	**Figures**
Study Population	1.13 to 1.34	1.1
Efficacy	2.1 to 2.49	2.1 to 2.17
Safety	3.53 to 3.107	3.1 to 3.2
Part D		
Section	**Tables**	**Figures**
Study Population	1.35 to 1.40	N/A
Efficacy	2.50	2.18
Safety	3.108 to 3.158	N/A
Listings		
Section	**Listings**	
ICH Listings	1 to 46	

11.11.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays will be provided on request.

11.11.3. Deliverables

Delivery[1]	Description
SAC	Final Statistical Analysis Complete

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

11.11.4. Study Parts A/B

11.11.4.1. Study Population Tables (Parts A/B)

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Population Analysed					
1.1.	ASE	ES4	Summary of Participant Disposition within Each Study Period	ICH E3 Presenting the number of subjects in each reporting period (Parts A/B, C, D)	SAC
1.2.	ASE	SHELL	Summary of Study Populations (Parts A/B)	IDSL Include All Subjects Enrolled and As Treated (Parts A/B) Populations Also include number of subjects entering immediately into Part A/Part B	SAC
Subject Disposition					
1.3.	ASE	ES6	Summary of Screening Status and Reasons for Screen Failure (Parts A/B)	Journal Requirements	SAC
1.4.	ASE	IE2	Summary of Failed Inclusion/Exclusion/Continuation Criteria for Screen Failures (Parts A/B)		SAC
1.5.	AT (Part A/B)	IE2	Summary of Failed Inclusion/Exclusion/Continuation Criteria for Subjects within the As Treated Population (Parts A/B)		SAC
1.6.	AT (Part A/B)	ES8	Summary of Subject Status and Reason for Study Withdrawal (Parts A/B)	ICH E3, FDAAA, EudraCT	SAC
Medical Conditions					
1.7.	AT (Part A/B)	MH4	Summary of Past Medical Conditions (Parts A/B)	ICH E3	SAC
1.8.	AT (Part A/B)	MH4	Summary of Current Medical Conditions (Parts A/B)	ICH E3	SAC
1.9.	AT (Part A/B)	FH1	Summary of Cardiovascular Assessments – Family History (Parts A/B)	Note: Family history in women <65 years or men < 55 years (first degree relatives only). Half siblings considered first degree relatives	SAC
1.10.	AT (Part A/B)	FH1	Summary of Cardiovascular Assessments – Screening Questions (Parts A/B)		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Protocol Deviation					
1.11.	AT (Part A/B)	DV1	Summary of Important Protocol Deviations (Parts A/B)	ICH E3	SAC
Exposure					
1.12.	AT (Part A/B)	SHELL	Summary of Exposure to Study Treatment (Parts A/B)	ICH E3 See Study Population Table 1.1 (204471 'FINAL_01' reporting effort)	SAC

11.11.4.2. Safety Tables (Parts A/B)

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	AT (Part A/B)	SHELL	Overview of Adverse Events (Parts A/B)		SAC
3.2.	AT (Part A/B)	AE1	Summary of On-Treatment Adverse Events by System Organ Class and Preferred Term (Parts A/B)	ICH E3	SAC
3.3.	AT (Part A/B)	AE5	Summary of On-Treatment Adverse Events by Maximum Intensity by System Organ Class and Preferred Term (Parts A/B)	ICH E3 Add a Total column across all severities	SAC
3.4.	AT (Part A/B)	AE3	Summary of Common (≥3%) On-treatment Adverse Events by Overall Frequency (Parts A/B)	ICH E3 ≥3% (prior to rounding to nearest percent)	SAC
3.5.	AT (Part A/B)	AE1	Summary of On-Treatment Drug-Related Adverse Events by System Organ Class and Preferred Term (Parts A/B)	ICH E3	SAC
3.6.	AT (Part A/B)	AE5	Summary of On-Treatment Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity (Parts A/B)	Add a Total column across all severities	SAC
3.7.	AT (Part A/B)	SHELL	Summary of On-Treatment Adverse Events by Age Group (12-17, 18-64, ≥65 years) (Parts A/B)		SAC
3.8.	AT (Part A/B)	SHELL	Summary of On-Treatment Adverse Events by Highest Anti Drug Antibody Result At Any Time On-Treatment (Parts A/B)		SAC
3.9.	AT (Part A/B)	AE15	Summary of Common (≥3%) Non-serious On-Treatment Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) (Parts A/B)	FDAAA, EudraCT ≥3% (prior to rounding to nearest percent)	SAC
3.10.	AT (Part A/B)	AE1	Summary of On-Treatment Drug-Related Non-Serious Adverse Events by System Organ Class and Preferred Term (Parts A/B)	Table required for plain language summary	SAC
Serious and Other Significant Adverse Events					
3.11.	AT (Part A/B)	AE1	Summary of Pre-Treatment Serious Adverse Events by System Organ Class and Preferred Term (Parts A/B)		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.12.	AT (Part A/B)	AE1	Summary of On-Treatment Serious Adverse Events by System Organ Class and Preferred Term (Parts A/B)		SAC
3.13.	AT (Part A/B)	SHELL	Summary of On-Treatment Serious Adverse Events by Age Group (12-17, 18-64, ≥65 years) (Parts A/B)		SAC
3.14.	AT (Part A/B)	AE1	Summary of On-Treatment Fatal Serious Adverse Events (Parts A/B)		SAC
3.15.	AT (Part A/B)	SHELL	Summary of On-Treatment Fatal Serious Adverse Events by Age Group (12-17, 18-64, ≥65 years) (Parts A/B)		SAC
3.16.	AT (Part A/B)	AE1	Summary of On-Treatment Non-Fatal Serious Adverse Events by System Organ Class and Preferred Term (Parts A/B)		SAC
3.17.	AT (Part A/B)	AE1	Summary of On-Treatment Drug-Related Serious Adverse Events by System Organ Class and Preferred Term (Parts A/B)	Table required for plain language summary	SAC
3.18.	AT (Part A/B)	AE1	Summary of On-Treatment Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term (Parts A/B)	IDSL	SAC
3.19.	AT (Part A/B)	AE16	Summary of On-Treatment Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) (Parts A/B)	FDAAA, EudraCT	SAC
Adverse Events of Special Interest					
3.20.	AT (Part A/B)	SHELL	Summary of On-treatment Serious Adverse Events and Adverse Events of Special Interest (Parts A/B)		SAC
3.21.	AT (Part A/B)	AE1	Summary of On-Treatment Systemic Reactions Meeting Anaphylaxis Criteria (Parts A/B)	Present by Anaphylactic Criterion 1, 2 and 3 rather than SOC as shown in AE1 Insert footnote: “Events displayed are a subset of reactions defined by the Investigator as being systemic”	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.22.	AT (Part A/B)	SHELL	Summary Profile of On-Treatment Systemic Reactions Meeting Anaphylaxis Criteria (Parts A/B)	Insert footnote: "Events displayed are a subset of reactions defined by the Investigator as being systemic"	SAC
3.23.	AT (Part A/B)	AE1	Summary of On-Treatment Adverse Events Defined by the Investigator as Being Systemic (non-allergic or allergic/hypersensitivity) Reactions (Parts A/B)		SAC
3.24.	AT (Part A/B)	SHELL	Summary Profile of On-Treatment Systemic (non-allergic or allergic/hypersensitivity) Reactions (Parts A/B)		SAC
3.25.	AT (Part A/B)	SHELL	Summary Profile of On-Treatment Systemic Allergic Reactions (Parts A/B)		SAC
3.26.	AT (Part A/B)	SHELL	Summary Profile of On-Treatment Systemic Non-Allergic Reactions (Parts A/B)		SAC
3.27.	AT (Part A/B)	AE1	Summary of On-Treatment Adverse Events Defined by the Investigator as being Local Injection Site Reactions (Parts A/B)		SAC
3.28.	AT (Part A/B)	SHELL	Summary Profile of On-Treatment Local Injection Site Reactions (Parts A/B)		SAC
3.29.	AT (Part A/B)	AE1	Summary of On-Treatment Opportunistic Infections (Parts A/B)		SAC
3.30.	AT (Part A/B)	SHELL	Summary Profile of On-Treatment Opportunistic Infections (Parts A/B)		SAC
3.31.	AT (Part A/B)	AE1	Summary of On-Treatment Malignancies (Parts A/B)		SAC
3.32.	AT (Part A/B)	SHELL	Summary Profile of On-Treatment Malignancies (Parts A/B)		SAC
3.33.	AT (Part A/B)	AE1	Summary of On-Treatment Serious Cardiac, Vascular and Thromboembolic Adverse Events (Parts A/B)		SAC
3.34.	AT (Part A/B)	SHELL	Summary Profile of On-Treatment Serious Cardiac, Vascular and Thromboembolic Adverse Events (Parts A/B)		SAC
3.35.	AT (Part A/B)	AE1	Summary of On-Treatment Serious Ischemic Adverse Events (Parts A/B)		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.36.	AT (Part A/B)	SHELL	Summary Profile of On-Treatment Serious Ischemic Adverse Events (Parts A/B)		SAC
Cardiovascular Events and Deaths (All Causes)					
3.37.	AT (Part A/B)	SHELL	Summary of Cardiovascular Events and Deaths (All Causes) Reported by the Investigator (On-Treatment, Parts A/B)		SAC
Laboratory: Chemistry					
3.38.	AT (Part A/B)	LB1	Summary of Chemistry Changes from Baseline (On-Treatment, Parts A/B)	ICH E3 Includes Baseline values.	SAC
3.39.	AT (Part A/B)	LB3	Summary of Chemistry Results (Changes from Baseline Relative to the Normal Range) (On-Treatment, Parts A/B)	ICH E3	SAC
3.40.	AT (Part A/B)	LB3	Summary of Chemistry Results (Changes from Baseline Relative to the Reference Range [Potential Clinical Importance]) (On-Treatment, Parts A/B)	ICH E3	SAC
Laboratory: Haematology					
3.41.	AT (Part A/B)	LB1	Summary of Haematology Changes from Baseline (On-Treatment, Parts A/B)	ICH E3 Includes baseline values.	SAC
3.42.	AT (Part A/B)	LB3	Summary of Haematology Results (Changes from Baseline Relative to the Normal Range) (On-Treatment, Parts A/B)	ICH E3	SAC
3.43.	AT (Part A/B)	LB3	Summary of Haematology Results (Changes from Baseline Relative to the Reference Range [Potential Clinical Importance]) (On-Treatment, Parts A/B)	ICH E3	SAC
Laboratory: Hepatobiliary (Liver)					
3.44.	AT (Part A/B)	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities (On-Treatment, Parts A/B)	IDSL	SAC
ECG					
3.45.	AT (Part A/B)	EG1	Summary of ECG Findings (On-Treatment, Parts A/B)	IDSL	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.46.	AT (Part A/B)	EG2	Summary of Change from Baseline in ECG Values by Visit (On-Treatment, Parts A/B)	IDSL Includes Baseline values.	SAC
3.47.	AT (Part A/B)	SHELL	Summary of Actual and Change From Baseline QTc(F) Values by Category (msec) (On-Treatment, Parts A/B)		SAC
3.48.	AT (Part A/B)	SHELL	Summary of Actual and Change From Baseline QTc(B) Values by Category (msec) (On-Treatment, Parts A/B)		SAC
Vital Signs					
3.49.	AT (Part A/B)	VS1	Summary of Change from Baseline in Vital Signs (On-Treatment, Parts A/B)	ICH E3 Includes Baseline values.	SAC
Immunogenicity					
3.50.	AT (Part A/B)	SHELL	Summary of ADA Assay Results (On-Treatment, Parts A/B)		SAC
3.51.	AT (Part A/B)	SHELL	Summary of Treatment Emergent ADA Assay Results (On-Treatment, Parts A/B)		SAC
3.52.	AT (Part A/B)	SHELL	Summary of NAb Assay Results (On-Treatment, Parts A/B)		SAC

11.11.5. Part C

11.11.5.1. Study Population Tables (Part C)

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Population Analysed					
1.13.	ASE	SHELL	Summary of Study Populations (Part C)	IDSL Include Randomized, Intent-to-Treat (Part C) and Per-Protocol Populations	SAC
Subject Disposition					
1.14.	ASE	ES6	Summary of Run-in Status and Reasons for Run-in Failure (Part C)	Journal Requirements	SAC
1.15.	ASE	IE2	Summary of Failed Randomization Inclusion/Exclusion Criteria for Run-in Failures (Part C)		SAC
1.16.	ITT (Part C)	IE2	Summary of Failed Randomization Inclusion/Exclusion Criteria for Subjects within the Intent-to-Treat Population (Part C)		SAC
1.17.	ITT (Part C)	ES8	Summary of Subject Status and Reason for Study Withdrawal (Part C)	ICH E3, FDAAA, EudraCT	SAC
1.18.	ITT (Part C)	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment (Part C)	ICH E3	SAC
1.19.	ITT (Part C)	SHELL	Summary of Attendance at Each Clinic Visit (Part C)		SAC
1.20.	ITT (Part C)	SHELL	Summary of Visit Where Subject Switched To Open-Label Mepolizumab Treatment within Part D (Part C)		SAC
Demographics					
1.21.	ITT (Part C)	DM1	Summary of Demographic Characteristics (Part C)	ICH E3, FDAAA, EudraCT	SAC
1.22.	ITT (Part C)	DM5	Summary of Race and Racial Combinations (Part C)	ICH E3, FDA, FDAAA, EudraCT	SAC
1.23.	ITT (Part C)	NS1	Summary of Number of Subjects by Region, Country and Site (Part C)	EudraCT/Clinical Operations Add total for regions and a total for country	SAC
Smoking Status					
1.24.	ITT (Part C)	SU1	Summary of History of Tobacco Use (Part C)		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Baseline Disease Characteristics					
1.25.	ITT (Part C)	SHELL	Summary of Asthma History and Baseline Disease Characteristics (Part C)	Include disease duration, Asthma Disease Characteristics (ATS Criteria), prior intubations related to asthma and maintenance OCS use	SAC
1.26.	ITT (Part C)	SHELL	Summary of Previous Exacerbation History (Part C)	Include number or preview exacerbations and reasons/causes of exacerbation	SAC
1.27.	ITT (Part C)	SHELL	Summary of Baseline Lung Function Tests (Part C)	Include FEV1, %Predicted FEV, FVC, FEV/FVC and Reversibility	SAC
Concomitant Medications					
1.28.	ITT (Part C)	CM1	Summary of Asthma Concomitant Medications Taken at Visit C1 by Respiratory Medication Class Group (Part C)	ICH E3 Footnote: Multi-component medications displayed under the respiratory medication class of each component Programming note: Display RMC and ingredient as per previous Asthma studies	SAC
1.29.	ITT (Part C)	CM1	Summary of Asthma Concomitant Medications Taken During Treatment by Respiratory Medication Class Group (Part C)	ICH E3 Footnote: Multi-component medications displayed under the respiratory medication class of each component Programming note: Display RMC and ingredient as per previous Asthma studies	SAC
1.30.	ITT (Part C)	CM1	Summary of Non-Asthma Medications Taken During Treatment (Part C)	ICH E3 Footnote: Medications may be displayed under more than one ATC classification	SAC
Protocol Deviation					
1.31.	ITT (Part C)	DV1	Summary of Important Protocol Deviations (Part C)	ICH E3	SAC
1.32.	ITT (Part C)	SP2	Summary of Exclusions from the Per Protocol Population (Part C)	IDSL	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Continuous Exposure to Mepolizumab Prior to Randomization					
1.33.	ITT (Part C)	SHELL	Summary of Continuous Exposure to Mepolizumab (Therapeutic Coverage) Prior to Randomization at Visit C1 (Part C)	See Study Population Table 2.1 (201312 'FINAL' reporting effort)	
Exposure					
1.34.	ITT (Part C)	SHELL	Summary of Exposure to Study Treatment (Part C)	ICH E3 See Study Population Table 1.1 (204471 'FINAL_01' reporting effort)	SAC

11.11.5.2. Study Population Figures (Part C)

Study Population Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	ITT (Part C)	SHELL	Time to Subject Withdrawal From Investigation Product (Part C)	See Study Population Figure 1.1 (204471 'FINAL_01' reporting effort)	SAC

11.11.5.3. Efficacy Tables (Part C)

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exacerbations					
2.1.	ITT (Part C)	SHELL	Overview of All Exacerbations (Part C)		SAC
2.2.	ITT (Part C)	SHELL	Summary of Frequency of Clinically Significant Exacerbations (Part C)		SAC
2.3.	ITT (Part C)	SHELL	Analysis of Time to First Clinically Significant Exacerbation (Part C)		SAC
2.4.	PP (Part C)	SHELL	Analysis of Time to First Clinically Significant Exacerbation (Part C)	Per protocol supportive analysis	SAC
2.5.	ITT (Part C)	SHELL	Analysis of Time to First Clinically Significant Exacerbation by Age (12-17, 18-64, ≥65 years) (Part C)		SAC
2.6.	ITT (Part C)	SHELL	Analysis of Time to First Clinically Significant Exacerbation by Sex (Part C)		SAC
2.7.	ITT (Part C)	SHELL	Analysis of Time to First Clinically Significant Exacerbation by Weight (<75kg, ≥75kg) (Part C)		SAC
2.8.	ITT (Part C)	SHELL	Analysis of Time to First Clinically Significant Exacerbation by Region (Europe, Rest of World) (Part C)		SAC
2.9.	ITT (Part C)	SHELL	Analysis of Time to First Clinically Significant Exacerbation by Exacerbations in the Year Prior to Randomization (0, 1, ≥2) (Part C)		SAC
2.10.	ITT (Part C)	SHELL	Analysis of Time to First Clinically Significant Exacerbation by Maintenance OCS Use (Part C)		SAC
2.11.	ITT (Part C)	SHELL	Analysis of Time to First Clinically Significant Exacerbation by Baseline Blood Eosinophils (<0.50, ≥0.50-<0.10, ≥0.10-<0.15, ≥0.15 GI/L) (Part C)		SAC
2.12.	ITT (Part C)	SHELL	Analysis of Time to First Clinically Significant Exacerbation by Baseline Anti-Drug Antibody (ADA) Status (Part C)		SAC
2.13.	ITT (Part C)	SHELL	Summary of Frequency of Exacerbations Requiring Hospitalisation or Emergency Department visit (Part C)		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.14.	ITT (Part C)	SHELL	Analysis of Time to First Exacerbation Requiring Hospitalisation or Emergency Department visit (Part C)		SAC
2.15.	ITT (Part C)	SHELL	Summary of Frequency of Exacerbations Requiring Hospitalisation (Part C)		SAC
2.16.	ITT (Part C)	SHELL	Analysis of Time to First Exacerbation Requiring Hospitalisation (Part C)		SAC
Blood Eosinophils					
2.17.	ITT (Part C)	SHELL	Summary of Blood Eosinophils (10^9/L) (Part C)		SAC
2.18.	ITT (Part C)	SHELL	Analysis of Ratio to Baseline in Blood Eosinophils (10^9/L) (Part C)		SAC
Asthma Control Questionnaire (ACQ-5)					
2.19.	ITT (Part C)	SHELL	Summary of Asthma Control Questionnaire (ACQ-5) Score (Part C)		SAC
2.20.	ITT (Part C)	SHELL	Analysis of Change from Baseline in Asthma Control Questionnaire (ACQ-5) Score (Part C)		SAC
2.21.	ITT (Part C)	SHELL	Analysis of Time to First 0.5 Point or More Increase in ACQ-5 Score from Baseline (Part C)		SAC
2.22.	ITT (Part C)	SHELL	Summary and Analysis of 0.5 Point or More Increase in ACQ-5 Score from Baseline (Part C)		SAC
St George's Respiratory Questionnaire (SGRQ)					
2.23.	ITT (Part C)	SHELL	Summary of St. George's Respiratory Questionnaire (SGRQ) Total Score (Part C)		SAC
2.24.	ITT (Part C)	SHELL	Analysis of Change From Baseline in St. George's Respiratory Questionnaire (SGRQ) Total Score (Part C)		SAC
2.25.	ITT (Part C)	SHELL	Summary of St. George's Respiratory Questionnaire (SGRQ) Symptom Domain Score (Part C)		SAC
2.26.	ITT (Part C)	SHELL	Analysis of Change From Baseline in St. George's Respiratory Questionnaire (SGRQ) Symptom Domain Score (Part C)		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.27.	ITT (Part C)	SHELL	Summary of St. George's Respiratory Questionnaire (SGRQ) Activity Domain Score (Part C)		SAC
2.28.	ITT (Part C)	SHELL	Analysis of Change From Baseline in St. George's Respiratory Questionnaire (SGRQ) Activity Domain Score (Part C)		SAC
2.29.	ITT (Part C)	SHELL	Summary of St. George's Respiratory Questionnaire (SGRQ) Impacts Domain Score (Part C)		SAC
2.30.	ITT (Part C)	SHELL	Analysis of Change From Baseline in St. George's Respiratory Questionnaire (SGRQ) Impacts Domain Score (Part C)		SAC
2.31.	ITT (Part C)	SHELL	Summary and Analysis of 4 Point or More Improvement in SGRQ Total Score From Baseline (Part C)		SAC
Spirometry					
2.32.	ITT (Part C)	SHELL	Summary of Clinic Pre-Bronchodilator FEV1 (mL) (Part C)		SAC
2.33.	ITT (Part C)	SHELL	Analysis of Change From Baseline in Clinic Pre-Bronchodilator FEV1 (mL) (Part C)		SAC
2.34.	ITT (Part C)	SHELL	Summary of Clinic Post-Bronchodilator FEV1 (mL) (Part C)		SAC
2.35.	ITT (Part C)	SHELL	Analysis of Change From Baseline in Clinic Post-Bronchodilator FEV1 (mL) (Part C)		SAC
Global Impression of Asthma Severity Rating					
2.36.	ITT (Part C)	SHELL	Summary and Analysis of Subject Global Impression of Asthma Severity Rating (Part C)		SAC
2.37.	ITT (Part C)	SHELL	Summary of Shift From Baseline in Subject Global Impression of Asthma Severity Rating (Part C)		SAC
2.38.	ITT (Part C)	SHELL	Summary and Analysis of Clinician Global Impression of Asthma Severity Rating (Part C)		SAC
2.39.	ITT (Part C)	SHELL	Summary of Shift From Baseline in Clinician Global Impression of Asthma Severity Rating (Part C)		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Rating of Response to Therapy					
2.40.	ITT (Part C)	SHELL	Summary and Analysis of Subject Rated Overall Evaluation of Response to Therapy (Part C)		SAC
2.41.	ITT (Part C)	SHELL	Summary and Analysis of Clinician Rated Overall Evaluation of Response to Therapy (Part C)		SAC
eDiary Parameters					
2.42.	ITT (Part C)	SHELL	Summary of Daily Salbutamol/Albuterol Use (occasions/day) by 4-Week Period (Part C)		SAC
2.43.	ITT (Part C)	SHELL	Summary of Daily Asthma Symptom Scores by 4-Week Period (Part C)		SAC
2.44.	ITT (Part C)	SHELL	Summary of Awakening at Night Due to Asthma Symptoms Requiring Rescue Medication Use by 4-Week Period (Part C)		SAC
2.45.	ITT (Part C)	SHELL	Summary of Morning Peak Expiratory Flow (PEF) by 4-Week Period (L/min) (Part C)		SAC
2.46.	ITT (Part C)	SHELL	Analysis of Time to First Worsening of Asthma Defined by Daily eDiary Parameters (Part C)	Footnote: Subjects meeting at least 2 of the possible 4 criteria for worsening of asthma for at least 2 consecutive days	SAC
Number of Days in Hospital Due to Asthma					
2.47.	ITT (Part C)	SHELL	Summary of Days in Hospital Due to Asthma Symptoms (Part C)		SAC
Unscheduled Healthcare Contacts/Resource Utilization					
2.48.	ITT (Part C)	SHELL	Summary of Unscheduled Healthcare Resource Use (Part C)	Separate pages for: 1) use associated with an exacerbation 2) use not associated with an exacerbation, 3) total resource use	SAC
Number of Days off Work/School					
2.49.	ITT (Part C)	SHELL	Summary of Days Off Work/School Due to Asthma Symptoms (Part C)		SAC

11.11.5.4. Efficacy Figures (Part C)

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exacerbations					
2.1.	ITT (Part C)	SHELL	Kaplan-Meier Cumulative Incidence Curve for Time to First Clinically Significant Exacerbation (Part C)		SAC
2.2.	ITT (Part C)	SHELL	Kaplan-Meier Cumulative Incidence Curve for Time to First Exacerbation Requiring Hospitalisation or Emergency Department visit (Part C)		SAC
2.3.	ITT (Part C)	SHELL	Kaplan-Meier Cumulative Incidence Curve for Time to First Exacerbation Requiring Hospitalisation (Part C)		SAC
2.4.	ITT (Part C)	SHELL	Figure of Hazard Ratio (Mepolizumab/Placebo) from Analysis of Time to First Exacerbation (Part C)		SAC
Blood Eosinophils					
2.5.	ITT (Part C)	SHELL	Figure of Analysis of Ratio to Baseline in Blood Eosinophils (Adjusted Mean at Each Visit by Treatment Group) (Part C)		SAC
2.6.	ITT (Part C)	SHELL	Figure of Analysis of Blood Eosinophils (Difference Between Treatment Groups in Ratio to Baseline at Each Visit) (Part C)		SAC
Asthma Control Questionnaire (ACQ-5)					
2.7.	ITT (Part C)	SHELL	Figure of Analysis of Change from Baseline in ACQ-5 Score (Adjusted Mean at Each Visit by Treatment Group) (Part C)		SAC
2.8.	ITT (Part C)	SHELL	Figure of Analysis of ACQ-5 Score (Difference Between Treatment Groups in Mean Change from Baseline at Each Visit) (Part C)		SAC
2.9.	ITT (Part C)	SHELL	Kaplan-Meier Cumulative Incidence Curve for Time to First 0.5 Point or More Increase in ACQ-5 Score from Baseline (Part C)		SAC
St George's Respiratory Questionnaire (SGRQ)					
2.10.	ITT (Part C)	SHELL	Figure of Analysis of Change from Baseline in SGRQ Total Score (Adjusted Mean at Each Visit by Treatment Group) (Part C)		SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.11.	ITT (Part C)	SHELL	Figure of Analysis of SGRQ Total Score (Difference Between Treatment Groups in Adjusted Mean Change from Baseline at Each Visit) (Part C)		SAC
2.12.	ITT (Part C)	SHELL	Figure of Analyses of SGRQ by Domain (Difference Between Treatment Groups in Adjusted Mean Change from Baseline at Each Visit) (Part C)		SAC
Spirometry					
2.13.	ITT (Part C)	SHELL	Figure of Analysis of Change from Baseline in Pre-bronchodilator FEV1 (mL) (Adjusted Mean at Each Visit by Treatment Group) (Part C)		SAC
2.14.	ITT (Part C)	SHELL	Figure of Analysis of Pre-Bronchodilator FEV1 (mL) (Difference Between Treatment Groups in Adjusted Mean Change from Baseline at Each Visit) (Part C)		SAC
2.15.	ITT (Part C)	SHELL	Figure of Analysis of Change from Baseline in Post-bronchodilator FEV1 (mL) (Adjusted Mean at Each Visit by Treatment Group) (Part C)		SAC
2.16.	ITT (Part C)	SHELL	Figure of Analysis of Post -Bronchodilator FEV1 (mL) (Difference Between Treatment Groups in Adjusted Mean Change from Baseline at Each Visit) (Part C)		SAC
eDiary Parameters					
2.17.	ITT (Part C)	SHELL	Kaplan-Meier Cumulative Incidence Curve for Time to First Worsening of Asthma Defined by Daily eDiary Parameters (Part C)	Footnote: Subjects meeting at least 2 of the possible 4 criteria for worsening of asthma for at least 2 consecutive days	SAC

11.11.5.5. Safety Tables (Part C)

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.53.	ITT (Part C)	SHELL	Overview of Adverse Events (Part C)		SAC
3.54.	ITT (Part C)	AE1	Summary of On-Treatment Adverse Events by System Organ Class and Preferred Term (Part C)	ICH E3	SAC
3.55.	ITT (Part C)	AE5	Summary of On-Treatment Adverse Events by Maximum Intensity by System Organ Class and Preferred Term (Part C)	ICH E3 Add a Total column across all severities	SAC
3.56.	ITT (Part C)	SHELL	Summary of Exposure Adjusted On-Treatment Adverse Events by System Organ Class and Preferred Term (Part C)		SAC
3.57.	ITT (Part C)	AE3	Summary of Common (≥3%) On-treatment Adverse Events by Overall Frequency (Part C)	ICH E3 ≥3% (prior to rounding to nearest percent)	SAC
3.58.	ITT (Part C)	SHELL	Summary of Exposure Adjusted On-Treatment Common (≥3%) Adverse Events by System Organ Class and Preferred Term (Part C)	≥3% (prior to rounding to nearest percent)	SAC
3.59.	ITT (Part C)	AE1	Summary of On-Treatment Drug-Related Adverse Events by System Organ Class and Preferred Term (Part C)	ICH E3	SAC
3.60.	ITT (Part C)	AE5	Summary of On-Treatment Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity (Part C)	Add a Total column across all severities	SAC
3.61.	ITT (Part C)	SHELL	Summary of Exposure Adjusted On-Treatment Drug-Related Adverse Events by System Organ Class and Preferred Term (Part C)		SAC
3.62.	ITT (Part C)	SHELL	Summary of On-Treatment Adverse Events by Age Group (12-17, 18-64, ≥65 years) (Part C)		SAC
3.63.	ITT (Part C)	SHELL	Summary of On-Treatment Adverse Events by Highest Anti Drug Antibody Result At Any Time On-Treatment (Part C)		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.64.	ITT (Part C)	AE15	Summary of Common (≥3%) Non-serious On-Treatment Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) (Part C)	FDAAA, EudraCT ≥3% (prior to rounding to nearest percent)	SAC
3.65.	ITT (Part C)	AE1	Summary of On-Treatment Drug-Related Non-Serious Adverse Events by System Organ Class and Preferred Term (Part C)	Table required for plain language summary	SAC
Serious and Other Significant Adverse Events					
3.66.	ITT (Part C)	AE1	Summary of On-Treatment Serious Adverse Events by System Organ Class and Preferred Term (Part C)		SAC
3.67.	ITT (Part C)	SHELL	Summary of Exposure Adjusted On-Treatment Serious Adverse Events by System Organ Class and Preferred Term (Part C)		SAC
3.68.	ITT (Part C)	SHELL	Summary of On-Treatment Serious Adverse Events by Age Group (12-17, 18-64, ≥65 years) (Part C)		SAC
3.69.	ITT (Part C)	AE1	Summary of On-Treatment Fatal Serious Adverse Events (Part C)		SAC
3.70.	ITT (Part C)	SHELL	Summary of On-Treatment Fatal Serious Adverse Events by Age Group (12-17, 18-64, ≥65 years) (Part C)		SAC
3.71.	ITT (Part C)	AE1	Summary of On-Treatment Non-Fatal Serious Adverse Events by System Organ Class and Preferred Term (Part C)		SAC
3.72.	ITT (Part C)	AE1	Summary of On-Treatment Drug-Related Serious Adverse Events by System Organ Class and Preferred Term (Part C)	Table required for plain language summary	SAC
3.73.	ITT (Part C)	AE1	Summary of On-Treatment Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term (Part C)	IDSL	SAC
3.74.	ITT (Part C)	AE16	Summary of On-Treatment Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) (Part C)	FDAAA, EudraCT	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events of Special Interest					
3.75.	ITT (Part C)	SHELL	Summary of On-treatment Serious Adverse Events and Adverse Events of Special Interest (Incidence, Relative Risk and Risk Difference) (Part C)		SAC
3.76.	ITT (Part C)	AE1	Summary of On-Treatment Systemic Reactions Meeting Anaphylaxis Criteria (Part C)	Present by Anaphylactic Criterion 1, 2 and 3 rather than SOC as shown in AE1 Insert footnote: "Events displayed are a subset of reactions defined by the Investigator as being systemic"	SAC
3.77.	ITT (Part C)	SHELL	Summary Profile of On-Treatment Systemic Reactions Meeting Anaphylaxis Criteria (Part C)	Insert footnote: "Events displayed are a subset of reactions defined by the Investigator as being systemic"	SAC
3.78.	ITT (Part C)	AE1	Summary of On-Treatment Adverse Events Defined by the Investigator as Being Systemic (non-allergic or allergic/hypersensitivity) Reactions (Part C)		SAC
3.79.	ITT (Part C)	SHELL	Summary Profile of On-Treatment Systemic (non-allergic or allergic/hypersensitivity) Reactions (Part C)		SAC
3.80.	ITT (Part C)	SHELL	Summary Profile of On-Treatment Systemic Allergic Reactions (Part C)		SAC
3.81.	ITT (Part C)	SHELL	Summary Profile of On-Treatment Systemic Non-Allergic Reactions (Part C)		SAC
3.82.	ITT (Part C)	AE1	Summary of On-Treatment Adverse Events Defined by the Investigator as being Local Injection Site Reactions (Part C)		SAC
3.83.	ITT (Part C)	SHELL	Summary Profile of On-Treatment Local Injection Site Reactions (Part C)		SAC
3.84.	ITT (Part C)	AE1	Summary of On-Treatment Opportunistic Infections (Part C)		SAC
3.85.	ITT (Part C)	SHELL	Summary Profile of On-Treatment Opportunistic Infections (Part C)		SAC
3.86.	ITT (Part C)	AE1	Summary of On-Treatment Malignancies (Part C)		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.87.	ITT (Part C)	SHELL	Summary Profile of On-Treatment Malignancies (Part C)		SAC
3.88.	ITT (Part C)	AE1	Summary of On-Treatment Serious Cardiac, Vascular and Thromboembolic Adverse Events (Part C)		SAC
3.89.	ITT (Part C)	SHELL	Summary Profile of On-Treatment Serious Cardiac, Vascular and Thromboembolic Adverse Events (Part C)		SAC
3.90.	ITT (Part C)	AE1	Summary of On-Treatment Serious Ischemic Adverse Events (Part C)		SAC
3.91.	ITT (Part C)	SHELL	Summary Profile of On-Treatment Serious Ischemic Adverse Events (Part C)		SAC
Cardiovascular Events and Deaths (All Causes)					
3.92.	ITT (Part C)	SHELL	Summary of Cardiovascular Events and Deaths (All Causes) Reported by the Investigator (On-Treatment, Part C)		SAC
Laboratory: Chemistry					
3.93.	ITT (Part C)	LB1	Summary of Chemistry Changes from Baseline (On-Treatment, Part C)	ICH E3 Includes Baseline values.	SAC
3.94.	ITT (Part C)	LB3	Summary of Chemistry Results (Changes from Baseline Relative to the Normal Range) (On-Treatment, Part C)	ICH E3	SAC
3.95.	ITT (Part C)	LB3	Summary of Chemistry Results (Changes from Baseline Relative to the Reference Range [Potential Clinical Importance]) (On-Treatment, Part C)	ICH E3	SAC
Laboratory: Haematology					
3.96.	ITT (Part C)	LB1	Summary of Haematology Changes from Baseline (On-Treatment, Part C)	ICH E3 Includes baseline values.	SAC
3.97.	ITT (Part C)	LB3	Summary of Haematology Results (Changes from Baseline Relative to the Normal Range) (On-Treatment, Part C)	ICH E3	SAC
3.98.	ITT (Part C)	LB3	Summary of Haematology Results (Changes from Baseline Relative to the Reference Range [Potential Clinical Importance]) (On-Treatment, Part C)	ICH E3	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Hepatobiliary (Liver)					
3.99.	ITT (Part C)	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities (On-Treatment, Part C)	IDSL	SAC
ECG					
3.100.	ITT (Part C)	EG1	Summary of ECG Findings (On-Treatment, Part C)	IDSL	SAC
3.101.	ITT (Part C)	EG2	Summary of Change from Baseline in ECG Values by Visit (On-Treatment, Part C)	IDSL Includes Baseline values.	SAC
3.102.	ITT (Part C)	SHELL	Summary of Actual and Change From Baseline QTc(F) Values by Category (msec) (On-Treatment, Part C)		SAC
3.103.	ITT (Part C)	SHELL	Summary of Actual and Change From Baseline QTc(B) Values by Category (msec) (On-Treatment, Part C)		SAC
Vital Signs					
3.104.	ITT (Part C)	VS1	Summary of Change from Baseline in Vital Signs (On-Treatment, Part C)	ICH E3 Includes Baseline values.	SAC
Immunogenicity					
3.105.	ITT (Part C)	SHELL	Summary of ADA Assay Results (On-Treatment, Part C)		SAC
3.106.	ITT (Part C)	SHELL	Summary of Treatment Emergent ADA Assay Results (On-Treatment, Part C)		SAC
3.107.	ITT (Part C)	SHELL	Summary of NAb Assay Results (On-Treatment, Part C)		SAC

11.11.5.6. Safety Figures (Part C)

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.1.	ITT (Part C)	AE10	Plot of Common (≥3%) On-treatment Adverse Events and Relative Risk (Part C)	IDSL ≥3% (prior to rounding to nearest percent)	SAC
3.2.	ITT (Part C)	SHELL	Figure of On-treatment Serious Adverse Events and Adverse Events of Special Interest (Relative Risk, 100mg SC vs Placebo) (Part C)		SAC

11.11.6. Part D

11.11.6.1. Study Population Tables (Part D)

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Population Analysed					
1.35.	ASE	SHELL	Summary of Study Populations (Part D)	IDSL Include As Treated (Part D) Population	SAC
Subject Disposition					
1.36.	AT (Part D)	ES8	Summary of Subject Status and Reason for Study Withdrawal (Part D)	ICH E3, FDAAA, EudraCT	SAC
1.37.	AT (Part D)	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment (Part D)	ICH E3	SAC
1.38.	ITT (Part D)	SHELL	Summary of Attendance at Each Clinic Visit (Part D)		SAC
Protocol Deviation					
1.39.	AT (Part D)	DV1	Summary of Important Protocol Deviations (Part D)	ICH E3	SAC
Exposure					
1.40.	AT (Part D)	SHELL	Summary of Exposure to Study Treatment (Part D)	ICH E3 See Study Population Table 1.1 (204471 'FINAL_01' reporting effort)	SAC

11.11.6.2. Efficacy Tables (Part D)

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Blood Eosinophils					
2.50.	AT (Part D)	SHELL	Summary of Blood Eosinophils (10^9/L) (Part D)		SAC

11.11.6.3. Efficacy Figures (Part D)

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Blood Eosinophils					
2.18.	AT (Part D)	SHELL	Figure of Ratio to Baseline in Blood Eosinophils (Part D)		SAC

11.11.6.4. Safety Tables (Part D)

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.108.	AT (Part D)	SHELL	Overview of Adverse Events (Part D)		SAC
3.109.	AT (Part D)	AE1	Summary of On-Treatment Adverse Events by System Organ Class and Preferred Term (Part D)	ICH E3	SAC
3.110.	AT (Part D)	AE5	Summary of On-Treatment Adverse Events by Maximum Intensity by System Organ Class and Preferred Term (Part D)	ICH E3 Add a Total column across all severities	SAC
3.111.	AT (Part D)	AE3	Summary of Common (≥3%) On-treatment Adverse Events by Overall Frequency (Part D)	ICH E3 ≥3% (prior to rounding to nearest percent)	SAC
3.112.	AT (Part D)	AE1	Summary of On-Treatment Drug-Related Adverse Events by System Organ Class and Preferred Term (Part D)	ICH E3	SAC
3.113.	AT (Part D)	AE5	Summary of On-Treatment Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity (Part D)	Add a Total column across all severities	SAC
3.114.	AT (Part D)	SHELL	Summary of On-Treatment Adverse Events by Age Group (12-17, 18-64, ≥65 years) (Part D)		SAC
3.115.	AT (Part D)	SHELL	Summary of On-Treatment Adverse Events by Highest Anti Drug Antibody Result At Any Time On-Treatment (Part D)		SAC
3.116.	AT (Part D)	AE15	Summary of Common (≥3%) Non-serious On-Treatment Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) (Part D)	FDAAA, EudraCT ≥3% (prior to rounding to nearest percent)	SAC
3.117.	AT (Part D)	AE1	Summary of On-Treatment Drug-Related Non-Serious Adverse Events by System Organ Class and Preferred Term (Part D)	Table required for plain language summary	SAC
Serious and Other Significant Adverse Events					
3.118.	AT (Part D)	AE1	Summary of On-Treatment Serious Adverse Events by System Organ Class and Preferred Term (Part D)		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.119.	AT (Part D)	SHELL	Summary of On-Treatment Serious Adverse Events by Age Group (12-17, 18-64, ≥65 years) (Part D)		SAC
3.120.	AT (Part D)	AE1	Summary of On-Treatment Fatal Serious Adverse Events (Part D)		SAC
3.121.	AT (Part D)	SHELL	Summary of On-Treatment Fatal Serious Adverse Events by Age Group (12-17, 18-64, ≥65 years) (Part D)		SAC
3.122.	AT (Part D)	AE1	Summary of On-Treatment Non-Fatal Serious Adverse Events by System Organ Class and Preferred Term (Part D)		SAC
3.123.	AT (Part D)	AE1	Summary of On-Treatment Drug-Related Serious Adverse Events by System Organ Class and Preferred Term (Part D)	Table required for plain language summary	SAC
3.124.	AT (Part D)	AE1	Summary of On-Treatment Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term (Part D)	IDSL	SAC
3.125.	AT (Part D)	AE16	Summary of On-Treatment Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) (Part D)	FDAAA, EudraCT	SAC
Adverse Events of Special Interest					
3.126.	AT (Part D)	SHELL	Summary of On-treatment Serious Adverse Events and Adverse Events of Special Interest (Part D)		SAC
3.127.	AT (Part D)	AE1	Summary of On-Treatment Systemic Reactions Meeting Anaphylaxis Criteria (Part D)	Present by Anaphylactic Criterion 1, 2 and 3 rather than SOC as shown in AE1 Insert footnote: “Events displayed are a subset of reactions defined by the Investigator as being systemic”	SAC
3.128.	AT (Part D)	SHELL	Summary Profile of On-Treatment Systemic Reactions Meeting Anaphylaxis Criteria (Part D)	Insert footnote: “Events displayed are a subset of reactions defined by the Investigator as being systemic”	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.129.	AT (Part D)	AE1	Summary of On-Treatment Adverse Events Defined by the Investigator as Being Systemic (non-allergic or allergic/hypersensitivity) Reactions (Part D)		SAC
3.130.	AT (Part D)	SHELL	Summary Profile of On-Treatment Systemic (non-allergic or allergic/hypersensitivity) Reactions (Part D)		SAC
3.131.	AT (Part D)	SHELL	Summary Profile of On-Treatment Systemic Allergic Reactions (Part D)		SAC
3.132.	AT (Part D)	SHELL	Summary Profile of On-Treatment Systemic Non-Allergic Reactions (Part D)		SAC
3.133.	AT (Part D)	AE1	Summary of On-Treatment Adverse Events Defined by the Investigator as being Local Injection Site Reactions (Part D)		SAC
3.134.	AT (Part D)	SHELL	Summary Profile of On-Treatment Local Injection Site Reactions (Part D)		SAC
3.135.	AT (Part D)	AE1	Summary of On-Treatment Opportunistic Infections (Part D)		SAC
3.136.	AT (Part D)	SHELL	Summary Profile of On-Treatment Opportunistic Infections (Part D)		SAC
3.137.	AT (Part D)	AE1	Summary of On-Treatment Malignancies (Part D)		SAC
3.138.	AT (Part D)	SHELL	Summary Profile of On-Treatment Malignancies (Part D)		SAC
3.139.	AT (Part D)	AE1	Summary of On-Treatment Serious Cardiac, Vascular and Thromboembolic Adverse Events (Part D)		SAC
3.140.	AT (Part D)	SHELL	Summary Profile of On-Treatment Serious Cardiac, Vascular and Thromboembolic Adverse Events (Part D)		SAC
3.141.	AT (Part D)	AE1	Summary of On-Treatment Serious Ischemic Adverse Events (Part D)		SAC
3.142.	AT (Part D)	SHELL	Summary Profile of On-Treatment Serious Ischemic Adverse Events (Part D)		SAC
Cardiovascular Events and Deaths (All Causes)					
3.143.	AT (Part D)	SHELL	Summary of Cardiovascular Events and Deaths (All Causes) Reported by the Investigator (On-Treatment, Part D)		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Chemistry					
3.144.	AT (Part D)	LB1	Summary of Chemistry Changes from Baseline (On-Treatment, Part D)	ICH E3 Includes Baseline values.	SAC
3.145.	AT (Part D)	LB3	Summary of Chemistry Results (Changes from Baseline Relative to the Normal Range) (On-Treatment, Part D)	ICH E3	SAC
3.146.	AT (Part D)	LB3	Summary of Chemistry Results (Changes from Baseline Relative to the Reference Range [Potential Clinical Importance]) (On-Treatment, Part D)	ICH E3	SAC
Laboratory: Haematology					
3.147.	AT (Part D)	LB1	Summary of Haematology Changes from Baseline (On-Treatment, Part D)	ICH E3 Includes baseline values.	SAC
3.148.	AT (Part D)	LB3	Summary of Haematology Results (Changes from Baseline Relative to the Normal Range) (On-Treatment, Part D)	ICH E3	SAC
3.149.	AT (Part D)	LB3	Summary of Haematology Results (Changes from Baseline Relative to the Reference Range [Potential Clinical Importance]) (On-Treatment, Part D)	ICH E3	SAC
Laboratory: Hepatobiliary (Liver)					
3.150.	AT (Part D)	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities (On-Treatment, Part D)	IDSL	SAC
ECG					
3.151.	AT (Part D)	EG1	Summary of ECG Findings (On-Treatment, Part D)	IDSL	SAC
3.152.	AT (Part D)	EG2	Summary of Change from Baseline in ECG Values by Visit (On-Treatment, Part D)	IDSL Includes Baseline values.	SAC
3.153.	AT (Part D)	SHELL	Summary of Actual and Change From Baseline QTc(F) Values by Category (msec) (On-Treatment, Part D)		SAC
3.154.	AT (Part D)	SHELL	Summary of Actual and Change From Baseline QTc(B) Values by Category (msec) (On-Treatment, Part D)		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
3.155.	AT (Part D)	VS1	Summary of Change from Baseline in Vital Signs (On-Treatment, Part D)	ICH E3 Includes Baseline values.	SAC
Immunogenicity					
3.156.	AT (Part D)	SHELL	Summary of ADA Assay Results (On-Treatment, Part D)		SAC
3.157.	AT (Part D)	SHELL	Summary of Treatment Emergent ADA Assay Results (On-Treatment, Part D)		SAC
3.158.	AT (Part D)	SHELL	Summary of NAb Assay Results (On-Treatment, Part D)		SAC

11.11.7. ICH Listings

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Subject Disposition					
1.	ASE	ES7	Listing of Reasons for Screen Failure (Parts A/B)	Journal Guidelines	SAC
2.	ASE	IE3	Listing of Failed Inclusion/Exclusion Criteria (Parts A/B)	ICH E3	SAC
3.	ASE	ES7	Listing of Reasons for Run-in Failure (Part C)	Journal Guidelines	SAC
4.	ASE	IE3	Listing of Failed Randomization Inclusion/Exclusion Criteria (Part C)	ICH E3	SAC
5.	ASE	SHELL	Listing of Randomised Subjects who Did Not Receive Double-Blind Treatment	ICH E3	SAC
6.	ASE	ES2	Listing of Reasons for Study Withdrawal (Parts A/B, Part C, Part D)	ICH E3 Including column of treatment and study part	SAC
7.	ASE	SD2	Listing of Reasons for Study Treatment Discontinuation (Part C, Part D)	ICH E3 Including column of treatment and study part	SAC
8.	ITT (Part C)	BL1	Listing of Participants for Whom the Treatment Blind was Broken (Part C)	ICH E3	SAC
9.	ITT (Part C)	TA1	Listing of Planned and Actual Treatments (Part C)	IDSL	SAC
Demographic and Baseline Characteristics					
10.	ASE	DM2	Listing of Demographic Characteristics (Part C)	ICH E3	SAC
11.	ASE	DM9	Listing of Race (Part C)	ICH E3	SAC
Protocol Deviations					
12.	ASE	DV2	Listing of Important Protocol Deviations (Parts A/B, Part C, Part D)	ICH E3 Listing also includes analysis population exclusions. Including column of treatment and study part	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Exposure					
13.	ASE	EX3	Listing of Exposure Data (Parts A/B, Part C, Part D)	ICH E3 Including column of treatment and study part	SAC
Efficacy					
14.	ASE	SHELL	Listing of Exacerbations (Parts A/B, Part C, Part D)	Including column of treatment, study part and phase	SAC
Adverse Events					
15.	ASE	SHELL	Listing of All Adverse Events (Parts A/B, Part C, Part D)	ICH E3 Including column of treatment, study part and phase	SAC
16.	ASE	AE7	Listing of Subject Numbers for Individual Adverse Events (Parts A/B, Part C, Part D)	ICH E3 Including column of treatment, study part and phase	SAC
17.	ASE	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text (Parts A/B, Part C, Part D)	IDSL	SAC
Serious and Other Significant Adverse Events					
18.	ASE	AE8CP	Listing of Fatal Serious Adverse Events (Parts A/B, Part C, Part D)	ICH E3 Including column of treatment, study part and phase	SAC
19.	ASE	AE8CP	Listing of Non-Fatal Serious Adverse Events (Parts A/B, Part C, Part D)	ICH E3 Including column of treatment, study part and phase	SAC
20.	ASE	AE14	Listing of Reasons for Considering as a Serious Adverse Event (Parts A/B, Part C, Part D)	ICH E3 Including column of treatment, study part and phase	SAC
21.	ASE	SHELL	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment (Parts A/B, Part C, Part D)	ICH E3 Including column of treatment, study part and phase	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Adverse Events of Special Interest					
22.	ASE	SHELL	Listing of Systemic Reactions Meeting Anaphylaxis Criteria (Parts A/B, Part C, Part D)	Including column of treatment, study part and phase Insert footnote: "Events displayed are a subset of reactions defined by the Investigator as being systemic"	SAC
23.	ASE	SHELL	Listing of Adverse Events Defined by the Investigator as a Systemic (non-allergic or allergic/hypersensitivity) Reaction (Parts A/B, Part C, Part D)	Including column of treatment, study part and phase Add a column stating whether AE is related to IP.	SAC
24.	ASE	SHELL	Listing of Adverse Events Defined by the Investigator as a Local Injection Site Reaction (Parts A/B, Part C, Part D)	Add a column stating whether AE is related to IP. Including column of treatment, study part and phase	SAC
25.	ASE	SHELL	Listing of Opportunistic Infections (Parts A/B, Part C, Part D)	Including column of treatment, study part and phase	SAC
26.	ASE	SHELL	Listing of Malignancies (Parts A/B, Part C, Part D)	Including column of treatment, study part and phase	SAC
27.	ASE	SHELL	Listing of Serious Cardiac, Vascular and Thromboembolic (CVT) Adverse Events (Parts A/B, Part C, Part D)	Including column of treatment, study part and phase	SAC
28.	ASE	SHELL	Listing of Serious Ischemic Adverse Events (Parts A/B, Part C, Part D)	Including column of treatment, study part and phase	SAC
Cardiovascular Events					
29.	ASE	SHELL	Listing of Investigator Reported Cardiovascular Events: Arrhythmias (Parts A/B, Part C, Part D)	Including column of treatment, study part and phase	SAC
30.	ASE	SHELL	Listing of Investigator Reported Cardiovascular Events: Congestive Heart Failure (Parts A/B, Part C, Part D)	Including column of treatment, study part and phase	SAC
31.	ASE	SHELL	Listing of Investigator Reported Cardiovascular Events: Cerebrovascular Events/Stroke (Parts A/B, Part C, Part D)	Including column of treatment, study part and phase	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
32.	ASE	SHELL	Listing of Investigator Reported Cardiovascular Events: Deep venous Thrombosis/Pulmonary Embolism (Parts A/B, Part C, Part D)	Including column of treatment, study part and phase	SAC
33.	ASE	SHELL	Listing of Investigator Reported Cardiovascular Events: Myocardial Infarction/Unstable Angina (Parts A/B, Part C, Part D)	Including column of treatment, study part and phase	SAC
34.	ASE	SHELL	Listing of Investigator Reported Cardiovascular Events: Peripheral Arterial Thrombosis Embolism (Parts A/B, Part C, Part D)	Including column of treatment, study part and phase	SAC
35.	ASE	SHELL	Listing of Investigator Reported Cardiovascular Events: Pulmonary Hypertension (Parts A/B, Part C, Part D)	Including column of treatment, study part and phase	SAC
36.	ASE	SHELL	Listing of Investigator Reported Cardiovascular Events: Revascularisation (Parts A/B, Part C, Part D)	Including column of treatment, study part and phase	SAC
37.	ASE	SHELL	Listing of Investigator Reported Cardiovascular Events: Valvulopathy (Parts A/B, Part C, Part D)	Including column of treatment, study part and phase	SAC
38.	ASE	SHELL	Listing of Investigator Reported Cardiovascular Events: All Cause Deaths (Parts A/B, Part C, Part D)	Including column of treatment, study part and phase	SAC
Hepatobiliary (Liver)					
39.	ASE	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting (Parts A/B, Part C, Part D)	Including column of treatment, study part and phase	SAC
40.	ASE	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events (Parts A/B, Part C, Part D)	IDSL	SAC
41.	ASE	SU2	Listing of Substance Use for Participants with Liver Stopping Events (Parts A/B, Part C, Part D)	IDSL	SAC
42.	ASE	LIVER13	Listing of Subjects Meeting Hepatobiliary Laboratory Criteria Post-Baseline (Parts A/B, Part C, Part D)	Including column of treatment, study part and phase	SAC
All Laboratory					
43.	ASE	LB5	Listing of All Chemistry Data for Participants with Liver Monitoring/Stopping Events Reported (Parts A/B, Part C, Part D)	ICH E3 Including column of treatment, study part and phase	SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
ECG					
44.	ASE	EG5	Listing of All ECG Findings for Subjects with an Abnormal ECG Interpretation (Parts A/B, Part C, Part D)	IDSL Including column of treatment, study part and phase	SAC
45.	ASE	EG3	Listing of All ECG Values for Subjects Meeting Protocol Defined QTc Stopping Criteria (Parts A/B, Part C, Part D)	Including column of treatment, study part and phase	SAC
Immunogenicity					
46.	ASE	SHELL	Listing of Immunogenicity Results (Parts A/B, Part C, Part D)	IDSL Including column of treatment, study part and phase	SAC

11.12. Appendix 12: Example Mock Shells for Data Displays

The data display shells are available on request.