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

Title	:	Reporting and Analysis Plan for Study 201312: A Multi-Centre, Open-Label, Study of Mepolizumab in a Subset of Subjects with a History of Life Threatening/Seriously Debilitating Asthma Who Participated in the MEA115661 Trial
Compound Number	:	SB-240563
Effective Date	:	25-OCT-2017

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 201312
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

RAP Author(s):

Approver	Date	Approval Method
PPD Statistician (Clinical Statistics)	25-OCT-2017	Email
PPD Principal Statistician (Clinical Statistics)	25-OCT-2017	Email

Clinical Statistics and Clinical Programming Line Approvals:

Approver	Date	Approval Method
PPD Director (Clinical Statistics)	24-OCT-2017	Email
PPD Director (Clinical Programming)	25-OCT-2017	Email

RAP Team Approvals:

Approver	Date	Approval Method
PPD Medical Director (Safety Evaluation & Risk Management)	24-OCT-2017	Email
PPD Manager (Clinical Programming)	25-OCT-2017	Email
PPD Project Physician Lead (Respiratory Therapeutic Unit)	23-OCT-2017	Email
PPD Clinical Investigation Leader (Respiratory Therapeutic Unit)	24-OCT-2017	Email
PPD Operational Science Lead (Respiratory Therapeutic Unit)	25-OCT-2017	Email
PPD Data Quality Leader (Clinical Data Management)	25-OCT-2017	Email

TABLE OF CONTENTS

PAGE

1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol 201312.

Revision Chronology:		
GSK Document Number	**DD-MMM-YYYY**	**Version**
2013N187987_00	11-FEB-2014	Original
2013N187987_01	27-JUN-2014	Amendment No. 1
2013N187987_02	14-NOV-2014	Amendment No. 2
2013N187987_03	19-JUN-2015	Amendment No. 3
2013N187987_04	06-JUL-2015	Republishing Protocol Amendment 3

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 3 (Dated: 06/JUL/2015).

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
To provide extended treatment with mepolizumab to subjects with a history of life-threatening or seriously debilitating asthma and a history of improved disease control while receiving mepolizumab as defined in the protocol.	• Annualized rate of exacerbations • Frequency of adverse events
Secondary Objectives	**Secondary Endpoints**
To further describe the long-term clinical experience of mepolizumab in a subset of subjects who demonstrated significant clinical benefit since receiving mepolizumab	• Asthma Control Questionnaire-5 score • Forced expiratory volume in 1 second (FEV1) • Number of withdrawals due to lack of efficacy • Number of withdrawals due to adverse events • Number of hospitalizations due to adverse events including asthma exacerbations • Frequency of both systemic (i.e., allergic and non-allergic) and local site reactions • 12-lead ECG parameters • Vital signs • Frequency of positive anti-mepolizumab binding antibodies/neutralizing antibodies

Objectives	Endpoints
	• Clinical Laboratory Parameters

2.3. Study Design

Overview of Study Design and Key Features	
Design Features	Study 201312 is a study of subcutaneously (SC) administered mepolizumab 100mg that will enrol a subset of subjects from Study MEA115661 who have demonstrated clear benefit from therapy and who without continuation of mepolizumab therapy are individuals at greatest risk of serious deterioration of their health status. This is a multi-centre, open-label, long-term study of mepolizumab 100mg administered SC, in addition to standard of care (SOC), in subjects with severe eosinophilic asthma. Only subjects who complete the MEA115661 Exit Visit (Visit 14) and meeting all eligibility criteria will be offered the opportunity to consent for this study of up to 172 weeks.
Dosing	Mepolizumab 100 mg SC will be administered approximately every 4 weeks with the first dose administered at Week 0 (Visit 1) and the last dose administered at Week 168 (Visit 43). Forty-three doses will provide therapeutic coverage for 172 weeks (4 weeks following the last dose). Subjects will continue to receive mepolizumab 100mg SC injections for up to 172 weeks or until one of the following occurs: • the risk/benefit profile for the subject is no longer positive in the opinion of the investigator or • the subject's physician withdraws the subject or • the subject withdraws consent or • the sponsor discontinues development of mepolizumab or • the sponsor discontinues the study in the relevant participating country or • mepolizumab becomes commercially available in the local country. The study closure process will begin, on a country by country basis, as mepolizumab becomes commercially available for prescription.
Time & Events	Refer to Appendix 1: Schedule of Activities
Treatment Assignment	All subjects are assigned to 100 mg SC mepolizumab.
Interim Analysis	No interim analysis was conducted.

2.4. Statistical Hypotheses

Since the study has a single treatment arm, statistical analyses of treatment effect will not be performed. Therefore, no hypotheses have been defined for this study.

3. PLANNED ANALYSES

3.1. Interim Analyses

While the protocol allowed for interim analyses to be performed as needed in order to provide open-label safety data to inform the risk-benefit assessment of mepolizumab in severe asthma, no interim analysis was required or conducted.

3.2. Final Analyses

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

1. All subjects have been withdrawn from the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database. release and database freeze has been declared by Data Management.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Subjects Enrolled (ASE)	The population will comprise all subjects for whom a record exists on the database.	• Screen failures
As Treated (AT)	The population will consist of all subjects who received at least one dose of an open label mepolizumab within study 201312.	• Study Population • Efficacy • Pharmacodynamic • Safety

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

4.1. Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan [Version 4 (24/AUG/2017)].

- Data will be reviewed prior to freezing the database to ensure all important deviations and deviations 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.

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

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
1	Mepolizumab 100mg SC	Mepolizumab 100mg SC	1

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.

5.2. Visit 1 Assessments (Copying from MEA115661)

Subjects will enter this study (201312) after completion of the MEA115661 study. To reduce the burden of repeated procedures during the ending of MEA115661 and the start of 201312, some baseline assessments will be copied from MEA115661. Detailed conditions for copying assessments are listed below:

Definition 1.
Condition:
i) Visit 1 Date is less than/equal to 8 weeks apart from the MEA115661 Visit 14 (Exit Visit) Date;
ii) MEA115661 Visit 15 (Follow Up) Visit assessment is not available;
Action: Copy assessment from MEA115661 Visit 14 (Exit Visit)

Definition 2.
Condition:
i) Visit 1 Date is less than/equal to 8 weeks apart from the MEA115661 Visit 14 (Exit Visit) Date;
ii) MEA115661 Visit 15 (Follow Up) Visit assessment is available;
Action: Copy assessment from MEA115661 Visit 15 (Follow Up) Visit

Definition 3.
Condition:
i) Visit 1 Date is greater than 8 weeks apart from the MEA115661 Visit 14 (Exit Visit) Date;
ii) MEA115661 Visit 15 (Follow Up) Visit Date is equal to the Visit 1 Date;
Action: Copy assessment from MEA115661 Visit 15 (Follow Up) Visit

Definition 4.
Condition:
i) Visit 1 Date is greater than 8 weeks apart from the MEA115661 Visit 14 (Exit Visit) Date;
ii) Visit 1 Date is after the MEA115661 Visit 15 (Follow Up) Visit Date
Action: New assessments to be performed at Visit 1, no copying from MEA115661 will be performed

Under definitions 1-3, a number of the following baseline assessments will be copied from either MEA115661 Visit 14 (Exit Visit) or MEA115661 Visit 15 (Follow Up Visit) where available:

- Pulmonary function test data (including FEV_1 and FVC)
- Asthma Control Questionnaire-5 (ACQ-5)
- Vital Sign data
- ECG data
- Laboratory data (including Haematology, Chemistry and Liver Event test panels)
- Immunogenicity data

The remaining baseline assessments will need to be performed at Visit 1 of the 201312 study, in which case, no copying from MEA115661 study will be performed. A list of the remaining baseline assessments based on each definition can be found in Appendix 5: Derived and Transformed Data.

5.3. Baseline Definition

Baseline will be defined for all subjects who are within the AT population.

The baseline assessment for each subject will be derived as the latest assessment prior to first dose of mepolizumab in this study. If the measurements are taken on the same date as the first administration of mepolizumab, they 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 mepolizumab.

5.3.1. Derivations and Handling of Missing Baseline Data

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

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 5.3 (Baseline Definition) will be used for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.

5.4. Multicentre Studies

The following regions are defined with consideration for standard of care medical practice, number of subjects enrolled and regulatory considerations:

Region	Countries
European Union	Belgium, Czech-Republic, France, Germany, Italy, Netherlands, Poland, Spain, Ukraine, United Kingdom
Rest of World	Argentina, Australia, Canada, Chile, Japan, Russia, South Korea, United States

5.5. Examination of Subgroups

The list of subgroups may be used in descriptive summaries and safety analyses. Additional subgroups of clinical interest may also be considered.

Subgroup	Categories
Age group	12-17,18-64, >=65 years

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
11.1	Appendix 1: Schedule of Activities
11.2	Appendix 2: Assessment Windows
11.3	Appendix 3: Treatment Phases
11.4	Appendix 4: Data Display Standards & Handling Conventions
11.5	Appendix 5: Derived and Transformed Data
11.6	Appendix 6: Reporting Standards for Missing Data
11.7	Appendix 7: Values of Potential Clinical Importance
11.8	Appendix 8: Model Checking and Diagnostics for Statistical Analyses

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the As Treated (AT) population, unless otherwise specified.

Study population analyses including analyses of subject's disposition, demographic and baseline characteristics, medical history, concomitant medications and protocol deviations will be based on GSK Core Data Standards. Details of the planned displays are presented Appendix 10: List of Data Displays.

6.2. Subject Disposition

A summary of the number of subjects included in each population will be produced.

The proportion of screen failures, the proportion who reported each reason for screen failure and the proportion who failed each eligibility criteria will be presented for the All Subject Enrolled (ASE) population.

The proportion of subjects in the AT population at each site and within each country and region will be presented.

The proportion of subjects in the AT population who withdrew from the study, and the reported reasons for withdrawal, will be presented. A Kaplan-Meier plot presenting the percentage of subjects withdrawing from the study over time will be produced for the AT Population.

6.3. Demographic and Baseline Characteristics

6.3.1. Demography and Race

Demographic characteristics (age, sex, ethnicity, height, weight and body mass index) will be summarised and listed.

The proportion of subjects reporting each race and racial combination will be presented. Race will also be listed.

6.3.2. Baseline Lung Function Tests

The following Baseline (as defined for this study) clinic lung function results will be summarised:

- Pre-bronchodilator FEV_1 (mL)
- Pre-bronchodilator percent predicted FEV_1 (%)
- Pre-bronchodilator Forced Vital Capacity (FVC) (mL)
- Pre-bronchodilator FEV_1/FVC

6.4. Medical Conditions

An update in each subject's medical history since the medical history form in the MEA115661 trial will be collected at Visit 1. If a subject reports no change in medical history, the respective subject's medical history information will be copied over from the MEA115661 trial.

The proportion of subjects who report medical conditions in each medical condition class will be presented, for past and current conditions separately.

6.5. Concomitant Medications

The proportion of subjects reporting each concomitant medication will be presented. 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, as well as into those taken during treatment and post-treatment (as described in Appendix 3: Treatment Phases). Asthma medication outputs will not display ATC grouping.

Classification of a medication as during or post-treatment will be made with reference to the study treatment start and stop dates and the medication start and stop dates. If the medication start date is missing or partial then the medication will be considered on-treatment unless there is evidence to the contrary (e.g. the month of the start date is present and is less than the month of the first dose of study medication).

A listing of the relationship between ATC level 1, ingredient and verbatim term will be produced.

6.6. Protocol Deviations

Important protocol deviations will be summarised and listed for the AT Population. More details are in Appendix 10: List of Data Displays.

7. SAFETY ANALYSES

The main interest of the study is to investigate the long-term safety and these analyses will be based on the As Treated (AT) population, unless otherwise specified.

7.1. Extent of Exposure

The number of treatments administered and the time spent on-treatment will be summarised and listed.

Additionally, the overall exposure will be summarised from study 201312 and preceding mepolizumab studies where the same subjects participated (MEA115588, MEA115575 and MEA115661).

7.2. 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 pre-treatment, on-treatment and post-treatment phase will be summarised separately. 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 will also be presented to account for the length of exposure within the trial. For the definition of exposure adjusted AEs, see Appendix 5: Derived and Transformed Data.

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

7.3. Adverse Events of Special Interest Analyses

Adverse events of special interest (AESIs) are adverse events associated with the identified and potential risks of mepolizumab. AESIs of anaphylaxis reactions, systemic reactions, and local injection site reactions are collected via targeted eCRF within the study. Events captured on the eCRF as systemic reactions will be further categorized as allergic/hypersensitivity reactions or non-allergic reactions. Events with preferred terms such as injection related reaction or administration related reaction will be considered non-allergic reactions. All remaining events will be considered allergic/hypersensitivity reactions.

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

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

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

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

Cardiovascular events will also be captured on targeted CV event pages of the CRF following AEs and SAEs. The following cardiovascular event listings will be produced for all investigator reported events:

- 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

Equivalent listings will be produced for all CEC adjudicated events. Note that Arrhythmias, pulmonary hypertension, revascularisation and valvulopathy events will not be sent for adjudication by the CEC, hence for such events listings will only be produced for investigator reported events.

Summaries of events which were reported and confirmed (or not) as cardiovascular following adjudication by the trial Clinical Endpoint Committee (CEC) will be summarised.

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

7.4. Clinical Laboratory Analyses

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

7.5. Other Safety Analyses

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

7.5.1. Immunogenicity

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

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

The mepolizumab ADA (screening/confirmation/titration) assay version 2011N122789_03 is performed at Alliance Pharma (method 120711M01.V02). The mepolizumab Nab assay version 2011N129752_03 is being performed within GSK.

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

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

8. EFFICACY ANALYSES

8.1. Primary Efficacy Analyses

8.1.1. Endpoint / Variables

The primary efficacy analyses endpoint is the annualized rate of exacerbations.

8.1.2. Summary Measure

The frequency of exacerbations of asthma collected during the on-treatment phase (Appendix 3: Treatment Phases) will be summarised.

8.1.3. Population of Interest

The primary efficacy analyses will be based on the AT population, unless otherwise specified.

8.1.4. Strategy for Intercurrent Events

For the primary analyses, only on-treatment exacerbations will be summarised. More details about phases can be found in Appendix 3: Treatment Phases.

8.1.5. Statistical Analyses / Methods

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

Unless otherwise specified, endpoints / variables defined in Section 8.1 will be summarised using descriptive statistics.

8.1.5.1. Statistical Methodology Specification

Endpoint / Variables
• Annualized rate of on-treatment exacerbations
Model Specification
• The frequency of exacerbations will be analysed using Negative Binomial generalised linear model. • Exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation. • The logarithm of time on treatment will be used as an offset variable.
Model Checking & Diagnostics
• Refer Appendix 8: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• The estimated mean rate per year and corresponding 95% confidence interval will be presented

Sensitivity and Supportive Analyses
• An additional analysis will be performed only for the subjects enrolled into study 201312 from previous exacerbation study MEA115588. This analysis will present the exacerbation rate during the current and preceding study periods (from studies MEA115588 and MEA115661) to assess if the exacerbation rate reduction has been maintained.

8.2. Secondary Efficacy Analyses

8.2.1. Endpoint / Variables

The secondary efficacy analysis consists of:

- Time to First Exacerbation
- Annualized rate of Exacerbations Requiring Hospitalisation or Emergency Department (ED) visit
- Annualized rate of Exacerbations Requiring Hospitalisation
- Asthma Control Questionnaire-5 Score
- Forced expiratory volume in 1 second (FEV_1)
- Oral Corticosteroid Dose (mg/day)

8.2.2. Summary Measure

The frequency of exacerbations requiring hospitalisation/hospitalisation or ED visit collected during the on-treatment phase (Appendix 3: Treatment Phases) will be summarised.

Asthma Control Questionnaire (ACQ-5) score (absolute value and change from baseline) and Pre-bronchodilator FEV_1 (absolute value and change from baseline (mL)) will be summarised by visit.

Additionally, OCS use will be summarised only for the subjects enrolled into study 201312 from previous OCS reduction study MEA115575. This analysis will present the median OCS Dose (mg/day) during the current and preceding study periods (from studies MEA115575 and MEA115661) to assess if the reduction in OCS use has been maintained.

8.2.3. Population of Interest

The secondary efficacy analyses will be based on the AT population, unless otherwise specified.

8.2.4. Strategy for Intercurrent Events

Only subjects who have on-treatment data will be included.

8.2.5. Statistical Analyses / Methods

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

Unless otherwise specified, endpoints / variables defined in Section 8.2.1 will be summarised using descriptive statistics and graphically presented (where appropriate).

8.2.5.1. Statistical Methodology Specification

Endpoint / Variables
• Time to First Exacerbation
Results Presentation
• Kaplan-Meier estimates will be summarised by study visit and presented graphically.

Endpoint / Variables
• Annualized rate of Exacerbations Requiring Hospitalisation or Emergency Department visits • Annualized rate of Exacerbations Requiring Hospitalisation
Results Presentation
• See Section 8.1.5.1 for details of the analysis model.

Endpoint / Variables
• Asthma Control Questionnaire-5 (ACQ-5) score
Results Presentation
• ACQ-5 score (absolute value and change from baseline) will be summarised by visit.

Endpoint / Variables
• Forced expiratory volume in 1 second (FEV_1)
Results Presentation
• Pre-bronchodilator FEV_1 (absolute value and changes from baseline (mL)) will be summarised by visit.

Endpoint / Variables
• Oral Corticosteroid Dose (mg/day)
Results Presentation
• OCS use will be summarised only for the subjects enrolled into study 201312 from previous OCS reduction study MEA115575. This analysis will present the median OCS Dose (mg/day) during the current and preceding study periods (from studies MEA115575 and MEA115661) to assess if the reduction in OCS use has been maintained.

9. PHARMACODYNAMIC ANALYSIS

9.1. Pharmacodynamic Analyses

9.1.1. Endpoint / Variables

The pharmacodynamic variable considered is blood eosinophils.

9.1.2. Summary Measure

Blood eosinophil count and ratio to baseline will be summarised by visit.

9.1.3. Population of Interest

The pharmacodynamic analyses will be based on the AT population, unless otherwise specified.

9.1.4. Strategy for Intercurrent (Post-Randomization) Events

Only on-treatment blood eosinophils will be analysed (See Section 11.3.1).

9.1.5. Statistical Analyses / Methods

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

Unless otherwise specified, endpoints / variables defined in Section 9.1.1 will be summarised using descriptive statistics.

9.1.5.1. Statistical Methodology Specification

Endpoint / Variables
• Ratio to baseline in blood eosinophil count
Data Specification
• A log-transformation will be applied to blood eosinophil count data prior to summarising the 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 GI/L = 0.005 GI/L for previous mepolizumab studies).
Results Presentation
• Blood eosinophil count and ratio to baseline will be summarised by visit. • Geometric mean and standard deviation (on natural log scale) will be summarised.

10. REFERENCES

GlaxoSmithKline Document Number 2011N122789_03 Study ID Across Studies. Electrochemiluminescent Immunoassay Method for the Detection of anti-SB240563 (Mepolizumab) Antibodies in Human Serum (6th Generation Assay). Report Date 09-Jun-2016.

GlaxoSmithKline Document Number 2011N129752_03 Study ID Across Studies. Indirect Ligand-Binding Assay for the Detection of Neutralizing Antibody Against SB-240563 in Human Serum. Report Date 07-Nov-2016.

GlaxoSmithKline Document Number 2013N187987_00 Study ID 201312. Study 201312: A Multi-Centre, Open-Label, Study of Mepolizumab in a Subset of Subjects with a History of Life Threatening/Seriously Debilitating Asthma Who Participated in the MEA115661 Trial. Original Report Date 2014-FEB-11.

GlaxoSmithKline Document Number 2013N187987_01 Study ID 201312. Study 201312: A Multi-Centre, Open-Label, Study of Mepolizumab in a Subset of Subjects with a History of Life Threatening/Seriously Debilitating Asthma Who Participated in the MEA115661 Trial. Amendment No. 1 Report Date 2014-JUN-27.

GlaxoSmithKline Document Number 2013N187987_02 Study ID 201312. Study 201312: A Multi-Centre, Open-Label, Study of Mepolizumab in a Subset of Subjects with a History of Life Threatening/Seriously Debilitating Asthma Who Participated in the MEA115661 Trial. Amendment No. 2 Report Date 2014-NOV-14.

GlaxoSmithKline Document Number 2013N187987_03 Study ID 201312. Study 201312: A Multi-Centre, Open-Label, Study of Mepolizumab in a Subset of Subjects with a History of Life Threatening/Seriously Debilitating Asthma Who Participated in the MEA115661 Trial. Amendment No. 3 Report Date 2015-JUN-19.

GlaxoSmithKline Document Number 2013N187987_04 Study ID 201312. Study 201312: A Multi-Centre, Open-Label, Study of Mepolizumab in a Subset of Subjects with a History of Life Threatening/Seriously Debilitating Asthma Who Participated in the MEA115661 Trial. Republished Amendment 3 Report Date 2015-JUL-06.

GlaxoSmithKline Document Number n/a Study ID Across Studies. Program Safety Analysis Plan for Mepolizumab (SB240563) Version 3. Report Date 31-Mar-2017.

Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J.* 1999;14:902–907.

Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respiratory Medicine.* 2005;99:553–558.

Quanjer P., Stanojevic S., Cole T., Baur X., Hall G., Culver B., Enright P., Hankinson J., Ip M., Zheng J., Stocks J., & ERS Global Lung Function Initiative. Multi-ethnic

reference values for spirometry for the 3-95-yr age range: The global lung function 2012 equations. *European Respiratory Journal.* 2012;40(6):1324-1343.

Quanjer P., Stanojevic S., Cole T., Baur X., Hall G., Culver B., Enright P., Hankinson J., Ip M., Zheng J., Stocks J., & ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95-yr age range: The global lung function 2012 equations - Supplemental Material. *European Respiratory Journal.* 2012;40(6):1324-1343.

Sampson HA, Munoz-Furlong A, Campbell RL et al. Second Symposium on the definition and management of anaphylaxis: Summary Report.Second National Institute of Allergy and Infectious Disease / Food Allergy and Anaphylaxis Network Symposium. *Journal of Allergy and Clinical Immunology.* 2006;117:391-397.

Winthrop KL, Novosad SA, Baddley JW, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases - consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. Ann Rheum Dis. 2015;0:1–10.

11. APPENDICES

11.1. Appendix 1: Schedule of Activities

Table 1 Time and Events Table

Procedures	Week 52 of MEA115661[1]	Treatment Period (Visit Window is ± 1 week)														
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Week of study	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60
Written Informed Consent	X															
Medical History Changes	X															
Smoking Status	X															
Inclusion/Exclusion Criteria	X															
Safety Assessments																
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X															
Vital Signs	X	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	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[2]																
Immunogenicity	X												X			
Hematology	X						X						X			
Chemistry	X						X						X			
Liver Analytes	X						X						X			
Pregnancy Test[3]	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Efficacy Assessments																
Exacerbation review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Asthma Control Questionnaire-5	X			X			X			X			X			X
Spirometry	X						X						X			

1. Before entry in to study 201312, determine which scenario the subject is best classified as and perform the relevant procedures as defined in Section 11.5.1 of the Protocol and the SPM.
2. All laboratory assessments to be completed prior to dosing
3. Pregnancy test (all females of childbearing potential) U = Urine

Procedures	Week 52 of MEA115661[1]	Treatment Period (Visit Window is ± 1 week)														
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Week of study	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**
Worksheets/IP/eCRF																
Administer Mepolizumab 100mg SC	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense paper worksheet	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect paper worksheet		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Register IVRS/IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Before entry in to study 201312, determine which scenario the subject is best classified as and perform the relevant procedures as defined in Section 11.5.1 of the Protocol and the SPM.
2. All laboratory assessments to be completed prior to dosing
3. Pregnancy test (all females of childbearing potential) U = Urine

Procedures	Treatment Period (Visit Window is ± 1 week)														
Visit	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**
Week of study	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104**	**108**	**112**	**116**	**120**
Safety Assessments															
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination															
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG			X						X						
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[2]															
Immunogenicity									X						
Hematology			X						X						X
Chemistry			X						X						X
Liver Analytes			X						X						X
Pregnancy Test[3]	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
Efficacy Assessments															
Exacerbation review	X	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/IP/eCRF															
Administer Mepolizumab 100mg SC	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense paper worksheet	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect paper worksheet	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Register IVRS/IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

2. All laboratory assessments to be completed prior to dosing
3. Pregnancy test (all females of childbearing potential) U = Urine

Procedure	Treatment Period (Visit Window is ± 1 Week)												Exit/ EW Visit[4]
Visit	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**43**	**44**
Week of study	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156**	**160**	**164**	**168**	**172**
Safety Assessments													
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination													X
Vital Signs	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
Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments[2]													
Immunogenicity						X							X
Hematology						X						X	X
Chemistry						X						X	X
Liver Analytes						X						X	X
Pregnancy Test[3]	U	U	U	U	U	U	U	U	U	U	U	U	U
Efficacy Assessments													
Exacerbation review	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/IP/eCRF													
Administer Mepolizumab 100mg SC	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Paper Worksheet	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect Paper Worksheet	X	X	X	X	X	X	X	X	X	X	X	X	X
Register IVRS/IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X

2. All laboratory assessments to be completed prior to dosing

3. Pregnancy test (all females of childbearing potential) U = Urine

4. In the event a subject withdraws early at a scheduled visit, all study procedures scheduled for the Exit Visit (Visit 44) should be performed at this visit instead. In the event a subject withdraws between visits, the subject should be asked to return to the clinic as soon as possible to complete the Exit Visit procedures.

11.2. Appendix 2: Assessment Windows

11.2.1. Assessment Windows

In some circumstances certain Visit 1 assessments will not be performed and assessments will be copied from either Visit 14 (Exit Visit) or Visit 15 (Follow Up) from the preceding study MEA115661. Refer to Section 5.2 for more details.

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

11.2.2. Early Withdrawal Visits

If a subject withdraws from the study at a scheduled visit (i.e. completes an Early Withdrawal), where endpoint data were scheduled to be collected, the data will be summarised and analysed (as appropriate) together with data from subjects who did not withdraw from the study. If a subject withdraws from the study at a scheduled visit at which endpoint data were not scheduled to be collected, or if a subject withdraws between scheduled visits, data will be slotted to the nearest adjacent visit where the endpoint data was scheduled to be collected (if data at that visit were not recorded) according to the Time and Events schedule (Appendix 1: Schedule of Activities).

For example, if a subject prematurely withdraws from the study and completed the Early Withdrawal Visit at Visit 6 (Week 20) and completes an Early Withdrawal Visit which includes an FEV_1 assessment, the FEV_1 data collected will need to be re-assigned to an adjacent visit where FEV_1 data is scheduled for collection. In this case the FEV_1 data will be reassigned to Visit 7 (Week 24) (if data at that visit were not recorded) as this is the closest nominal visit at which collection of FEV_1 data is scheduled.

11.2.3. Unscheduled Visits

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

After Visit 31 (Week 120) all the visits will be collected in an unscheduled manner. As a result, all assessments following Visit 31 will be slotted to the appropriate scheduled visit using the closest assessment to the expected/target visit date.

11.3. Appendix 3: Treatment Phases

11.3.1. Treatment Phases (Efficacy Data)

Exacerbation data and efficacy data collected at scheduled visits (including: ACQ-5 Questionnaire, PFT and Blood Eosinophils) will be classified according to time of occurrence/assessment relative to the first and last date of mepolizumab in study 201312 and the attendance dates of specific visits.

Treatment Phase	Definition
Pre-Treatment	Date & Time < First dose of mepolizumab Date & Time in study 201312
On-Treatment	First dose of mepolizumab in study 201312 ≤ Date & Time ≤ Earliest of (1) or (2): (1) Last dose of mepolizumab Date in study 201312 + 28 days or (2) Early Withdrawal Visit Date
Post-Treatment	Date & Time > Earliest of (1) or (2): (1) Last dose of mepolizumab in study 201312 + 28 days or (2) Early Withdrawal Visit Date

11.3.2. Treatment Phases (Adverse Events)

Adverse events will be classified according to time of occurrence relative to the first and last date of the study treatment in study 201312.

Treatment Phase	Definition
Pre-Treatment	AE Onset Date & time < First dose of mepolizumab in study 201312 If mepolizumab treatment in study 201312 is never started then all AEs will be classified as pre-treatment.
On-Treatment	First dose of mepolizumab in study 201312 ≤ AE Onset Date & Time ≤ Last dose of mepolizumab in study 201312 + 28 Days. If an AE start date is missing or partial then the AE will be considered on-treatment unless there is evidence to the contrary (e.g. month/year of onset date is present and is earlier than the month/year of First dose of mepolizumab in study 201312).
Post-Treatment	AE Onset Date & time > Last dose of mepolizumab in study 201312 + 28 days

11.3.2.1. Adverse Events Data Derivations

Treatment Phase	Definition
Onset Time Since 1st Dose (Days)	If First dose of mepolizumab in study 201312 > AE Onset Date = AE Onset Date - First dose of mepolizumab in study 201312 If First dose of mepolizumab in study 201312 ≤ AE Onset Date = AE Onset Date - First dose of mepolizumab in study 201312 +1 day If First dose of mepolizumab in study 201312 or AE Onset Date is missing = missing.
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	If relationship is marked 'YES' on Inform/eCRF OR value is missing.

11.3.3. Treatment Phases (Concomitant Medications)

Concomitant medications will be classified according to time of occurrence relative to the first and last date of the study treatment in study 201312.

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

Treatment Phase	Definition
Taken During Treatment	If Con-med Start Date < First dose of mepolizumab in study 201312 and Con-med Stop Date ≥ First dose of mepolizumab in study 201312 or If First dose of mepolizumab in study 201312 ≤ Con-med Start Date ≤ Last dose of mepolizumab in study 201312+28 days If the con-med start or stop date is missing or partial then the con-med will be considered on-treatment unless there is evidence to the contrary (e.g. month/year of con-med stop date is present and is before the month/year of the first dose of mepolizumab in study 201312).
Started During Treatment	Subset of con-meds taken during Treatment for which: First dose of mepolizumab in study 201312 ≤ Con-med Start Date ≤ Last dose of mepolizumab in study 201312 + 28 days
Taken Post Treatment	Last dose of mepolizumab in study 201312+ 28 days < Con-med Stop Date

11.4. Appendix 4: Data Display Standards & Handling Conventions

11.4.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Compound	: /arenv/arprod/sb240563/ mid201312 /final
Quality Control (QC) Spread sheet	: /arenv/arprod/sb240563/ mid201312/final/documents
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards. • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files will be generated only for summary tables.	

11.4.2. 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

Formats
• 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) will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of decimal places.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Nominal visits (planned time relative to start of 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. If an unscheduled visit occurs between two completed scheduled visits, the data from the unscheduled visit will not be used in summary tables which are based on by-visit assessments. The information from the unscheduled visit will be included in 'any time post-baseline' summaries and will also be presented in any relevant listings. Note additionally all assessments following Visit 31 will be slotted to the appropriate scheduled visit. See Appendix 2: Assessment Windows 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.	

11.5. Appendix 5: Derived and Transformed Data

11.5.1. General

Multiple Measurements at One Analysis Time Point
• There are no scheduled multiple measurements, however, if multiple measurements are recorded at a given time point the following process will be followed, unless a process for selection of the measurement for the visit is specified: • Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of 'Any visit post-baseline' row of related summary tables.
Study Day
• Calculated as the number of days from date of first dose of mepolizumab in study 201312: Ref Date = Missing → Study Day = Missing • Ref Date < Date of first dose of mepolizumab in study 201312→ Study Day = Ref Date – Date of first dose of mepolizumab in study 201312 • Ref Data ≥ Date of first dose of mepolizumab → • Study Day = Ref Date – (Date of first dose of mepolizumab in study 201312) + 1

Critical Baseline Assessments
Subjects meeting Baseline Definition 1 from Section 5.2: 1. Demographic information review and update for 201312 2. General medical history review and update in 201312 3. Physical examination and update in 201312 4. Assessment of Inclusion/Exclusion criteria. 5. Urine pregnancy test for females of childbearing potential (Protocol Appendix 2: Acceptable Birth Control) **Subjects meeting Baseline Definition 2 and 3 from Section 5.2:** 1. Demographic information review and update for 201312 2. General medical history review and update in 201312 3. Physical examination and update in 201312 4. Pulmonary function tests and assessment 5. Assessment of Inclusion/Exclusion criteria. 6. Urine pregnancy test for females **Subjects meeting Baseline Definition 4 from Section 5.2:** 1. Demographic information review and update for 201312 2. General medical history review and update in 201312 3. Physical examination and update in 201312 4. Pulmonary function tests and assessment 5. Assessment of Inclusion/Exclusion criteria. 6. Asthma Control Questionnaire-5 (Protocol Section 6.2.1.2) 7. Vital signs (Protocol Section 6.3.10.3) 8. 12-lead ECG (Protocol Section 6.3.10.4) 9. Blood sampling for the following: ○ Clinical chemistry ○ Haematology ○ Liver Analytes ○ Immunogenicity 10. Urine pregnancy test for females

11.5.2. Study Population

Age
Only year of birth was collected for subjects; actual birth data was not collected. • GSK standard IDSL algorithms will be used for calculating age where the birth date of all subjects will be imputed as '30th June'. • Birth date will be presented in listings as 'YYYY'. • Each subject's derived age will be calculated as an integer value based on their imputed date of birth relative to the date of the subject's Visit 1 date. [(30th June of the year of birth reported on eCRF – date of Visit 1)/365.25]
Body Mass Index (BMI)
• Calculated as Weight (kg) / Height^2 (m^2)

Percent Predicted FEV1

FEV1 % of predicted normal will be derived using the Global Lung Function Initiative 2012 lookup 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- Southeast 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

NOTES:

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

FEV1/FVC Ratio

Pre-bronchodilator FEV1/FVC ratio will be calculated as the ratio of the FEV1 and FVC values.

Baseline OCS daily dose

- Only corticosteroids administered via oral, intravenous (IV) and intramuscular (IM) routes are to be considered when calculating a subject's total daily prednisone/prednisolone asthma maintenance dose at baseline. All steroids administered via a sublingual route will also be considered as oral.
- The corticosteroid conversion factors shown below will be used, regardless of the route of administration, to scale each corticosteroid dose to a prednisone equivalent dose. These three routes of administration (oral, IV and IM) are to be considered equivalent as it has been noted that the bioavailability of methylprednisolone is considered to be roughly equivalent following administration as an oral, IV or IM steroid.

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

11.5.3. Efficacy

Patient Reported Outcomes/Questionnaires

ACQ-5

- 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 a responder if the subject has a ≥0.5 reduction in ACQ score from Baseline. ACQ-5 Responder/Non-responder category will be missing if the overall ACQ-5 score is missing.

Exacerbations

An exacerbation of asthma as defined as:

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

- *[1]For all subjects, i.v. or oral steroid (e.g., prednisone) for at least 3 days or a single IM CS dose is required. For subjects on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days is required.*
- Within each subject, exacerbations that occurred less than seven days apart will be collapsed into a single exacerbation. Exacerbations for which the collapsing has already been performed

Exacerbations
will be included in the summaries and analyses. Exacerbations will be displayed in listings as captured within the eCRF. Exacerbations which are collapsed into a single exacerbation will be highlighted. • The collapsed exacerbation records will be constructed as follows: o Start date (ASTDT) is the start date of the first exacerbation in the series o End date (AENDT) is the end date of the last exacerbation in the series o Outcome (CEOUT) is the worst outcome in the series (worst to best is Fatal, Not Resolved, Resolved) o Cause (EBCAUSE) is the cause associated with the first exacerbation in the series o 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' o 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

11.5.4. Safety

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: Duration of Exposure in Days = Last mepolizumab dose in study 201312 – (First mepolizumab dose in study 201312) + 29 days • The extent of exposure will also be summarised as the number of study treatments administered

Adverse Events
Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Classification of an AE as pre-, on- or post-treatment will be made with reference to the study treatment start and stop dates and the AE onset date. If the AE onset date is missing or partial then the AE will be considered on-treatment unless there is evidence to the contrary (e.g. the month of the onset date is present and is less than the month of the first dose of study medication). AEs with onset up to 4 weeks after the last dose of treatment will be considered on-treatment. AEs with onset after this period will be considered post-treatment but will be assigned to the treatment previously received. Any SAEs for screen failures or run-in failures will be classified as pre-treatment SAEs. The most frequent on-treatment AEs will be defined as AEs with frequency ≥3% (prior to rounding).

Adverse Events of Special Interest

Section 7.3 provides a full list of AEs of special interest for this compound.

Adverse events of special interest (AESIs) of anaphylaxis reactions, systemic reactions, and local injection site reactions are collected via targeted eCRF. Systemic reactions with preferred terms such as injection related reaction or administration related reaction will be considered non-allergic reactions; those with other preferred terms will be considered allergic/hypersensitivity reactions.

The AESIs of opportunistic infections, malignancies, serious CVT events and serious ischemic events will be identified from a list of relevant preferred terms maintained within a project level reference dataset; created based on the latest version of the MedDRA dictionary available at the time of database freeze for this study (See Program Safety Analysis Plan for additional details).

Exposure Adjusted Adverse Events

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

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

ECG Parameters

RR Interval

All ECG parameters required in this study will be databased, and therefore, further derivations will not be performed by Stats and Programming. The definitions of these parameters are given in this section.

- If RR interval (msec) is not databased, then RR can be derived as:
  [1] If QTcB is machine read & QTcF is not provided, then:

$$RR = \left[\left(\frac{QT}{QTcB}\right)^2\right] * 1000$$

  [2] If QTcF is machine read and QTcB is not provided, then:

$$RR = \left[\left(\frac{QT}{QTcF}\right)^3\right] * 1000$$

- If ECGs are manually read, the RR value should be a collected value and will not be derived.

Corrected QT Intervals

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

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

- Individual maximum QTc(F) and QTc(B) values will also be summarised by treatment group for each scheduled study visit to show the number of subjects with maximum values (msec) in the following categories:
  - <= 450

ECG Parameters

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

Laboratory Parameters
• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database (values below the lower limit of quantification), where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the lower limit of quantification for that particular parameter will be used to impute the corresponding numeric value as half the lower limit of quantification for that measure (LLQ/2). • Regarding blood eosinophil laboratory data please reference Section 11.5.5.

11.5.5. Pharmacodynamic

Laboratory Assessments
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 has typically been 0.5 * 0.01 GI/L = 0.005 GI/L for previous mepolizumab studies).

11.6. Appendix 6: Reporting Standards for Missing Data

11.6.1. Premature Withdrawals

Element	Reporting Detail
General	• Subjects will receive mepolizumab 100 mg SC every for weeks, but it is expected that subjects would withdraw before the Exist Visit due to NUCALA becoming commercially available before the end of the study. Thus, this study will not have any completers and all subjects will eventually withdraw (See Section 2.3). • Withdrawn subjects will not replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data up to and including the date of early withdrawal will be included in summary tables and figures, unless otherwise specified. • The number of subjects who withdraw early will be summarised and listed. • Early withdrawal visits will be slotted as per Appendix 2: Assessment Windows.
Screen Failures	For the purposes of this study screen failures will be defined as follows: • Subjects will be assigned a study number at the time of signing the informed consent (Baseline Visit). Those subjects that complete at least one Visit 1 (Baseline Visit) procedure but do not subsequently receive study treatment will be designated as screen failures.

11.6.2. 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. ○ 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 11.5.4 for the handling of this data. • The ACQ-5 score will be considered as missing if <4 items of the questionnaire are completed at a visit. ACQ-5 Responder/Non-responder category will be missing if the overall ACQ-5 score is missing. • If a blood eosinophil count of zero is reported, it will be imputed with half of the lowest possible blood eosinophil count, where applicable, prior to log transforming the data (Note: this imputation has typically been 0.5 * 0.01 GI/L = 0.005 GI/L for previous mepolizumab studies). • Missing values will not be imputed for any of the other endpoints.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

11.6.2.1. 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' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.
Adverse Events, Exacerbations	• Any partial dates for adverse events and exacerbations will be raised to data management. If the full date cannot be ascertained, the following assumptions will be made: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month. ○ However, if these result 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 and hence the event is considered On-treatment (worst case),

Element	Reporting Detail
	as per Appendix 3: Treatment Phases. ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The 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. • Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

11.7. Appendix 7: Values of Potential Clinical Importance

11.7.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Aged 12+	0.201	0.599
Haemoglobin	g/L	Aged 12+	71	199
Platelet Count	$x10^9$/ L	Aged 1+	31	1499
While Blood Cell Count (WBC)	$x10^9$/ L	Aged 12+	1.1	-

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Calcium	mmol/L	Aged 3+	1.50	3.24
Glucose	mmol/L	Aged 1+	2.2	27.8
Phosphorus	mmol/L	Aged 3+	0.32	-
Potassium	mmol/L	Aged 3+	2.8	6.5
Sodium	mmol/L	Aged 0+	120	160

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	Aged 3-12	>143 (and Total Bilirubin > 43)
ALT/SGPT	U/L	Aged 13+	>239 (and Total Bilirubin > 43)

11.8. Appendix 8: Model Checking and Diagnostics for Statistical Analyses

11.8.1. Statistical Analysis Assumptions

Endpoint(s)	• Frequency of asthma exacerbations during the treatment period
Analysis	• Negative binomial regression analysis

- In the event that this model fails to converge, the model will be reviewed and alternatives explored.
- Distributional assumptions underlying the model used for analysis will be examined by:
  - assessing if a sufficient number of events occurred.
- If there are any important departures from the distributional assumptions, transformations of covariates may be considered or alternative models may be explored as supporting analyses.

11.9. Appendix 9: Abbreviations & Trade Marks

11.9.1. 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
ASE	All Subjects Enrolled
AT	As Treated
ATC	Anatomical Therapeutic Chemical
BLQ	Below Limit of Quantification
BMI	Body Mass Index
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CEC	Clinical Endpoint Committee
CI	Confidence Interval
CIL	Clinical Investigation Leader
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Corticosteroid
CSR	Clinical Study Report
CTR	Clinical Trial Register
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
ED	Emergency Department
EMA	European Medicines Agency
EW	Early Withdrawal
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
FEV_1	Forced expiratory volume in 1 second
FVC	Forced Vital Capacity
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
IDSL	Integrated Data Standards Library
IG	Implementation Guide
IM	Intramuscular

Abbreviation	Description
IMMS	International Modules Management System
IP	Investigational Product
IV	Intravenous
LFT	Liver Function Test
LLQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
NAb	Neutralising Antibody
OCS	Oral Corticosteroids
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
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	Randomization & Medication Ordering System
RAP	Reporting & Analysis Plan
RTF	Rich Text File
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SC	Subcutaneous
SD	Standard Deviation
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
SE	Standard Error
SMQ	Standard MedDRA Query
SOC	System Organ Class
SOP	Standard Operation Procedure
SRM	Study Reference Manual
TA	Therapeutic Area
TFL	Tables, Figures & Listings
TST	Therapeutic Standards Team

11.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
HARP

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

11.10. Appendix 10: List of Data Displays

11.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.17	1.1
Safety	2.1 to 2.67	2.1 to 2.2
Efficacy	3.1 to 3.12	3.1
Pharmacodynamic	4.1	N/A
Section	**Listings**	
ICH Listings	1 to 50	

11.10.2. Mock Example Shell Referencing

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

11.10.3. Deliverables

Delivery	Description
SAC	Final Statistical Analysis Complete

11.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Populations Analysed					
1.1.	ASE	SP1	Summary of Study Populations	IDSL Include All Subjects Enrolled and As Treated Populations	SAC
Subject Disposition					
1.2.	ASE	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC
1.3.	ASE	IE2	Summary of Failed Inclusion/Exclusion/Continuation Criteria for Screen Failures		SAC
1.4.	AT	IE2	Summary of Failed Inclusion/Exclusion/Continuation Criteria for Subjects within the As Treated Population		SAC
1.5.	AT	NS1	Summary of Number of Subjects by Region, Country and Site	Add in a column for region, add a total for regions and a total for country EudraCT/Clinical Operations	SAC
1.6.	AT	ES1	Summary of Disposition and Reasons for Study Withdrawal	ICH E3, FDAAA, EudraCT	SAC
Demographic and Baseline Characteristics					
1.7.	AT	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	SAC
1.8.	ASE	DM11	Summary of Age Ranges	EudraCT, keep rows ≥12-17, ≥18-<64, ≥65-<84, ≥85	SAC
1.9.	AT	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC
1.10.	AT	DM6	Summary of Race and Racial Combinations Details	ICH E3, FDA	SAC
1.11.	AT	SHELL	Summary of Baseline Lung Function Tests	Include FEV1, FVC, FEV/FVC, %Predicted	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Medical Conditions					
1.12.	AT	MH4	Summary of Past Medical Conditions	ICH E3	SAC
1.13.	AT	MH4	Summary of Current Medical Conditions	ICH E3	SAC
Concomitant Medications					
1.14.	AT	CM1	Summary of Asthma Concomitant Medications Taken During Treatment by Respiratory Medication Class Group	Footnote: Multi-component medications displayed under the respiratory medication class of each component Programming note: Display RMC and ingredient as previous Asthma studies	SAC
1.15.	AT	CM1	Summary of Asthma Concomitant Medications Taken Post-Treatment by Respiratory Medication Class Group	Footnote: Multi-component medications displayed under the respiratory medication class of each component Programming note: Display RMC and ingredient as previous Asthma studies	SAC
1.16.	AT	CM1	Summary of Non-Asthma Medications Taken During Treatment	Footnote: Medications may be displayed under more than one ATC classification	SAC
Protocol Deviation					
1.17.	AT	DV1	Summary of Important Protocol Deviations	ICH E3	SAC

11.10.5. Study Population Figures

Study Population: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1	AT	SHELL	Time to End of Study	See Study Population Figure 1.1 (MEA117113 'final' reporting effort), but exclude 'Placebo' and Mepo 300mg SC	SAC

11.10.6. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Exposure					
2.1.	AT	SHELL	Summary of Exposure to Study Medication	ICH E3 See format of Study Population Table 1.28 (200862 'final' reporting effort).	SAC
2.2.	AT	SHELL	Summary of Exposure to Study Medication (Therapeutic Coverage) From Studies MEA115588, MEA115575, MEA115661 and 201312	See format of Study Population Table 7.74 (MEA115661 'manuscript1' reporting effort).	SAC
Adverse Events (AEs)					
2.3.	AT	SHELL	Overview of Adverse Events		SAC
2.4.	AT	AE1	Summary of On-Treatment Adverse Events by System Organ Class and Preferred Term	ICH E3	SAC
2.5.	AT	SHELL	Summary of Exposure Adjusted On-Treatment Adverse Events by System Organ Class and Preferred Term		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.6.	AT	AE5	Summary of On-Treatment Adverse Events by Maximum Intensity by System Organ Class and Preferred Term	ICH E3 Add a Total column across all severities	SAC
2.7.	AT	AE1	Summary of Post-Treatment Adverse Events by System Organ Class and Preferred Term		SAC
2.8.	AT	AE5	Summary of Post-Treatment Adverse Events by Maximum Intensity by System Organ Class and Preferred Term	ICH E3 Add a Total column across all severities	SAC
2.9.	AT	AE3	Summary of Common (>=3%) On-Treatment Adverse Events by Overall Frequency	ICH E3 ≥3% (prior to rounding to nearest percent)	SAC
2.10.	AT	SHELL	Summary of Exposure Adjusted On-Treatment Common (>=3%) Adverse Events by System Organ Class and Preferred Term	≥3% (prior to rounding to nearest percent)	SAC
2.11.	AT	AE1	Summary of On-Treatment Drug-Related Adverse Events by System Organ Class and Preferred Term	ICH E3	SAC
2.12.	AT	SHELL	Summary of Exposure Adjusted On-Treatment Drug-Related Adverse Events by System Organ Class and Preferred Term		SAC
2.13.	AT	AE5	Summary of On-Treatment Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Intensity	Add a Total column across all severities	SAC
2.14.	AT	AE1	Summary of Adverse Events Reported on Day of Dosing by System Organ Class and Preferred Term		SAC
2.15.	AT	SHELL	Summary of On-Treatment Adverse Events by Age Group (12-17, 18-64, >=65 years)		SAC
2.16.	AT	SHELL	Summary of On-Treatment Adverse Events by Highest Anti Drug Antibody Result At Any Time Post Baseline		SAC
2.17.	AT	SHELL	Summary of Post-Treatment Adverse Events by Highest Anti Drug Antibody Result At Any Time Post Baseline		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.18.	AT	AE15	Summary of Common (>=3%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT ≥3% (prior to rounding to nearest percent)	SAC
Serious and Other Significant Adverse Events					
2.19.	AT	AE1	Summary of Pre-Treatment Serious Adverse Events by System Organ Class and Preferred Term		SAC
2.20.	AT	AE1	Summary of On-Treatment Serious Adverse Events by System Organ Class and Preferred Term		SAC
2.21.	AT	AE1	Summary of Post-Treatment Serious Adverse Events by System Organ Class and Preferred Term		SAC
2.22.	AT	SHELL	Summary of Exposure Adjusted On-Treatment Serious Adverse Events by System Organ Class and Preferred Term		SAC
2.23.	AT	SHELL	Summary of On-Treatment Serious Adverse Events by Age Group (12-17, 18-64, >=65 years)		SAC
2.24.	AT	AE1	Summary of Fatal Serious Adverse Events		SAC
2.25.	AT	SHELL	Summary of Fatal Serious Adverse Events by Age Group (12-17, 18-64, >=65 years)		SAC
2.26.	AT	AE1	Summary of Non-Fatal Serious On-Treatment Adverse Events by System Organ Class and Preferred Term		SAC
2.27.	AT	AE1	Summary of Non-Fatal Serious Post-Treatment Adverse Events by System Organ Class and Preferred Term		SAC
2.28.	AT	SHELL	Summary of Exposure Adjusted On-Treatment Non-Fatal Serious Adverse Events by System Organ Class and Preferred Term		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.29.	AT	AE1	Summary of Drug-Related Fatal Serious Adverse Events by System Organ Class and Preferred Term		SAC
2.30.	AT	AE5	Summary of Drug-Related Serious Adverse Events by System Organ Class and Preferred Term and Maximum Intensity	Add a Total column across all severities	SAC
2.31.	AT	AE3	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term /by Overall Frequency	IDSL	SAC
2.32.	AT	SHELL	Summary of Exposure Adjusted On-Treatment Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term		SAC
2.33.	AT	AE16	Summary of On-Treatment Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	SAC
Adverse Events of Special Interest					
2.34.	AT	AE1	Summary of On-Treatment Adverse Events Meeting Anaphylaxis Criteria	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
2.35.	AT	SHELL	Summary Profile of On-Treatment Adverse Events Meeting Anaphylaxis Criteria	Insert footnote: “Events displayed are a subset of reactions defined by the Investigator as being systemic”	SAC
2.36.	AT	AE1	Summary of On-Treatment Adverse Events Defined by the Investigator as Being Systemic (non-allergic or allergic/hypersensitivity) Reactions		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.37.	AT	SHELL	Summary Profile of On-Treatment Systemic (non-allergic or allergic/hypersensitivity) Reactions		SAC
2.38.	AT	SHELL	Summary Profile of On-Treatment Systemic Allergic Reactions		SAC
2.39.	AT	SHELL	Summary Profile of On-Treatment Systemic Non-Allergic Reactions		SAC
2.40.	AT	AE1	Summary of On-Treatment Adverse Events Defined by the Investigator as being Local Injection Site Reactions		SAC
2.41.	AT	SHELL	Summary Profile of On-Treatment Local Injection Site Reactions		SAC
2.42.	AT	AE1	Summary of On-Treatment Opportunistic Infections		SAC
2.43.	AT	SHELL	Summary Profile of On-Treatment Opportunistic Infections		SAC
2.44.	AT	AE1	Summary of On-Treatment Malignancies		SAC
2.45.	AT	SHELL	Summary Profile of On-Treatment Malignancies		SAC
2.46.	AT	AE1	Summary of On-Treatment Serious Cardiac, Vascular and Thromboembolic Adverse Events		SAC
2.47.	AT	SHELL	Summary Profile of On-Treatment Serious Cardiac, Vascular and Thromboembolic Adverse Events		SAC
2.48.	AT	AE1	Summary of On-Treatment Serious Ischemic Adverse Events		SAC
2.49.	AT	SHELL	Summary Profile of Serious Ischemic Adverse Events		SAC
2.50.	AT	SHELL	Summary of Serious Adverse Events and Adverse Events of Special Interest		SAC
Cardiovascular Events					
2.51.	AT	SHELL	Summary of All Cause Deaths and Cardiovascular Events Reported by the Investigator		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.52.	AT	SHELL	Summary of CEC Adjudicated All Cause Deaths and Cardiovascular Events of Interest		SAC
Laboratory: Chemistry					
2.53.	AT	LB1	Summary of Chemistry Changes from Baseline	ICH E3 Includes Baseline values.	SAC
2.54.	AT	LB3	Summary of Chemistry Results (Changes from Baseline Relative to the Normal Range)	See also format of Safety Table 7.36 (MEA115588 'final reporting effort)	SAC
2.55.	AT	LB3	Summary of Chemistry Results (Changes from Baseline Relative to the Reference Range [Potential Clinical Importance])	See also format of Safety Table 7.36 (MEA115588 'final reporting effort)	SAC
Laboratory: Haematology					
2.56.	AT	LB1	Summary of Haematology Changes from Baseline	ICH E3 Includes baseline values.	SAC
2.57.	AT	LB3	Summary of Haematology Results (Changes from Baseline Relative to the Normal Range)	See also format of Safety Table 7.42 (MEA115588 'final reporting effort)	SAC
2.58.	AT	LB3	Summary of Haematology Results (Changes from Baseline Relative to the Reference Range [Potential Clinical Importance])	See also format of Safety Table 7.42 (MEA115588 'final reporting effort)	SAC
Laboratory: Hepatobiliary (Liver)					
2.59.	AT	LIVER10	Summary of Subjects Meeting Emergent Hepatobiliary Laboratory Abnormality Criteria	IDSL	SAC
ECG					
2.60.	AT	EG1	Summary of ECG Findings	IDSL	SAC
2.61.	AT	EG2	Summary of Change from Baseline in ECG Values by Visit	Includes baseline values.	SAC
2.62.	AT	SHELL	Summary of Actual and Change From Baseline QTc(F) Values by Category (msec)		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.63.	AT	SHELL	Summary of Actual and Change From Baseline QTc(B) Values by Category (msec)		SAC
Vital Signs					
2.64.	AT	VS1	Summary of Change from Baseline in Vital Signs	ICH E3 Includes Baseline values.	SAC
Immunogenicity					
2.65.	AT	SHELL	Summary of ADA Assay Results	See format of Other Assessments Table 8.01 (MEA115588 'final' reporting effort)	SAC
2.66.	AT	SHELL	Summary of Treatment Emergent ADA Assay Results		SAC
2.67.	AT	SHELL	Summary of NAb Assay Results	See format of Other Assessments Table 8.02 (MEA115588 'final' reporting effort)	SAC

11.10.7. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory					
2.1.	AT	LIVER14	Scatter Plot of Maximum Post-Baseline vs. Baseline for ALT	IDSL	SAC
2.2.	AT	LIVER9	Scatter Plot of Maximum Post-Baseline ALT vs. Maximum Post-Baseline Total Bilirubin	IDSL	SAC

11.10.8. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exacerbations					
3.1	AT	SHELL	Overview of All Exacerbations	See Efficacy Table 2.61 (200862 'final' reporting effort)	SAC
3.2	AT	SHELL	Summary of Frequency of All Exacerbations	See Efficacy Table 2.62 (200862 'final' reporting effort)	SAC
3.3	AT	SHELL	Annualised Rate of Exacerbations	See Efficacy Table 2.64 (200862 'final' reporting effort)	SAC
3.4	AT	SHELL	Overview of Exacerbation Rate by Treatment Allocated Within MEA115588 and Study Period (MEA115588, MEA115661 and 201312 combined)	See Efficacy Table 6.15 (MEA115661 'final' reporting effort)	SAC
3.5	AT	SHELL	Analysis of Time to First Exacerbation	See Efficacy Table 2.68 (200862 'final' reporting effort)	SAC
3.6	AT	SHELL	Summary of Frequency of Exacerbations Requiring Hospitalisation or Emergency Department visits	See Efficacy Table 2.62 (200862 'final' reporting effort)	SAC
3.7	AT	SHELL	Annualised Rate of Exacerbations Requiring Hospitalisation or Emergency Department visits	See Efficacy Table 2.64 (200862 'final' reporting effort)	SAC
3.8	AT	SHELL	Summary of Frequency of Exacerbations Requiring Hospitalisation	See Efficacy Table 2.62 (200862 'final' reporting effort)	SAC
3.9	AT	SHELL	Annualised Rate of Exacerbations Requiring Hospitalisation	See Efficacy Table 2.64 (200862 'final' reporting effort)	SAC
Asthma Control Questionnaire (ACQ-5)					
3.10	AT	SHELL	Summary of Asthma Control Questionnaire (ACQ-5) Score	See Efficacy Table 2.34 (200862 'final' reporting effort)	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pre – Bronchodilator FEV1					
3.11	AT	SHELL	Summary of Clinic Pre-Bronchodilator FEV1 (mL)	See Efficacy Table 2.27 (200862 'final' reporting effort)	SAC
Oral Corticosteroid Use					
3.12	AT	SHELL	Summary of OCS Dose (mg/day) During Each Reporting Period by Treatment Allocated Within MEA115575 and Study Period (MEA115588, MEA115661 and 201312 combined)	See Efficacy Table 6.16 (MEA115661 'final' reporting effort)	SAC

11.10.9. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exacerbations					
3.1	AT	SHELL	Kaplan-Meier Cumulative Incidence Curve for Time to First Exacerbation	See Efficacy Figure 2.15 (200862 'final' reporting effort)	SAC

11.10.10. Pharmacodynamic Tables

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Blood Eosinophils					
4.1.	AT	SHELL	Summary of Blood Eosinophils (10^9/L)	See Efficacy Table 2.73 (200862 'final' reporting effort), but exclude 'Placebo' column	SAC

11.10.11. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	ASE	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC
2.	ASE	IE3	Listing of Failed Inclusion/Exclusion criteria	ICH E3	SAC
3.	AT	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC
4.	AT	SHELL	Listing of Current and Previous Treatment		SAC
Demographics					
5.	AT	DM2	Listing of Demographic Characteristics	ICH E3	SAC
6.	AT	DM9	Listing of Race	ICH E3	SAC
Medication Use					
7.	AT	CM6	Relationship Between ATC Level 1, Ingredient and Verbatim Text		SAC
Protocol Deviations					
8.	AT	DV2	Listing of Important Protocol Deviations	ICH E3	SAC
Exposure and Treatment Compliance					
9.	AT	EX3	Listing of Exposure Data	ICH E3	SAC
Adverse Events					
10.	ASE	AE8	Listing of All Adverse Events	ICH E3	SAC
11.	ASE	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC
12.	ASE	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Serious and Other Significant Adverse Events					
13.	ASE	AE8	Listing of Fatal Serious Adverse Events	ICH E3	SAC
14.	ASE	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3	SAC
15.	ASE	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC
16.	AT	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	SAC
Adverse Events of Special Interest					
17.	AT	SHELL	Listing of Adverse Events Meeting Anaphylaxis Criteria	See format of Safety Listing 7.10 (MEA115588 'final' reporting effort) Insert footnote: "Events displayed are a subset of reactions defined by the Investigator as being systemic"	SAC
18.	AT	SHELL	Listing of Adverse Events Defined by the Investigator as a Systemic (non-allergic or allergic/hypersensitivity) Reaction	See format of Safety Listing 7.07 (MEA115588 'final' reporting effort). Also add a column stating whether AE is related to IP.	SAC
19.	AT	SHELL	Listing of All Adverse Events Experienced by Subjects with at least one Adverse Event Defined by the Investigator as a Systemic (non-allergic or allergic/hypersensitivity) Reaction		SAC
20.	AT	SHELL	Listing of Adverse Events Defined by the Investigator as a Local Injection Site Reaction	See format of Safety Listing 7.09 (MEA115588 'final' reporting effort). Also add a column stating whether AE is related to IP.	SAC
21.	AT	SHELL	Listing of Opportunistic Infections	See format of Safety Listing 7.10 (MEA115588 'final' reporting effort)	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
22.	AT	SHELL	Listing of Malignancies	See format of Safety Listing 2.03 (mid_mepo_iss 'iss_nda' reporting effort)	SAC
23.	AT	SHELL	Listing of Serious Cardiac, Vascular and Thromboembolic (CVT) Adverse Events	See format of Safety Listing 7.10 (MEA115588 'final' reporting effort)	SAC
24.	AT	SHELL	Listing of Serious Ischemic Adverse Events	See format of Safety Listing 7.10 (MEA115588 'final' reporting effort)	SAC
Cardiovascular Events					
25.	AT	SHELL	Listing of Investigator Reported Cardiovascular Events: Arrhythmias	See format of Safety Listing 7.11 (MEA115588 'final' reporting effort)	SAC
26.	AT	SHELL	Listing of Investigator Reported Cardiovascular Events: Congestive Heart Failure	See format of Safety Listing 7.12 (MEA115588 'final' reporting effort)	SAC
27.	AT	SHELL	Listing of Investigator Reported Cardiovascular Events: Cerebrovascular Events/Stroke	See format of Safety Listing 7.13 (MEA115588 'final' reporting effort)	SAC
28.	AT	SHELL	Listing of Investigator Reported Cardiovascular Events: Deep venous Thrombosis/Pulmonary Embolism	See format of Safety Listing 7.14 (MEA115588 'final' reporting effort)	SAC
29.	AT	SHELL	Listing of Investigator Reported Cardiovascular Events: Myocardial Infarction/Unstable Angina	See format of Safety Listing 7.15 (MEA115588 'final' reporting effort)	SAC
30.	AT	SHELL	Listing of Investigator Reported Cardiovascular Events: Peripheral Arterial Thrombosis Embolism	See format of Safety Listing 7.16 (MEA115588 'final' reporting effort)	SAC
31.	AT	SHELL	Listing of Investigator Reported Cardiovascular Events: Pulmonary Hypertension	See format of Safety Listing 7.17 (MEA115588 'final' reporting effort)	SAC
32.	AT	SHELL	Listing of Investigator Reported Cardiovascular Events: Revascularisation	See format of Safety Listing 7.18 (MEA115588 'final' reporting effort)	SAC
33.	AT	SHELL	Listing of Investigator Reported Cardiovascular Events: Valvulopathy	See format of Safety Listing 7.19 (MEA115588 'final' reporting effort)	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
34.	AT	SHELL	Listing of Investigator Reported Cardiovascular Events: All Cause Deaths	See format of Safety Listing 7.20 (MEA115588 'final' reporting effort)	SAC
35.	AT	SHELL	Listing of CEC Adjudicated Cardiovascular Events: Congestive Heart Failure	See format of Safety Listing 7.17 (MEA115666 'fina_01l' reporting effort)	SAC
36.	AT	SHELL	Listing of CEC Adjudicated Cardiovascular Events: Cerebrovascular Events/Stroke	See format of Safety Listing 7.18 (MEA115666 'fina_01l' reporting effort)	SAC
37.	AT	SHELL	Listing of CEC Adjudicated Cardiovascular Events: Deep venous Thrombosis/ Pulmonary Embolism	See format of Safety Listing 7.19 (MEA115666 'fina_01l' reporting effort)	SAC
38.	AT	SHELL	Listing of CEC Adjudicated Cardiovascular Events: Myocardial Infarction /Unstable Angina	See format of Safety Listing 7.20 (MEA115666 'fina_01l' reporting effort)	SAC
39.	AT	SHELL	Listing of CEC Adjudicated Cardiovascular Events: Peripheral Arterial Thrombosis Embolism	See format of Safety Listing 7.21 (MEA115666 'fina_01l' reporting effort)	SAC
40.	AT	SHELL	Listing of CEC Adjudicated Events: All Cause Deaths	See format of Safety Listing 7.22 (MEA115666 'fina_01l' reporting effort)	SAC
Hepatobiliary (Liver)					
41.	AT	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting		SAC
42.	AT	LB5	Chemistry Results for Subjects Meeting Liver Monitoring/Stopping Event Criteria		SAC
43.	AT	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
44.	AT	SU2	Listing of Substance Use for Subjects with Liver Stopping Events	See format of Safety Listing 7.22 (MEA112997 'final' reporting effort)	SAC
45.	AT	LIVER13	Listing of Subjects Meeting Hepatobiliary Laboratory Criteria Post-Baseline		SAC
46.	AT	SHELL	Mepolizumab Concentrations Following Onset of Liver Event		SAC
All Laboratory					
47.	AT	LB5	Listing of All Laboratory Data for Subjects with Any Value of Potential Clinical Importance	ICH E3	SAC
ECG					
48.	AT	EG6	Listing of All ECG Findings for Subjects with an Abnormal ECG Interpretations	IDSL	SAC
Immunogenicity					
49.	AT	SHELL	Listing of Immunogenicity Results	See format of Other Assessments Listing 8.01 (MEA115588 'final' reporting effort)	SAC
Efficacy					
50.	AT	SHELL	Listing of Exacerbations	See format of Efficacy Listing 6.01 (MEA115588 'final' reporting effort)	SAC

11.11. Appendix 11: Example Mock Shells for Data Displays

The data display shells are available on request.