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

Title	:	Reporting and Analysis Plan for Study 204471, A multi-centre, open label, single arm, 32-week treatment study in subjects with severe eosinophilic asthma not optimally controlled with current omalizumab treatment who are switched from omalizumab to mepolizumab 100mg subcutaneous (the OSMO study).
Compound Number	:	SB-240563
Effective Date	:	08-MAY-2017

Description :

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report (CSR) for Protocol 204471.
- The critical components RAP was completed on the 10th February 2016. This document represents the final RAP and will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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1. REPORTING & ANALYSIS PLAN SYNPOSIS

Overview	Key Elements of the RAP
Purpose	• This reporting and analysis plan (RAP) details all planned analyses and outputs required for the final Clinical Study Report (CSR) of study 204471. • The critical components RAP was completed on the 10th February 2016. This document represents the final RAP and will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.
Protocol	• This RAP is based on protocol amendment 1 (Dated: 23-MAR-2016) for study 204471 (GSK Document No.: 2015N243304_01) and the latest version of the electronic Case Report Form (eCRF) [eCRF Version 2.1].
Primary Objective	• To determine in a pragmatic setting whether there is an improvement in asthma control, from the beginning to the end of the study, when directly switched from omalizumab to mepolizumab in subjects with a severe eosinophilic asthma phenotype not optimally controlled on omalizumab.
Primary Endpoint	• Mean change from baseline in ACQ-5 score at Week 32
Study Design	• An open label, single arm, 32-week treatment, multi-center study in subjects with severe eosinophilic asthma not optimally controlled with current omalizumab treatment who are switched from omalizumab to mepolizumab 100mg administered subcutaneously (SC) every 4 weeks. • Approximately 120 subjects are expected to be treated with open label mepolizumab.
Planned Analyses	• No interim analysis of data is planned for this study. • A complete analysis in accordance with all study objectives and endpoints will be performed after all subjects have completed the study. • Decisions regarding the analyses, specified in this RAP document, will be made prior to Database Freeze of the study data.
Analysis Populations	• The 'All Subjects Enrolled' population will be used to summarise Screen and run-in failures. • The 'Intent-to-Treat' population will be used as the primary population to summarise the study population, and to evaluate efficacy, safety and PD/Biomarkers. • The 'Per Protocol' population will also be used as a supporting population to evaluate efficacy. Subjects excluded will have protocol deviations considered to potentially have an effect on efficacy.
Hypothesis	• As there is no control arm within this study, comparisons in ACQ score will be made back to baseline. • The potential of a 'placebo effect' within the mepolizumab treated subjects was considered when the study was designed and was estimated as an improvement of -0.55 from baseline in ACQ score, based on placebo subjects within historical mepolizumab severe asthma studies. However, when only previous Xolair users were considered, an improvement of -0.11 from baseline in ACQ score was observed. • This study is designed to test the superiority of mepolizumab 100 mg SC

Overview	Key Elements of the RAP
	treatment vs. baseline. Improvements will also be assessed against the historical 'placebo effects' estimated from previous mepolizumab studies. Significance tests will be performed at the two-sided 5% alpha level (one-sided 2.5%).
Primary Analyses	• ACQ-5 score will be analysed using a mixed models repeated measures analyses allowing for covariates of region, use of baseline maintenance oral corticosteroids therapy (OCS vs no OCS), exacerbations in the year prior to the study (as an ordinal variable), and visit (including baseline visit).
Secondary Analyses	• SGRQ score will be analysed using a mixed models repeated measures analysis as for ACQ-5. • Frequency of clinically significant asthma exacerbations will be analysed using a negative binomial regression analysis • Blood eosinophil count will be analysed using a mixed model repeated measures analysis after log transformation
Safety Analysis	• Safety data including adverse events, vital signs, clinical laboratory, electrocardiogram (ECG), and immunogenicity data will be summarised descriptively.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Statistical analysis changes to the originally planned statistical analysis specified in the protocol amendment 1 (Dated: 23-MAR-2016) (GSK Document No.: 2015N243304_01) are outlined in Table 1.

Table 1 Changes to Protocol Defined Statistical Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rational for Changes**
• Analysis of change from baseline in ACQ, SQRQ scores will be performed using a mixed models repeated measures (MMRM) analysis, allowing for covariates of baseline ACQ score, region, baseline maintenance OCS therapy, exacerbations in the year prior to the study (as an ordinal variable), visit and an interaction term for visit by baseline ACQ score.	• Baseline values will be included as a data point in the analysis, and there will be no covariate adjustment made in the model. The change from the baseline at Visit X will be calculated by: Estimated Score at Visit X minus Estimated Score at Baseline.	• This is a single treatment arm study and comparisons are being made directly to the baseline values.
• Clinically significant exacerbations will be analyzed using a generalized linear model with covariates for region, baseline maintenance OCS therapy and number of exacerbations in the year prior to the study (as an ordinal variable).	• Clinically significant exacerbations will be examined using a generalized estimating equation (GEE) with no adjustments for covariates.	• Generalised estimating equations (GEEs) will compare the on-treatment exacerbation rate to the rate within the 12 months prior to study.

2.2. Study Objectives and Endpoints

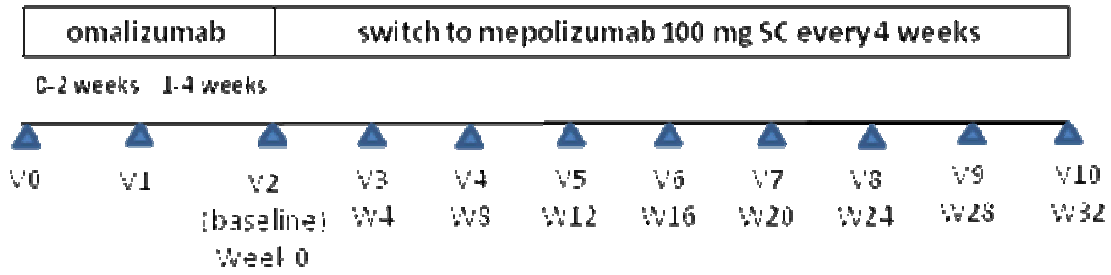
The below objectives and endpoints will be assessed when subjects with a severe eosinophilic asthma phenotype who are not optimally controlled on omalizumab are directly switched from omalizumab to mepolizumab:

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To describe in a pragmatic situation/setting whether there is an improvement in asthma control from the beginning to the end of the study	• Mean change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at Week 32
Secondary Objectives	**Secondary Endpoints**
• To determine whether there is an improvement in Health related Quality of Life (HR-QoL)	• Mean change from baseline in St. George's Respiratory Questionnaire (SGRQ) score at Week 32
• To determine the frequency of asthma exacerbations	• Frequency of clinically significant asthma exacerbations over 32 week treatment
• To evaluate the pharmacodynamic effects	• Ratio to baseline in blood eosinophils at Week 32
Other Objectives	**Other Endpoints**
• To determine the response to asthma clinical parameters	• Percentage of subjects achieving a 0.5-point or greater reduction from baseline in ACQ-5 score at Week 32 • Percentage of subjects achieving a 4-point or greater reduction from baseline in SGRQ score at Week 32 • Mean change from baseline in pre- and post bronchodilator FEV1 at Week 32 • Frequency of exacerbations requiring ED visit/hospitalization during the treatment period • Subject/Clinician rated response to therapy • Mean change from baseline in treatment satisfaction questionnaire
Exploratory Objectives	**Exploratory Endpoints**
• To determine the effect on inflammatory biomarkers • To characterize patient treatment benefit of mepolizumab	• Change from baseline in some inflammatory biomarkers expression at week 32 • Subject Exit Interviews
Safety Objectives	**Safety Endpoints**
• To determine the safety, immunogenicity and tolerability of mepolizumab	• Incidence and frequency of Adverse/Serious Adverse Events (including systemic and injection site reactions) • Clinically significant change in electrocardiogram (ECGs) • Clinically significant change in vital signs

Objectives	Endpoints
	• Incidence of immunogenicity

2.3. Study Design

Overview of Study Design and Key Features



Design Features	• An open label, single arm, 32-week treatment, multi-center study in subjects with severe eosinophilic asthma not optimally controlled with current omalizumab treatment who are switched from omalizumab to mepolizumab 100mg administered subcutaneously (SC) every 4 weeks. • Patients with severe eosinophilic asthma who are receiving omalizumab, but are not optimally controlled will be eligible to participate and will be identified through the ACQ-5 with a screening (Visit 1) and baseline (Visit 2) score of ≥1.5 and a history of ≥2 exacerbations in the past 12 months.
Dosing	• Subjects will remain on their current maintenance therapy throughout the run-in period, including Omalizumab. At Visit 2 subjects will discontinue their Omalizumab treatment and be switched to open-label mepolizumab (100 mg SC) every 4 weeks for 32 weeks (there is no wash-out period between the therapies). If patients require any additional maintenance therapy (except for omalizumab), they will remain receiving it throughout the treatment period.
Treatment Assignment	• At week 0 (Visit 2) approximately 120 eligible subjects who meet the continuation to treatment criteria will receive open-label mepolizumab 100 mg SC into the upper arm or thigh every 4 weeks with the last dose being given at week 28 (Visit 9). A web based interactive system RAMOS NG will be used to dispense mepolizumab from Visit 2 to Visit 9.
Planned Analysis	• No interim analysis of data is planned for this study. • A complete analysis in accordance with all study objectives and endpoints will be performed after all subjects have completed the study. • Decisions regarding the analyses, specified in this RAP document, will be made prior to Database Freeze of the study data.

2.4. Statistical Hypotheses

This study is designed to investigate whether subjects not optimally controlled on omalizumab can be effectively and safely switched to treatment with mepolizumab to improve asthma control. As there is no control arm in this study, comparisons in ACQ-5 score will be made to baseline. The first hypothesis to be tested will be for superiority of mepolizumab 100 mg SC treatment vs. baseline.

The potential of a 'placebo effect' within the mepolizumab treated subjects has been considered. In the protocol this was estimated as an improvement of -0.55 (SE: 0.05) from baseline in ACQ-5 score, based on the placebo effect observed in mepolizumab subjects from Phase 3 severe asthma studies (meta-analysis of double-blind studies MEA112997 and MEA115588). Improvements from baseline in ACQ-5 score will be assessed against this historical 'placebo effect'. For further information regarding this historical 'placebo effect' please refer to Section 7.1.3.

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

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analysis of data is planned for this study.

3.2. Final Analyses

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

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

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Subjects Enrolled (ASE) Population	• Comprised of all subjects enrolled and for whom a record exists on the study database.	• Screen and run-in failures
Intent-to-Treat (ITT) Population	• Comprised of all subjects who receive at least one dose of mepolizumab.	• Study Population • Efficacy • Safety
Per Protocol (PP) Population	• Comprised of all subjects in the ITT population who have not been identified as full protocol deviators with respect to criteria that are considered to impact the primary efficacy analysis. The decision to exclude a subject from the PP Population or exclude part of their data from the PP Population analyses will be made prior to freezing the study database. Protocol deviations that would exclude subjects from the PP population are defined in Section 4.1 (Protocol Deviations) and (Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).	• Supplementary analysis of the primary endpoint

NOTES :

- Please refer to Appendix 13: List of Data Displays which details the population to be used for each displays being generated.

4.1. Protocol Deviations

- All protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
  - Data will be reviewed prior to freezing the database to ensure all important deviations and deviations which may lead to exclusion from the Per Protocol analysis are captured and categorised on the protocol deviations dataset.
  - This dataset will be the basis for the summaries and listings of protocol deviations.
- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.
- Important deviations which result in exclusion from the Per Protocol population will also be summarised and listed. (Please refer to Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).
- 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

Table 2 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 2 Overview of Appendices

Section	Component
10.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
10.2	Appendix 2: Time & Events
10.3	Appendix 3: Assessment Windows & Visit Slotting
10.4	Appendix 4: Treatment Phases
10.5	Appendix 5: Data Display Standards & Handling Conventions
10.6	Appendix 6: Derived and Transformed Data
10.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
10.8	Appendix 8: Values of Potential Clinical Importance
10.9	Appendix 9: Multicenter Studies
10.10	Appendix 10: Examination of Covariates and Subgroups
10.11	Appendix 11: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
10.12	Appendix 12: Abbreviations & Trade Marks
10.13	Appendix 13: List of Data Displays
10.14	Appendix 14: Example Mock Shells for Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the Intent-To-Treat (ITT) population, unless otherwise specified.

Table 3 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 13: List of Data Displays.

Table 3 Overview of Planned Study Population Analyses

Endpoint / Parameter / Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Analysis Populations	Y		
Reasons for Screen and Run-in Failure	Y		Y
Failed Inclusion/Exclusion/Continuation criteria	Y		Y
Subjects by Region, Country and Site	Y		
Reasons for Subject Withdrawal From Study	Y		Y
Reasons for Subject Withdrawal From Investigational Product	Y		Y
Time to Withdrawal From Investigational Product		Y[1]	
Demographic and Baseline Characteristics			
Demographic Characteristics	Y		Y
Age Ranges	Y		
Race and Racial Combinations	Y		Y[2]
Race and Racial Combination Details	Y		
Demographic and Baseline Disease Characteristics			
Asthma History and Baseline Disease Characteristics	Y		
Previous Exacerbation History	Y		
History of Tobacco Use	Y		
Baseline Lung Function Results	Y		
Past and Current Medical Conditions	Y		
Cardiovascular Assessments (Family History/Screen Questions)	Y		
Prior and Concomitant Medications			
History Xolair Use (including regime, duration of treatment)	Y		
Asthma Concomitant Medications by Respiratory Medication Class	Y		
Non-Asthma Concomitant Medications Taken During Treatment	Y		
Relationship between ATC level 1, Ingredient and verbatim text			Y

Endpoint / Parameter / Display Type	**Data Displays Generated**		
	Table	Figure	Listing
Protocol Deviations			
Important Protocol Deviations	Y		Y
Protocol Deviations Resulting in Exclusion from PP Population			Y

NOTES : Y = Yes display generated. [1] Kaplan Meier plot; [2] Listing of race as collected in eCRF.

7. PRIMARY STATISTICAL ANALYSES

7.1. Efficacy Analyses

7.1.1. Overview of Planned Efficacy Analyses

The primary efficacy analyses will be based on the Intent-To-Treat (ITT) population. Additional sensitivity analysis will be performed on the Per Protocol population.

Table 4 provides an overview of the planned efficacy analyses, with full details of data displays being presented in Appendix 13: List of Data Displays.

Table 4 Overview of Planned Efficacy Analyses

Endpoint	Absolute [1]							Change from Baseline [1]						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Primary Endpoint														
Asthma Control Questionnaire (ACQ-5)														
On-treatment & Off-treatment [2] [3]	Y[4]			Y				Y[4]	Y[5]		Y	Y		Y

NOTES :

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

1. Absolute and change from baseline summaries combined into a single display.
2. To be generated for Intent-To-Treat (ITT) population and Per-Protocol (PP) population.
3. Subgroup analyses to be repeated for Intent-To-Treat (ITT) population and all subgroups listed within Section 10.10.2.
4. Table to include both Least Square Means and Least Square Mean Changes and estimated treatment difference (Mepolizumab-Historical Placebo) and 95% confidence interval at each visit from Mixed Model Repeated Measures (MMRM) Analysis.
5. Figure to present Least Square Mean Changes and corresponding 95% confidence intervals at each visit from MMRM Analysis

7.1.2. Planned Efficacy Statistical Analyses

Primary Statistical Analyses
Endpoint(s)
• Mean change from baseline in ACQ-5 score at Week 32 (ADaM Dataset : ADACQ5)
Model Specification
• Endpoint will be analysed using a mixed models repeated measures (MMRM) analysis • Dependent variable will be ACQ-5 score at each visit including the baseline • Terms fitted in the MMRM analysis will include: Fixed Categorical Covariates : Region, Baseline maintenance OCS use, Visit Fixed Continuous Covariates : Exacerbations in the year prior to study (as an ordinal variable), Repeated : Visit See Section 10.10.1 for further details around model covariates.
Model Checking & Diagnostics
• Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Adjusted means and the corresponding 95% confidence intervals will be presented by visit. • The estimated adjusted means will be presented using the observed marginal distribution of the sample covariates (OM option in LSMEANS statement). • The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used (DDMF=KR). • An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line. • Change from the baseline at each Visit X will be calculated by (Estimated Score at Visit X minus Estimated Score at Baseline) and the corresponding 95% confidence intervals. Adjusted means at each visit will also be presented. • Plots of LS means change from baseline in ACQ-5 Score and 95% confidence intervals from the model will be generated by visit. • Adjusted mean and corresponding standard error of mean will be presented, together with estimated between treatment difference (Mepolizumab – Historical Placebo) and the corresponding 95% confidence intervals at Week 32.
Treatment Phase
• All subjects in the ITT population will be included within this analysis. • All data collected up to and including Week 32 from patients, including those who have discontinued study treatment, will be included in the analysis.
Sensitivity and Supportive Statistical Analyses
• Additional comparisons to historical placebo effect will be presented at Week 32 (refer to Section 7.1.3 for more details). • A supporting sensitivity analysis of the Per Protocol (PP) population will also be performed. • Subgroup analyses of the primary endpoint will be performed for all subgroups listed within Section 10.10.2.

7.1.3. Analysis Comparing Against A Historical Placebo Effect

We will perform two separate analyses of the primary endpoint comparing to a historical 'placebo effect'.

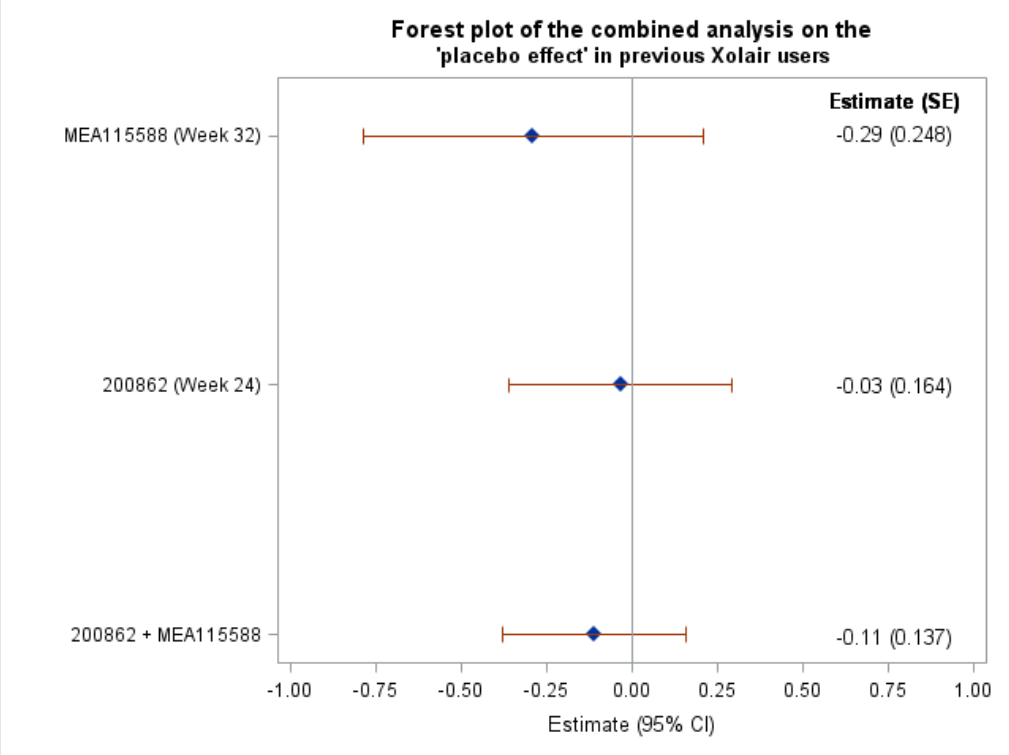
Firstly, as specified in the protocol, a meta-analysis of previous exacerbation double-blind studies, MEA112997 and MEA115588, gave an estimate of -0.55 (SE: 0.05), for the improvement in the ACQ-5 score for placebo subjects at Week 32 compared to baseline. The observed improvement in this study for following mepolizumab treatment will be compared to this historical improvement on placebo.

Secondly, a meta-analysis has been performed of subjects within studies MEA115588 and 200862 who reported previous Xolair use, which may represent a more comparable population for this study. Study 200862 has completed since the protocol was finalised and previous Xolair usage was not collected in study MEA112997.

At Week 32 an estimate of -0.29 (SE: 0.248) was reported in the MEA115588 study while at Week 24 study 200862 reported an estimate of -0.03 (SE: 0.164) for the improvement in the ACQ-5 score for placebo subjects who previously used Xolair.

Weighted meta-analysis was performed on these values to get the combined estimate of -0.11 (SE: 0.14) for the historical placebo effect (Figure 1). This shows a reduction in the ACQ-5 score, but not as large as that specified in the protocol. The observed improvement in this study for mepolizumab vs. baseline will be also compared to this historical improvement on placebo.

Figure 1 Meta-analysis of ACQ-5 Placebo Effect in Previous Xolair Users



8. SECONDARY STATISTICAL ANALYSES

8.1 Efficacy Analyses

8.1.1. Overview of Planned Efficacy Analyses

The secondary efficacy analyses will be based on the Intent-To-Treat (ITT) population, unless otherwise specified in Appendix 13: List of Data Displays.

Table 5 provides an overview of the planned efficacy analyses, with further details of data displays being presented in Appendix 13: List of Data Displays.

Table 5 Overview of Planned Efficacy Analyses

Endpoint	Absolute [1]							Change from Baseline [1] [2]						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Secondary Endpoints														
St George's Respiratory Questionnaire (SGRQ)														
On-treatment & Off-treatment	Y			Y				Y	Y		Y	Y		
Blood Eosinophil Count														
On-treatment & Off-treatment	Y			Y				Y	Y		Y			
On-treatment [3]	Y							Y						
Other Endpoints														
>= 0.5-point reduction from baseline in ACQ-5 score at Week 32														
On-treatment & Off-treatment											Y	Y		
>= 4-point or greater reduction from baseline in SGRQ Total score at Week 32														
On-treatment & Off-treatment											Y	Y		
Pre-Bronchodilator FEV1														
On-treatment & Off-treatment	Y			Y				Y	Y		Y			
Post-Bronchodilator FEV1														
On-treatment & Off-treatment	Y			Y				Y	Y		Y			
Subject/Clinician Rated Response to Therapy														
On-treatment [3]				Y										
Treatment Satisfaction Questionnaire for Medication (TSQM-9)														
On-treatment [3]				Y							Y			
Biomarkers														
On-treatment				Y							Y			

Endpoint	Incidence of Events						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
Secondary Endpoints							
Clinically Significant Exacerbations							
On-treatment & Off-treatment	Y[4]			Y	Y		Y
On-treatment [3]	Y[4]						
Exacerbations requiring ED visit/hospitalization							
On-treatment & Off-treatment	Y[4]			Y			Y
On-treatment [3]	Y[4]						
Exacerbations requiring hospitalization							
On-treatment & Off-treatment	Y[4]			Y			Y

NOTES :

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

1. Absolute and change from baseline summaries combined into a single display.
2. Ratio to Baseline to be shown for Blood Eosinophil Count and Biomarker data.
3. To analyse data collected whilst On-Treatment, not considering any data collected following treatment discontinuation (see Section 10.4).
4. Table to include annualised exacerbation rate and 95% confidence intervals from negative binomial model.

8.1.2. Secondary Efficacy Statistical Analyses

Secondary Statistical Analyses
Secondary Endpoint(s)
• Mean change from baseline in SGRQ at Week 32
Model Specification
• See Primary Efficacy Statistical Analysis, Section 7.1.2
Model Checking & Diagnostics
• Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Adjusted means and the corresponding 95% confidence intervals will be presented by visit. • The estimated adjusted means will be presented using the observed marginal distribution of the sample covariates (OM option in LSMEANS statement). • The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used (DDMF=KR). • An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line. • Change from the baseline at each Visit X will be calculated by (Estimated Score at Visit X minus Estimated Score at Baseline) and the corresponding 95% confidence intervals. Adjusted means at each visit will also be presented. • Plots of LS means change from baseline in SGRQ Score and 95% confidence intervals from the model will be generated by visit.
On-treatment Phase
• See Primary Efficacy Statistical Analysis, Section 7.1.2

Secondary Statistical Analyses
Secondary Endpoint(s)
• Frequency of clinically significant asthma exacerbations over 32 week treatment • Frequency of exacerbations requiring ED visit/hospitalization during the 32 week treatment period • Frequency of exacerbations requiring hospitalization during the 32 week treatment period
Model Specification
• The frequency of clinically significant exacerbations will be analysed using Negative Binomial regression via generalised estimating equations with a covariate of time period (pre-, post-mepolizumab). • Exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation. • The pre-mepolizumab exacerbation values (in the 12 months prior) will be obtained at screening, while the post-meplizumab exacerbation values will be observed during the study. • The variance of the mean estimate will be corrected for within-subject correlation. The logarithm of time on treatment will be used as an offset variable.
Model Checking & Diagnostics
• Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses.

Secondary Statistical Analyses
Model Results Presentation
• Adjusted exacerbation rate and the corresponding 95% confidence interval will be presented.
On-treatment Phase
• All subjects in the ITT population will be included within this analysis. • All data collected up to and including Week 32 from patients, including those who have discontinued study treatment, will be included in the analysis. • An On-Treatment "de jure" analysis will also be performed which does not consider any data collected following treatment discontinuation (see On-Treatment definition within Section 10.4).
Sensitivity and Supportive Statistical Analyses
• The On-Treatment "de jure" analysis will be also performed with a subset of patients who were on omalizumab for more than 12 months.

Secondary Statistical Analyses
Secondary Endpoint(s)
• Ratio to baseline in blood eosinophil count at week 32
Model Specification
• See Primary Efficacy Statistical Analysis, Section 7.1.2 • A log-transformation will be applied to blood eosinophil count data prior to analysis. • 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).
Model Checking & Diagnostics
• Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses..
Model Results Presentation
• Adjusted means and the corresponding 95% confidence intervals will be presented by visit. • Plots of LS means ratio to baseline in blood eosinophil count and 95% confidence intervals from the model will be generated by visit.
On-treatment Phase
• All subjects in the ITT population will be included within this analysis. • All data collected up to and including Week 32 from patients, including those who have discontinued study treatment, will be included in the analysis. • An On-Treatment "de jure" analysis will also be performed which does not consider any data collected following treatment discontinuation (see On-Treatment definition within Section 10.4.

Other Statistical Analyses
Other Endpoint
• Percentage of subjects achieving a 0.5-point or greater reduction from baseline in ACQ-5 score at Week 32
Results Presentation
• The number and percentage of subjects achieving a 0.5-point or greater reduction in ACQ-5 Score compared to baseline will be presented for each visit. • The number of subjects with a missing ACQ-5 Score at each visit will be presented in a separate category.

On-treatment Phase
• See Primary Efficacy Statistical Analysis, Section 7.1.2

Other Statistical Analyses
Other Endpoint
• Percentage of subjects achieving a 4-point or greater reduction from baseline in SGRQ score at Week 32
Results Presentation
• The number and percentage of subjects achieving a 4-point or greater reduction in SGRQ Total score compared to baseline will be presented for each visit. • The number of subjects with a missing SGRQ Total Score at each visit will be presented in a separate category.
On-treatment Phase
• See Primary Efficacy Statistical Analysis, Section 7.1.2

Other Statistical Analyses
Other Endpoint
• Mean change from baseline in pre- and post- bronchodilator FEV1 at Week 32
Model Specification
• See Primary Efficacy Statistical Analysis, Section 7.1.2
Model Checking & Diagnostics
• Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Adjusted means and the corresponding 95% confidence intervals will be presented by visit • The estimated adjusted means will be presented using the observed marginal distributions of the sample covariates (OM option in LSMEANS statement). • The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used (DDMF=KR). • An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line. • Change from the baseline at each Visit X will be calculated by (Estimated Score at Visit X minus Estimated Score at Baseline) and the corresponding 95% confidence intervals. Adjusted means at each visit will also be presented. • Plots of Least Squares (LS) mean change from baseline pre- and post bronchodilator FEV1 and 95% confidence intervals from the model will be generated at each visit.
On-treatment Phase
• See Primary Efficacy Statistical Analysis, Section 7.1.2

Other Statistical Analyses
Other Endpoint
• Subject rated response to therapy at Week 32 • Clinician rated response to therapy at Week 32
Results Presentation

• The number and percentage of subjects in each response category will be presented for each visit. • The number of subjects with a missing responses at each visit will be presented in a separate category.
On-treatment Phase
• An On-Treatment "de jure" analysis will also be performed which does not consider any data collected following treatment discontinuation (see On-Treatment definition within Section 10.4).

Other Statistical Analyses
Other Endpoint
• Mean change from baseline in Treatment Satisfaction Questionnaire for Medication (TSQM-9)
Model Specification
• The Mean Change at Week 32 will be tested to see if it is significantly different from zero using Wilcoxon signed-rank test
Model Checking & Diagnostics
• Check for the extreme outliers by plotting the differences between TSQM-9 at Week 32 and Baseline
Model Results Presentation
• Summary Statistics will be represented by study visit • The mean change at Week 32 will presented with the corresponding 95% CI and p-value in the table • The mean change at Week 32 will presented with the corresponding 95% CI in the figure
On-treatment Phase
• An On-Treatment "de jure" analysis will also be performed which does not consider any data collected following treatment discontinuation (see On-Treatment definition within Section 10.4)

Other Statistical Analyses
Other Endpoint
• Change from baseline in inflammatory biomarkers expression at week 32. The following biomarker parameters will be reported: CCL13, CCL17, ECP, EDN, Eotaxin1, Total IL-5, IL-13, MDC, Periostin, TSLP
Model Results Presentation
• A log-transformation will be applied to each biomarker parameter prior to analysis. • Summary Statistics will be represented by study visit, including ratio to baseline • See Section 10.6.4 for further information regarding biomarker results below the lower limit of quantification
On-treatment Phase
• An On-Treatment "de jure" analysis will also be performed which does not consider any data collected following treatment discontinuation (see On-Treatment definition within Section 10.4).

8.2. Safety Analyses

8.2.1. Overview of Planned Analyses

The safety analyses will be based on the Intent-To-Treat (ITT) population, unless otherwise specified in Appendix 13: List of Data Displays. The safety displays to be created as part of the RAP include all the required and relevant displays identified as per the RAP Core Safety Reporting Template Version 1.0.

Table 6 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 13: List of Data Displays.

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

Table 6 Overview of Planned Adverse Event Analyses

Endpoint / Parameter/ Display Type	Absolute		
	Summary		Individual
	T	F	L
Exposure			
Number of treatments administered and time on-treatment	Y		Y
Adverse Events (AEs)			
Overview of Adverse Events	Y		
AEs by SOC and Maximum Intensity	Y		Y
Common Adverse Events by Overall Frequency [1]	Y		
All Drug-Related AEs by SOC and Maximum Intensity	Y		
AEs on the Day of Dosing	Y		
AEs by the Age Group (<18 year, ≥18 years)	Y		
AEs by Highest Antidrug Antibody Result At Any Time Post Baseline	Y		
Number of subjects & occurrences of common[1] non-serious AEs by SOC and PT	Y		
Subject Numbers for Individual AEs			Y
Relationship between AE SOCs, PT & verbatim text			Y
Serious and Other Significant AEs			
Fatal Serious AEs	Y		Y
Non-Fatal Serious AEs	Y		Y
Serious AEs by SOC	Y		
Reasons for Considering as a Serious AE			Y
Drug-Related Serious AEs by SOC and Maximum Intensity	Y		
AEs Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment by Overall Frequency	Y		Y
Number of Subjects and Occurrences of Serious, Drug-Related Serious, Fatal Serious, and Drug-Related Fatal Serious AEs	Y		
Adverse Events of Special Interest (AESI) (On-Treatment) [2]			
Anaphylaxis	Y		Y
Systemic Allergic/Hypersensitivity and Non-allergic Reactions	Y		Y

Endpoint / Parameter/ Display Type	Absolute		
	Summary		Individual
	T	F	L
Systemic Allergic/Hypersensitivity Reactions	Y		
Systemic Non-allergic Reactions	Y		
Local Injection Site Reactions	Y		Y
Opportunistic Infections	Y		Y
Malignancies	Y		Y
Serious Cardiac, Vascular and Thromboembolic Events	Y		Y
Serious Ischemic Events	Y		Y
Cardiovascular Events			
All Cardiovascular Events	Y		Y

NOTES:

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

[1] Common AEs will be defined as AEs with frequency ≥3% (prior to rounding to nearest percent).
[2] On-treatment Summary Profiles of each type of AE of Special Interest will also be presented.

8.2.2. Adverse Events of Special Interest

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

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

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

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

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

Anaphylaxis [Sampson , 2006] will be provided. Adverse events experienced on a day of dosing will be summarised and presented by SOC and preferred term.

A listing of all adverse events experienced by subjects who have had at least one investigator defined systemic reaction will be provided.

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

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

8.2.3. Overview of Planned Clinical Laboratory Analyses

Safety analyses will be based on the Intent-To-Treat (ITT) population, unless otherwise specified in Appendix 13: List of Data Displays. The safety displays to be created as part of the RAP include all the required and relevant displays identified as per the RAP Core Safety Reporting Template Version 1.0.

Table 7 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 13: List of Data Displays.

Table 7 Overview of Planned Clinical Laboratory Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Chemistry						
Change from Baseline in Clinical Chemistry by Visit				Y		
Chemistry Results (Change from Baseline Relative to Normal Range)	Y			Y		
Hematology						
Change From Baseline in Haematology by Visit				Y		
Haematology Results (Change from Baseline Relative to Normal Range)	Y			Y		
Hepatobiliary (Liver)						
Liver Monitoring/Stopping Event Reporting			Y			
Chemistry Results for Subjects Meeting Liver			Y			

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Monitoring/Stopping Event Criteria						
Medical Conditions for Subjects with Liver Stopping Events			Y			
Alcohol Intake for Subjects with Liver Stopping Events			Y			
Hepatobiliary Laboratory Abnormalities	Y		Y			
Scatter Plot of Maximum Post-Baseline vs. Baseline for ALT		Y				
Scatter Plot of Maximum Post-Baseline ALT vs Maximum Post-Baseline Total Bilirubin		Y				
All Laboratory						
All Laboratory Data for Subjects with any Value of Potential Clinical Concern			Y			

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, PCI = Potential Clinical Importance
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

8.2.4. Overview of Planned Other Safety Analyses

The safety analyses will be based on the Intent-To-Treat (ITT) population, unless otherwise specified in Appendix 13: List of Data Displays. The safety displays to be created as part of the RAP include all the required and relevant displays identified as per the RAP Core Safety Reporting Template Version 1.0.

Table 8 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 13: List of Data Displays.

Table 8 Overview of Planned Other Safety Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
ECG						
ECG Findings	Y		Y			
Change from Baseline in ECG Values by Visit				Y		
Actual and Change From Baseline QTc(F) Values by Category	Y			Y		
Actual and Change From Baseline QTc(B) Values by Category	Y			Y		

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Vital Signs						
Change from Baseline in Vital Signs by Visits				Y		
Immunogenicity						
Immunogenicity (ADA and NAb results)	Y		Y			
Treatment Emergent ADA results	Y					

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, PCI = Potential Clinical Importance
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

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

- A table will be produced summarising the number and percentage of negative and confirmed positive subjects ADA samples by treatment group and visit in the ITT 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 ITT Population, by treatment group and visit.

- An additional summary of treatment emergent positive confirmatory binding antibody assay and results in the subset of subjects who did not have a positive confirmatory binding antibody assay result prior to the first dose of study treatment will also be presented.
- All immunogenicity results (i.e. ADA screening and confirmatory assay results, titre values, neutralising antibody results and observed mepolizumab concentration) will be listed.

9. REFERENCES

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10. APPENDICES

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Section 10.14	Appendix 14: Example Mock Shells for Data Displays

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

10.1.1. Exclusions from Per Protocol Population

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

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

Number	Exclusion Description
01	Inclusion criteria # 2 – Insufficient evidence of asthma for ≥2 years that meets the National Heart and Lung Institute guidelines or GINA guidelines
02	Inclusion criteria # 3 – No persistent airflow obstruction as indicated by For subjects ≥18 years of age at Visit 1, a pre-bronchodilator FEV1 <80% predicted [Quanjer, 2012] recorded at Visit 1. For subjects 12-17 years of age at Visit 1, a pre-bronchodilator FEV1 <90% predicted [Quanjer, 2012] OR FEV1/FVC ratio <0.8 recorded at Visit 1.
03	Inclusion criteria # 4 – No eosinophilic airway inflammation as defined by: • Peripheral blood eosinophil level of ≥300 cells/μL that is related to asthma demonstrated in the 12 months prior to visit 1 OR • Peripheral blood eosinophil level of ≥150 cells/μL demonstrated at Visit 1 that is related to asthma
04	Inclusion criteria # 5 – Absence of evidence of a well-documented requirement for regular treatment with high dose ICS (equivalent to ≥880μg/day fluticasone propionate (FP) (ex-actuator) or equivalent daily in adults and ≥440μg/day FP (ex-actuator) or equivalent daily for subjects aged 12-17) in the 12 months prior to Visit 1 [Note: For ICS/LABA combination preparations, the highest approved maintenance dose in the local country will meet this ICS criterion.]
05	Inclusion criteria # 6 – Absence of current treatment with an additional controller medication, besides ICS, for at least 3 months or a documented failure in the past 12 months of an additional controller medication for at least 3 successive months [e.g., long-acting beta-2-agonist (LABA), leukotriene receptor antagonist (LTRA), or theophylline]
06	Inclusion criteria # 7 – Asthma symptoms not uncontrolled at Visit 1, as defined by an ACQ-5 score of <1.5.
07	Inclusion criteria # 8 – Not receiving Omalizumab treatment based on weight and IgE levels, for at least the 4 months prior to Visit 1.
08	Inclusion criteria # 9 – No history of two or more exacerbations requiring treatment with systemic corticosteroids (intramuscular, intravenous, or oral) in the 12 months prior to Visit 1 despite the use of high-dose ICS. [Note: For subjects receiving omalizumab for ≥8 months, at least one exacerbation must have occurred while on omalizumab treatment. For subjects receiving maintenance oral corticosteroids, the corticosteroid treatment for the exacerbations must have been a two-fold dose increase or greater.]
09	Continuation to treatment criteria # 1 – Asthma symptoms not uncontrolled at Visit 2, as

Number	Exclusion Description
	defined by an ACQ-5 score of <1.5.
10	Continuation to treatment criteria # 2 – Subjects who experience an asthma exacerbation during run-in who have not returned to their baseline asthma status within one week of Visit 2.
11	Continuation to treatment criteria # 3 – Any subject with changes in the dose or regimen of ICS, and/or additional controller medication (except for treatment of an exacerbation) during the run-in period.
12	Continuation to treatment criteria # 4 – Subjects who do not receive their last dose of Omalizumab during the correct period, as defined by: • For subjects receiving omalizumab every 4 weeks, their last dose is received <3 or >5 weeks prior to Visit 2. • For subjects receiving omalizumab every 2 weeks, their last dose is received <1 or >3 weeks prior to Visit 2.
13	Any subject with changes in the dose or regimen of baseline ICS, and/or additional controller medication during open-label treatment. N.B. This excludes the use of OCS for the treatment of an asthma exacerbation.
14	Use of any prohibited medication during the study [1].
15	Receiving the incorrect study treatment at any point during the study.

NOTES:

- [1] See Protocol Section 6.8.2 for the list of prohibited medications within this study.

10.2. Appendix 2: Time & Events

10.2.1. Protocol Defined Time & Events

Table 9 Time and Events Table

Procedures	**Pre-screen[1]**	**Screen Run-in**	**Treatment (visit window is ±7days)**								**Exit Visit/ Early withdrawal Visit[3]**
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Week	**-6 to -4**	**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**4 weeks post last dose ±7 days**
Informed Consent [2]	**x**										
Subject Demography	**x**										
Medical History		**x**									
Asthma History (including triggers)	**x**	**x**									
Therapy History[4]		**x**									
Smoking History		**x**									
Cardiovascular History/Risk Factors		**x**									
Inclusion/Exclusion Criteria		**x**									
Continuation to treatment Criteria			**x**								
Efficacy Assessments[5]											
ACQ-5		**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Exacerbation review	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Spirometry including pre- and post bronchodilator FEV_1, FVC [6]		**x**	**x**			**x**			**x**		**x**
Health Outcome Assessments[5]											
SGRQ			**x**			**x**			**x**		**x**

Procedures	**Pre-screen[1]**	**Screen Run-in**	**Treatment (visit window is ±7days)**								**Exit Visit/ Early withdrawal Visit[3]**
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Week	**-6 to -4**	**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**4 weeks post last dose ±7 days**
Clinician & Subject rated response to therapy					**x**		**x**		**x**		**x**
Treatment Satisfaction with Medication Questionnaire (TSQM-9)		**x**									**x**
Exit Interview[7]											**x**
Safety Assessments[5]											
Concomitant Medication	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Physical Examination, including nasal exam		**x**									**x**
Vital Signs		**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**
Serious Adverse Events	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Laboratory Assessments[5]											
Haematology with differential		**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Clinical Chemistry (incl. LFT)		**x**	**x**	**x**	**x**	**x**			**x**		**x**
Parasitic Screening[8]		**x**									
Pharmacogenetic sample[9]			⟷	⟷	⟷	⟷	⟷	**X**	⟷	⟷	
Pregnancy test[10]		**U**	**U**	**U**	**U**	**U**	**U**	**U**	**U**	**U**	**U**
HBsAg and hepatitis C antibody[11]		**x**									
Immunogenicity sample			**x**			**x**				**x**	**x**
Biomarker sample		**x**	**x**		**x**						**x**

Procedures	**Pre-screen[1]**	**Screen Run-in**	**Treatment (visit window is ±7days)**								**Exit Visit/ Early withdrawal Visit[3]**
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Week	**-6 to -4**	**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**4 weeks post last dose ±7 days**
Investigational product (Mepolizumab) and rescue medication											
Administer mepolizumab. Contact RAMOS NG to register dispensing visit.			**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	
Albuterol/salbutamol dispensed (as needed)		**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	
Collect dispensed albuterol/salbutamol			**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
eCRF/ paper diary/worksheet											
Complete eCRF	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Dispense paper diary/worksheet	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	
Collect/review paper diary/worksheet		**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**

1. Pre-screen Visit 0 must be completed prior to Visit 1 (Screening). It can be completed on the same day as Visit 1 or at up to 2 weeks prior to Visit 1.
2. Subjects will be assigned a subject number at the time ICF signed. The ICF must be signed before any study procedures including medication wash out period(s).
3. Exit Visit may be completed 3 to 5 weeks post last dose.
4. Therapy history to include a detailed review of prior biologics received for treatment of asthma, including omalizumab dose and regimen and prior investigational therapies e.g anti-IL5 or anti-IL13 preparations.
5. All study efficacy, safety and all patient reported questionnaires must be completed prior any study procedure.
6. Spirometry to include pre- and post bronchodilator FEV1 from V2.
7. Exit interview will be conducted only in a subset of sites and in a subset of subjects who choose to participate in the Exit interview. Subjects must be consented prior to interview
8. Parasitic screening is only required in countries with high-risk or for subjects who have visited high-risk countries in the past 6 months. Sites should use local laboratories.
9. Pharmacogenetic sample may be drawn at Visit 2 or any at any visit after.
10. Pregnancy test, U= urine
11. Hepatitis B Surface Antigen and Hepatitis C antibody. (if hepatitis C antibody is positive, hepatitis C will be confirmed by PCR)

10.3. Appendix 3: Assessment Windows & Visit Slotting

10.3.1. Assessment Windows

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

10.3.2. Early Withdrawal / Treatment Discontinuation Visits

If a subject withdraws from the study at a scheduled visit (i.e. completes an Early Withdrawal or Treatment Discontinuation Visit), where endpoint data were scheduled to be collected, the data will be summarised and analysed (as appropriate) together with data from subjects who did not withdraw from the study. If a subject withdraws from the study at a scheduled visit at which endpoint data were not scheduled to be collected, or if a subject withdraws between scheduled visits, data will be slotted to the nearest adjacent visit where the endpoint data was scheduled to be collected (if data at that visit were not recorded) according to the Time and Events schedule (Appendix 2: Time & Events).

For example, if a subject prematurely withdraws from the study and completed the Early Withdrawal Visit at Visit 6 (Week 16) 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 5 (Week 12) (if data at that visit were not recorded) as this is the closest nominal visit at which collection of FEV_1 data is scheduled.

10.3.3. 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 already exists at that visit. If an unscheduled visit occurred between two scheduled visits for which data has been reported, then the data from the unscheduled visit will remain in the unscheduled visit and will not be used in summary tables and analyses (except for endpoints using any post-baseline data) but will be presented in any relevant listings.

10.4. Appendix 4: Treatment Phases

10.4.1. Treatment Phases (Exacerbations)

Exacerbation data will be classified according to time of occurrence/assessment relative to the first and last date of mepolizumab and the attendance dates of specific visits.

Treatment Phase	Definition
Pre-Treatment	Date & time < First dose of mepolizumab
On-Treatment	Subjects completing treatment and completing the study: First dose of mepolizumab ≤ Date & time ≤ Visit 10 (Exit Visit)* visit date Subjects discontinuing study treatment/withdrawing early from the study: First dose of mepolizumab ≤ Date & time ≤ Earliest of (1) Last dose of mepolizumab + 28 days or (2) Early Withdrawal/Treatment Discontinuation visit date
Off-Treatment	Subjects completing treatment and completing the study: Date & time > Visit 10 (Exit Visit)* visit date Subjects discontinuing study treatment/withdrawing early from the study: Date & time > Earliest of : (1) Last dose of mepolizumab + 28 days or (2) Early Withdrawal/Treatment Discontinuation visit date

* Data may be considered off treatment if beyond acceptable protocol defined limits.

10.4.2. Treatment Phases (Visit Based Efficacy Data)

Efficacy data collected at scheduled visits (including: Questionnaires, PFT, Blood Eosinophils and Biomarkers) will be classified according to time of occurrence/assessment relative to the first and last date of mepolizumab and the attendance dates of specific visits.

Treatment Phase	Definition
Pre-Treatment	Visit date/time ≤ First dose of mepolizumab
On-Treatment	Subjects completing treatment and completing the study: Visit date/time < First dose of mepolizumab ≤ Visit 10 (Exit Visit)* visit date/time Subjects discontinuing study treatment/withdrawing early from the study: Visit date/time < First dose of mepolizumab ≤ Earliest of (1) Last dose of mepolizumab + 28 days or (2) Early Withdrawal/Treatment Discontinuation visit date date/time
Off-Treatment	Subjects completing treatment and completing the study: Date & time > Visit 10 (Exit Visit)* visit date/time Subjects discontinuing study treatment/withdrawing early from the study: Date & time > Earliest of: (1) Last dose of mepolizumab + 28 days or (2) Early Withdrawal/Treatment Discontinuation visit date/time

* Data may be considered off treatment if beyond acceptable protocol defined limits.

10.4.3. 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.

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

10.4.3.1. Adverse Event Data Derivations

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

10.4.4. 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.

Treatment/Study Phase	Definition
Taken Before the Run-in	If Con-med Start Date < Date of Visit 1
Taken During the Run-in	• If Con-med Start Date < Date of Visit 1 and Con-med Stop Date ≤ Date of Visit 1, or • If Date of Visit 1 ≤ Con-med Start Date < First dose of mepolizumab
Taken During Treatment	• If Con-med Start Date < First dose of mepolizumab and Con-med Stop Date ≥ First dose of mepolizumab or • If First dose of mepolizumab≤ Con-med Start Date ≤ Last dose of mepolizumab+ 28 days • If the con-med start or stop date is missing or partial then the con-med will be considered on-treatment unless there is evidence to the contrary (e.g. month/year of con-med stop date is present and is before the month/year of the first dose of mepolizumab).
Started During Treatment	Subset of con-meds Taken During Treatment for which: First dose of mepolizumab ≤ Con-med Start Date ≤ Last dose of mepolizumab + 28 days
Taken Post Treatment	• Last dose of mepolizumab + 28 days < Con-med Stop Date

A medication will be summarised in every treatment/study phase in which it was taken,

so for example a medication that was started in the run-in and stopped during treatment will appear in both the during the run-in and during treatment tables.

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Study Treatment & Subgroup 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.

10.5.2. Baseline Definition & Derivations

10.5.2.1. Baseline Definition

- Baseline will be defined for all subjects who are within the ITT population.
- For all endpoints the baseline values for each assessment will be the latest available assessment prior to first dose of mepolizumab.
- Measurements on the same date as the first administration of mepolizumab will be considered within the baseline derivation if measurement time is not captured. Where the measurement time is captured this should be compared against the time of first receiving mepolizumab.

10.5.2.2. Derivations and Handling of Missing Baseline Data

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

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 10.5.2.1 Baseline Definitions 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.

10.5.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Area	: /arenv/arprod/sb240563/mid204471/final01
Quality Control (QC) Spread sheet	: /arenv/arprod/sb240563/mid204471/final01/documents

Reporting Process
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.

Reporting Standards	
General	
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: ○ 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	
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • 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 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. See Section 10.3 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

Reporting Standards	
	non-missing values), frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

10.6. Appendix 6: Derived and Transformed Data

10.6.1. General

Multiple Measurements at One Time Point
• There are no scheduled multiple measurements, however, if multiple measurements are recorded at a given time point the following process will be followed, unless a process for selection of the measurement for the visit is specified: • Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • 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: • Ref Date = Missing → Study Day = Missing • Ref Date < Date of first dose of mepolizumab → Study Day = Ref Date – Date of first dose of mepolizumab • Ref Data ≥ Date of first dose of mepolizumab → Study Day = Ref Date – (Date of first dose of mepolizumab) + 1

10.6.2. Study Population

Demographics
Age
• Only year of birth was collected for subjects; actual birth data was not collected. • GSK standard IDSL algorithms will be used for calculating age where 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 screening visit (Visit 1). [(30th June of the year of birth reported on eCRF – date of Screening)/365.25]
Body Mass Index (BMI)
• Calculated as **Weight (kg) / Height (m)^2**
Percent Predicted FEV1
• FEV1 % of predicted normal will be derived using the Global Lung Function Initiative 2012 look-up tables which are based on the Quanjer equations [Quanjer, 2012] according to the Race/Ethnicity designations specified below:

Collected Race[1]	Quanjer Designation
African American/African Heritage	African-American calculation will be applied
American Indian or Alaskan Native	Other calculation will be applied

Demographics

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.

FEV_1/FVC Ratio

- Pre- and post-bronchodilator FEV_1/FVC ratio will be calculated as the ratio of the FEV_1 and FVC values.

Length of Omalizumab (Xolair) Use

- Number of days exposed to Omalizumab (Xolair) will be calculated based on the formula:
  For subjects receiving Omalizumab (Xolair) monthly:
  Duration of Exposure in Days = Last Omalizumab dose – (First Omalizumab dose) + 29
  For subjects receiving Omalizumab (Xolair) twice monthly:
  Duration of Exposure in Days = Last Omalizumab dose – (First Omalizumab dose) + 15

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

Demographics	
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

10.6.3. 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.
St George's Respiratory Questionnaire (SGRQ)
• The SGRQ comprises 50 questions with a recall period of 4 weeks. • Scores are expressed as the percentage of overall impairment with 100 equal to the worst possible health and 0 the best. • Scoring of each domain of the SGRQ (Symptoms, Activity, Impacts) and the Total score are described in the St George's Respiratory Questionnaire Manual (Version 2.3).

Patient Reported Outcomes/Questionnaires

Treatment Satisfaction with Medication Questionnaire (TSQM-9)

- TSQM Scale scores range from 0 to 100, with higher scores indicating higher satisfaction. No computed score should be lower or higher than these limits. [Atkinson, 2005]
- Effectiveness scale: ([(Item 1 + Item 2 + Item 3) − 3] divided by 18) × 100
  If one item is missing: ([(Sum of Item 1 + Item 2 + Item 3)) − 2] divided by (12) × 100
- Convenience scale: ([Sum of Item 4 to Item 6) − 3] divided by 18) × 100
  If one item is missing: ([(Sum of Item 4 to Item 6)) − 2] divided by (12) × 100
- Overall Satisfaction scale: First recode Item 9 = (Item 9 - 1) x 5/6
- Then: ([Sum of Item 7 to Item 9) - 3] divided by (12) × 100
  If any one Item is missing: ([Sum of Item 7 to Item 9) - 2] divided by (8) x 100

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 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:
  - Start date (ASTDT) is the start date of the first exacerbation in the series
  - End date (AENDT) is the end date of the last exacerbation in the series
  - Outcome (CEOUT) is the worst outcome in the series (worst to best is Fatal, Not Resolved, Resolved)
  - Cause (EBCAUSE) is the cause associated with the first exacerbation in the series
  - Withdrawal due to exacerbation (EBWD), OCS taken for exacerbation (OCSEXB), corticosteroids taken for exacerbation (CTSEXB), hospitalization due to exacerbation (HSPEXB), emergency visit due to exacerbation (EREXB), and intubation for exacerbation (INTUBEXB) are set to 'Y' if any value for the respective variable in the series equals 'Y'
  - Number of telephone calls (TPCNUM), home day visits (HMDYVSN), home night visits (HMNTVSN), home day+night visits (HMDYNTV), office visits (OFCVSN), urgent care/outpatient visits (UCOUTVSN), emergency room visits (ERVSN), days in intensive care (ICSDYNUM), days in general ward (GWDYNUM) and days hospitalized (HSPDYNUM) are the sum of all of the values in the series for each respective variable

Blood Eosinophils

- Blood eosinophils will be log-transformed prior to analysis. Summary statistics will include geometric mean, and a measure of spread (SD or SE) on the natural log scale.

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

10.6.4. 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 – (First mepolizumab dose) + 29
- The extent of exposure will also be summarised as the number of study treatments administered

Adverse Events

Adverse Events of Special Interest

Section 8.2.2 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).

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 :

ECG Parameters

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

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

Laboratory Parameters

- If a laboratory value which is expected to have a numeric value for summary purposes, has a 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).
- The above imputation of half the lower limit of quantification for that measure (LLQ/2) will also be applied to all biomarker parameters.
- Regarding blood eosinophil laboratory data please reference Section 10.6.3.

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

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	• A subject will be considered to have completed study treatment if he/she receives study treatment at Visit 9 (Week 28) and completes the Visit 10/Exit Visit (Week 32). • A subject will be considered to have completed the study if they continue to participate in the study until the Exit Visit assessments have been completed (regardless of whether the subject completed the study treatment schedule). • Subjects who discontinue study treatment or withdraw early will not be replaced in the study. • The number of subjects who discontinue study treatment or withdraw early will be summarised and listed. • All available data from subjects who were withdrawn from the study will be listed and all available data up to and including the date of early withdrawal will be included in summary tables and figures, unless otherwise specified.
Pre-Screen Failures, Screen Failures and Run-in Failures	For the purposes of this study pre-screen failures, screen failures and run-in failures will be defined as follows: • Subjects will be assigned a study number at the time of signing the informed consent (Pre-screen Visit). Subjects who do not progress to the Screening Visit will be deemed a pre-screen failure. • Those subjects that complete at least one additional Visit 1 (Screening) procedure but do not enter the run-in period will be designated as screen failures. • Those subjects that enter the run-in but do not subsequently receive study treatment will be designated as run-in failures.

10.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument : ○ These data will be indicated by the use of a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the listing. ○ Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as missing. ○ 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 10.6 for the handling of this data. • The ACQ-5 score will be considered as missing if <4 items of the questionnaire

Element	Reporting Detail
	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.

10.7.2.1. Handling of Missing or 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), as per Appendix 4: Treatment Phases. ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (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.

10.8. Appendix 8: Values of Potential Clinical Importance

10.8.1. Laboratory Values

Chemistry Values of Potential Clinical Concern

ANALYTE	Age	Sex	SI Units	F3 low	F3 high
SODIUM	0+	Both	MMOL/L	120	160
POTASSIUM	3+	Both	MMOL/L	2.8	6.5
CALCIUM	3+	Both	MMOL/L	1.50	3.24
PHOSPHORUS, INORG	3+	Both	MMOL/L	0.32	
GLUCOSE	1+	Both	MMOL/L	2.2	27.8
ALT (SGPT)	3-12	Both	U/L		>143 (and Total Bilirubin > 43)
ALT (SGPT)	13+	Both	U/L		>239 (and Total Bilirubin > 43)

Haematology Values of Potential Clinical Concern

ANALYTE	Age	Sex	SI Units	F3 low	F3 high
HAEMOGLOBIN	12+	Both	G/L	71	199
HAEMATOCRIT	12+	Both	1	0.201	0.599
PLATELET COUNT	1+	Both	GI/L	31	1499
WHITE CELL COUNT	12+	Both	GI/L	1.1	

10.9. Appendix 9: Multicenter Studies

10.9.1. Methods for Handling Centres

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

Region	Countries
European Union	Belgium, France, Germany, Netherlands, Spain, Sweden
Rest of World	Argentina, Canada, United States

10.10. Appendix 10: Examination of Covariates and Subgroups

10.10.1. Handling of Covariates

- The following is a list of covariates that will be used in all model-based statistical analyses.

Category	Subgroups
Region	Europe, Rest of World (See Section 10.9 for further details)
Exacerbations in the year prior to study (to be included as an ordinal variable)	2,3,4+
Use of baseline maintenance oral corticosteroids	OCS use, no OCS use

- Additional covariates of clinical interest may also be considered.
- If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined prior to database freeze.
- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup.

10.10.2. Handling of Subgroups

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

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

The following subgroups are of interest for the primary efficacy endpoint:

- Exacerbations in previous year: <=2, 3, 4+ exacerbations
- Baseline blood eosinophils: <150, ≥150-<300, ≥300-<500, ≥500 cells/µl

10.11. Appendix 11: Model Checking and Diagnostics for Statistical Analyses

10.11.1. Statistical Analysis Assumptions

Endpoint(s)	• Mean change from baseline in ACQ-5 score at Week 32 • Mean change from baseline in SGRQ at Week 32 • Ratio to baseline in blood eosinophil count at Week 32 • Mean change Pre- and Post- bronchodilator FEV1 at Week 32
Analysis	• Mixed Model Repeated Measures (MMRM)
• In the event that this model fails to converge, the list of covariates may be adjusted and/or reduced. • If there are any important departures from the distributional assumptions, transformations of covariates may be considered or alternative models may be explored as supporting analysis.	

Endpoint(s)	• Frequency of clinically significant asthma exacerbations over 32 week treatment • Frequency of exacerbations requiring ED visit/hospitalization during the 32 week treatment period • Frequency of exacerbations requiring hospitalization during the 32 week treatment period
Analysis	• Negative binomial regression analysis
• In the event that this model fails to converge, the list of covariates may be adjusted and/or reduced. • Distributional assumptions underlying the model used for analysis will be examined by: ○ assessing if a sufficient number of events occurred within covariate categories. • If there are any important departures from the distributional assumptions, transformations of covariates may be considered or alternative models may be explored as supporting analysis.	

10.12. Appendix 12: Abbreviations & Trade Marks

10.12.1. Abbreviations

Abbreviation	Description
ACQ	Asthma Control Questionnaire
ADA	Anti-drug Antibody
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIC	Akaike's Information Criteria
ALT	Alanine Transaminase
ASE	All Subjects Enrolled
ATC	Anatomical Therapeutic Chemical
BLQ	Below Limit of Quantification
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CIL	Clinical Investigation Leader
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Corticosteroid
CSR	Clinical Study Report
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
ED	Emergency Department
EW	Early Withdrawal
FEV_1	Forced expiratory volume in 1 second
FVC	Forced Vital Capacity
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
HbsAg	Hepatitis B Surface Antigen
ICH	International Conference on Harmonisation
ICS	Inhaled Corticosteroids
IDSL	Integrated Data Standards Library
IG	Implementation Guide
IM	Intramuscular
IP	Investigational Product
IPDISC	Investigational Product Discontinuation
IRT	Interactive Response Technology
ITT	Intent-To-Treat
IV	Intravenous

Abbreviation	Description
LFT	Liver Function Test
LLQ	Lower Limit of Quantification
MMRM	Mixed Model Repeated Measures
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
PP	Per Protocol
PT	Preferred Term
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAMOS NG	Randomization & Medication Ordering System Next Generation
RAP	Reporting and Analysis Plan
RTF	Rich Text File
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SC	Subcutaneous
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SGRQ	St. George's Respiratory Questionnaire
SMQ	Standard MedDRA Query
SOC	System Organ Class
SRM	Study Reference Manual
TFL	Tables, Figures & Listings
TST	Therapeutic Standards Team
TSQM	Treatment Satisfaction with Medication Questionnaire
VS	Versus/against

10.12.2. Trademarks

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10.13. Appendix 13: List of Data Displays

10.13.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.25	1.1
Efficacy	2.1 to 2.46	2.1 to 2.11
Safety	3.1 to 3.56	3.1 to 3.2
Section	**Listings**	
ICH and Other Listings	1 to 44	

10.13.1.1. Study Population Tables

Study Population: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable[1] [Priority]**
Population Analysed					
1.1.	ASE	SP1	Summary of Study Populations	IDSL Include All Subjects Enrolled, Intention to Treat, Per Protocol	SAC
Subject Disposition					
1.2.	ASE	ES6	Summary of Reasons for Screening and/or Run-In Failures	Journal Requirements	SAC
1.3.	ASE	IE2	Summary of Failed Inclusion/Exclusion/Continuation Criteria for Screening or Run-in Failures		SAC
1.4.	ASE	IE2	Summary of Failed Inclusion/Exclusion/Continuation Criteria for Subjects within the Intent to Treat Population		SAC
1.5.	ITT	NS1/SHELL	Summary of Number of Subjects by Region, Country and Centre	Add in a column for region, add a total for regions and a total for country EudraCT	SAC
1.6.	ITT	ES1	Summary of Subject Disposition	ICH E3, GSK CTR, FDAAA, EudraCT	SAC
1.7.	ITT	SD1/SHELL	Summary of Reasons for Withdrawal From Investigational Product		SAC
Demographic and Baseline Characteristics					
1.8.	ITT	DM1	Summary of Demographic Characteristics	ICH E3, GSK CTR, FDAAA, EudraCT	SAC
1.9.	ASE	DM11	Summary of Age Ranges	EMA, keep row ≥12-17, ≥18-<64, ≥65-<84, ≥85	SAC
1.10.	ITT	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, GSK CTR, FDAAA, EudraCT	SAC
1.11.	ITT	DM6	Summary of Race and Racial Combination Details	ICH E3, FDA	SAC

Study Population: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable[1] [Priority]**
1.12.	ITT	SHELL	Summary of Asthma History and Baseline Disease Characteristics	Include GERD, CCI, mMRC	SAC
1.13.	ITT	SHELL	Summary of Previous Exacerbation History		SAC
1.14.	ITT	SU1/SHELL	Summary of History of Tobacco Use		SAC
1.15.	ITT	SHELL	Summary of Screening and Baseline Lung Function Tests	Include FEV1, FVC, FEV/FVC, %Predicted, Reversibility	SAC
Medical Conditions					
1.16.	ITT	MH4	Summary of Past Medical Conditions	ICH E3	SAC
1.17.	ITT	MH4	Summary of Current Medical Conditions	ICH E3	SAC
1.18.	ITT	FH1	Summary of Cardiovascular Assessments – Family History	Note: Family history in women <65 years or men < 55 years (first degree relatives only). Half siblings considered first degree relatives	SAC
1.19.	ITT	FH1	Summary of Cardiovascular Assessments – Screening Questions		SAC
Prior and Concomitant Medications					
1.20.	ITT	SHELL	Summary of Use of Omalizumab Therapy Prior to Treatment		SAC

Study Population: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable[1] [Priority]**
1.21.	ITT	CM1	Summary of Asthma Concomitant Medications Started Prior to Treatment by Respiratory Medication Class Group	ICH E3 Footnote: Includes all Asthma medications started before the first dose of investigational product. Multi-component medications displayed under the respiratory medication class of each component Programming note: Display RMC and ingredient as previous Asthma studies	SAC
1.22.	ITT	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
1.23.	ITT	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
1.24.	ITT	CM1	Summary of Non-Asthma Medications Taken During Treatment	Footnote: Medications may be displayed under more than one ATC classification	SAC
Protocol Deviation					
1.25.	ITT	DV1B	Summary of Protocol Deviations	ICH E3	SAC

10.13.1.2. Study Population Figures

Study Population: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1	ITT	SHELL	Time to Subject Withdrawal From Investigation Product	See Study Population Table 1.1 (MEA117113 'final' reporting effort), but exclude 'Placebo' and Mepo 300mg SC	SAC

10.13.1.3. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Asthma Control Questionnaire (ACQ-5) Endpoints					
2.1.	ITT	SHELL	Summary of Asthma Control Questionnaire (ACQ-5) Score	See Efficacy Table 2.34 (MID200862 'final' reporting effort), but exclude 'Placebo' column Include screening visit in addition to baseline and post-baseline visits	SAC
2.2.	ITT	SHELL	Analysis of Change from Baseline in Asthma Control Questionnaire (ACQ-5) Score Mixed Model Repeated Measures		SAC
2.3.	PP	SHELL	Sensitivity Analysis of Asthma Control Questionnaire (ACQ-5) Score Responders: Subjects With At Least 0.5-point Improvement from Baseline (Per Protocol Population only)		SAC
2.4.	ITT	SHELL	Analysis of Change from Baseline in Asthma Control Questionnaire (ACQ-5) by number of exacerbations in previous year		SAC
2.5.	ITT	SHELL	Analysis of Change from Baseline in Asthma Control Questionnaire (ACQ-5) by baseline blood eosinophils		SAC
2.6.	ITT	SHELL	Summary of Asthma Control Questionnaire (ACQ-5) Score Responders: Subjects With At Least 0.5-point Improvement from Baseline	See Efficacy Table 2.41 (MID200862 'final' reporting effort), but exclude 'Placebo' column, and rename 'Odd Ratio to Historical Placebo'	SAC
St. George's Respiratory Questionnaire (SGRQ) Endpoints					
2.7.	ITT	SHELL	Summary of St George's Respiratory Questionnaire (SGRQ) Total Score	See Efficacy Table 2.01 (MID200862 'final' reporting effort), but exclude 'Placebo' column	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.8.	ITT	SHELL	Analysis of Change from Baseline in St George's Respiratory Questionnaire (SGRQ) Total Score Mixed Model Repeated Measures		SAC
2.9.	ITT	SHELL	Summary of St. George's Respiratory Questionnaire (SGRQ) Symptom Domain Score		SAC
2.10.	ITT	SHELL	Analysis of Change From Baseline in St. George's Respiratory Questionnaire (SGRQ) Symptom Domain Score		SAC
2.11.	ITT	SHELL	Summary of St. George's Respiratory Questionnaire (SGRQ) Activity Domain Score		SAC
2.12.	ITT	SHELL	Analysis of Change From Baseline in St. George%'s Respiratory Questionnaire (SGRQ) Activity Domain Score		SAC
2.13.	ITT	SHELL	Summary of St. George's Respiratory Questionnaire (SGRQ) Impacts Domain Score		SAC
2.14.	ITT	SHELL	Analysis of Change From Baseline in St. George's Respiratory Questionnaire (SGRQ) Impacts Domain Score		SAC
2.15.	ITT	SHELL	Summary of St George's Respiratory Questionnaire (SGRQ) Responders: Subjects With At Least 4-point Improvement in Total Score from Baseline	See Efficacy Table 2.24 (MID200862 'final' reporting effort), but exclude 'Placebo' column, and rename 'Odd Ratio to Historical Placebo'	SAC
Exacerbations					
2.16.	ITT	SHELL	Overview of Exacerbations	See Efficacy Table 2.61 (MID200862 'final' reporting effort), but exclude 'Placebo' column	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.17.	ITT	SHELL	Summary of Frequency of Clinically Significant Exacerbations	See Efficacy Table 2.62 (MID200862 'final' reporting effort), but exclude 'Placebo' column	SAC
2.18.	ITT	SHELL	Annualised Rate of Clinically Significant Exacerbations		SAC
2.19.	ITT	SHELL	Analysis of Time to First Clinically Significant Exacerbation	See Efficacy Table 2.68 (MID200862 'final' reporting effort), but exclude 'Placebo' column and Hazard Ration Analysis	SAC
2.20.	ITT	SHELL	Sensitivity Analysis of Annualised Rate of Clinically Significant Exacerbations (on–treatment data only)		SAC
2.21.	ITT	SHELL	Sensitivity Analysis of Annualised Rate of Clinically Significant Exacerbations (Patients with at least 12 months of prior omalizumab use)		SAC
2.22.	ITT	SHELL	Summary of Frequency of Exacerbations Requiring Hospitalisation or Emergency Department visits	See Efficacy Table 2.64 (MID200862 'final' reporting effort), but exclude 'Placebo' column	SAC
2.23.	ITT	SHELL	Annualised Rate of Exacerbations Requiring Hospitalisation or Emergency Department visits		SAC
2.24.	ITT	SHELL	Sensitivity Analysis of Annualised Rate of Exacerbations Requiring Hospitalisation or Emergency Department visits (on–treatment data only)		SAC
2.25.	ITT	SHELL	Summary of Frequency of Exacerbations Requiring Hospitalisation	See Efficacy Table 2.66 (MID200862 'final' reporting effort), but exclude 'Placebo' column	SAC
2.26.	ITT	SHELL	Annualised Rate of Exacerbations Requiring Hospitalisation		SAC
Blood Eosinophils					

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.27.	ITT	SHELL	Summary of Blood Eosinophils (10^9/L)	See Efficacy Table 2.73 (MID200862 'final' reporting effort), but exclude 'Placebo' column	SAC
2.28.	ITT	SHELL	Analysis of Change from Baseline in Blood Eosinophils (10^9/L)		SAC
2.29.	ITT	SHELL	Analysis of Change from Baseline in Blood Eosinophils (10^9/L) (on–treatment data only)		SAC
Pre – Bronchodilator and Post – Bronchodilator FEV1					
2.30.	ITT	SHELL	Summary of Clinic Pre-Bronchodilator FEV1 (mL)	See Efficacy Table 2.27 (MID200862 'final' reporting effort), but exclude 'Placebo' column	SAC
2.31.	ITT	SHELL	Analysis of Change From Baseline in Clinic Pre-Bronchodilator FEV1 (mL)	See Efficacy Table 2.28 (MID200862 'final' reporting effort), but exclude 'Placebo' column and Difference Analysis	SAC
2.32.	ITT	SHELL	Summary of Clinic Post-Bronchodilator FEV1 (mL)	See Efficacy Table 2.49 (MID200862 'final' reporting effort), but exclude 'Placebo' column	SAC
2.33.	ITT	SHELL	Analysis of Change From Baseline in Clinic Post-Bronchodilator FEV1 (mL)	See Efficacy Table 2.68 (MID200862 'final' reporting effort), but exclude 'Placebo' column and Difference Analysis	SAC
Response to Therapy					
2.34.	ITT	SHELL	Summary of Subject Rated Overall Evaluation of Response to Therapy (on–treatment data only)	See Efficacy Table 2.47 (MID200862 'final' reporting effort), but exclude 'Placebo' column and Odds Ratio Analysis	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.35.	ITT	SHELL	Summary of Clinician Rated Overall Evaluation of Response to Therapy (on–treatment data only)		SAC
Treatment Satisfaction Questionnaire for Medication (TSQM–9)					
2.36.	ITT	SHELL	Summary of Treatment Satisfaction Questionnaire for Medication (TSQM – 9) (on–treatment data only)	Summarise the Effectiveness, Convenience and Overall Satisfaction scales separately	SAC
Biomarkers					
2.37.	ITT	SHELL	Summary of CCL13 (on–treatment data only)		SAC
2.38.	ITT	SHELL	Summary of CCL17 (on–treatment data only)		SAC
2.39.	ITT	SHELL	Summary of ECP (on–treatment data only)		SAC
2.40.	ITT	SHELL	Summary of EDN (on–treatment data only)		SAC
2.41.	ITT	SHELL	Summary of Eotaxin1 (on–treatment data only)		SAC
2.42.	ITT	SHELL	Summary of Total IL-5 (on–treatment data only)		SAC
2.43.	ITT	SHELL	Summary of IL-13 (on–treatment data only)		SAC
2.44.	ITT	SHELL	Summary of MDC (on–treatment data only)		SAC
2.45.	ITT	SHELL	Summary of Periostin (on–treatment data only)		SAC
2.46.	ITT	SHELL	Summary of TSLP (on–treatment data only)		SAC

10.13.1.4. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Asthma Control Questionnaire (ACQ-5) Endpoints					
2.1.	ITT	SHELL	Figure of Analysis of Asthma Control Questionnaire (ACQ-5) Score at Each Visit: Mean Change from Baseline	See format of Efficacy Figure 2.11 (MID200862 'final' reporting effort), but exclude 'Placebo'	SAC
2.2.	ITT	SHELL	Cumulative Distribution Function for Change from Baseline in Asthma Control Questionnaire (ACQ-5) Score at Week 32	See format of Efficacy Figure 2.14 (MID200862 'final' reporting effort), but exclude 'Placebo'	SAC
2.3.	ITT	SHELL	Figure of Asthma Control Questionnaire (ACQ-5) Responders: Subjects With At Least 0.5-point Improvement in the Score from Baseline		SAC
St. George's Respiratory Questionnaire (SGRQ) Endpoints					
2.4.	ITT	SHELL	Figure of Analysis of St George's Respiratory Questionnaire (SGRQ) Total Score at Each Visit: Mean Change from Baseline	See format of Efficacy Figure 2.01 (MID200862 'final' reporting effort), but exclude 'Placebo'	SAC
2.5.	ITT	SHELL	Figure of St George's Respiratory Questionnaire (SGRQ) Total Score: Change from Baseline At Week 52: Cumulative Distribution Function	See format of Efficacy Figure 2.07 (MID200862 'final' reporting effort), but exclude 'Placebo'	SAC
2.6.	ITT	SHELL	Figure of Analysis of SGRQ by Domain (Mean Change from Baseline at Each Visit)		SAC
2.7.	ITT	SHELL	Figure of St George's Respiratory Questionnaire (SGRQ) Responders: Subjects With At Least 4-point Improvement in Total Score from Baseline		SAC
Exacerbations					

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.8.	ITT	SHELL	Kaplan-Meier Cumulative Incidence Curve for Time to First Clinically Significant Exacerbations	See format of Efficacy Figure 2.07 (MID200862 'final' reporting effort), but exclude 'Placebo'	SAC
Blood Eosinophils					
2.9.	ITT	SHELL	Figure of Analysis of Blood Eosinophils Ratio Compared to Baseline	See format of Efficacy Figure 6.18 (MEA 115588 'final' reporting effort), but exclude 'Placebo' and mepo 75 mg IV	SAC
Pre – bronchodilator and post – bronchodilator FEV1					
2.10.	ITT	SHELL	Figure of Analysis of Pre-Bronchodilator FEV1 (mL) Mean Change From Baseline at Each Visit	See format of Efficacy Figure 2.09 (MID200862 'final' reporting effort), but exclude 'Placebo'	SAC
2.11.	ITT	SHELL	Figure of Analysis of Post-Bronchodilator FEV1 (mL) Mean Change From Baseline at Each Visit	See format of Efficacy Figure 2.09 (MID200862 'final' reporting effort), but exclude 'Placebo'	SAC

10.13.1.5. Safety Tables

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Exposure					
3.1	ITT	SHELL	Summary of Number of Treatments Administered and Time On-Treatment	See format of Study Population Table 1.28 (200862 'final' reporting effort).	SAC
Adverse Events					
3.2	ITT	SHELL	Overview of All Adverse Events	Add a Total column across all severities	SAC
3.3	ITT	AE1	Summary of All On-Treatment Adverse Events by System Organ Class		SAC
3.4	ITT	AE5	Summary of All On-Treatment Adverse Events by System Organ Class and Maximum Intensity	Add a Total column across all severities	SAC
3.5	ITT	AE1	Summary of All Post-Treatment Adverse Events by System Organ Class		SAC
3.6	ITT	AE5	Summary of All Post-Treatment Adverse Events by System Organ Class and Maximum Intensity	Add a Total column across all severities	SAC
3.7	ITT	AE3	Summary of Common On-Treatment Adverse Events (>=3% in Any Treatment Group) by Overall Frequency	GSK CTR; ≥3% (prior to rounding to nearest percent)	SAC
3.8	ITT	AE1	Summary of All On-Treatment Drug-Related Adverse Events by System Organ Class		SAC
3.9	ITT	AE5	Summary of All On-Treatment Drug-Related Adverse Events by System Organ Class and Maximum Intensity	Add a Total column across all severities	SAC
3.10	ITT	AE1	Summary of Adverse Events Reported on Day of Dosing by System Organ Class		SAC
3.11	ITT	SHELL	Summary of All On-Treatment Adverse Events by Age Group	Add a Total column across all severities	SAC

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.12	ITT	SHELL	Summary of On-Treatment Adverse Events by Highest Anti Drug Antibody Result At Any Time Post Baseline		SAC
3.13	ITT	SHELL	Summary of Post-Treatment Adverse Events by Highest Anti Drug Antibody Result At Any Time Post Baseline		SAC
3.14	ITT	AE15	Summary of Number of Subjects and Occurrences of Common non-Serious Adverse Events by System Organ Class and Preferred Term	GSK CTR; ≥3% (prior to rounding to nearest percent)	SAC
Serious and Other Significant AEs					
3.15	ITT	AE1	Summary of Fatal Serious Adverse Events		SAC
3.16	ITT	AE1	Summary of Non-Fatal Serious On-Treatment Adverse Events by System Organ Class		SAC
3.17	ITT	AE1	Summary of Non-Fatal Serious Post-Treatment Adverse Events by System Organ Class		SAC
3.18	ITT	AE1	Summary of Serious Adverse Events by System Organ Class (Pre-Treatment)		SAC
3.19	ITT	AE1	Summary of Serious Adverse Events by System Organ Class (On-Treatment)		SAC
3.20	ITT	AE1	Summary of Serious Adverse Events by System Organ Class (Post-Treatment)		SAC
3.21	ITT	AE1	Summary of Drug-Related Fatal Serious Adverse Events by System Organ Class		SAC
3.22	ITT	AE1	Summary of Drug-Related Serious Adverse Events by System Organ Class and Maximum Intensity	Add a Total column across all severities	SAC

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.23	ITT	AE3	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by Overall Frequency		SAC
3.24	ITT	AE16	Summary of Number of Subjects and Occurrences of Serious Adverse Events by System Organ Class and Preferred Term		SAC
Adverse Events of Special Interest					
3.25	ITT	AE1	Summary of AEs meeting Anaphylaxis Criteria (On-Treatment)	Present by Anaphylactic Criterion 1, 2 and 3 rather than SOC as shown in AE1	SAC
3.26	ITT	SHELL	Summary Profile of AEs meeting Anaphylaxis Criteria (On-Treatment)		SAC
3.27	ITT	AE1	Summary of AEs Defined by the Investigator as being Systemic (non-allergic or allergic/hypersensitivity) Reactions (On-Treatment)		SAC
3.28	ITT	SHELL	Summary Profile of Systemic (non-allergic or allergic/hypersensitivity) Reactions (On-Treatment)		SAC
3.29	ITT	SHELL	Summary Profile of Systemic Allergic Reactions (On-Treatment)		SAC
3.30	ITT	SHELL	Summary Profile of Systemic Non-Allergic Reactions (On-Treatment)		SAC
3.31	ITT	AE1	Summary of AEs Defined by the Investigator as being Local Injection Site Reactions (On-Treatment)		SAC
3.32	ITT	AE1	Summary of AEs Defined by the Investigator as being Local Injection Site Reactions by Relation to IP (On-Treatment)		SAC
3.33	ITT	SHELL	Summary Profile of Local Injection Site Reactions (On-Treatment)		SAC

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.34	ITT	AE3	Summary of Opportunistic Infections (On-Treatment)		SAC
3.35	ITT	SHELL	Summary Profile of Opportunistic Infections (On-Treatment)		SAC
3.36	ITT	AE3	Summary of Malignancies (On-Treatment)		SAC
3.37	ITT	SHELL	Summary Profile of Malignancies (On-Treatment)		SAC
3.38	ITT	AE1	Summary of Serious Cardiac, Vascular and Thromboembolic Adverse Events (On-Treatment)		SAC
3.39	ITT	SHELL	Summary Profile of Serious Cardiac, Vascular and Thromboembolic Adverse Events (On-Treatment)		SAC
3.40	ITT	AE1	Summary of Serious Ischemic AEs (On-Treatment)		SAC
3.41	ITT	SHELL	Summary Profile of Serious Ischemic AEs (On-Treatment)		SAC
3.42	ITT	SHELL	Summary of Serious AEs and AEs of Special Interest	See format of Safety Table 7.32 (MEA115588 'final' reporting effort)	SAC
Cardiovascular Events					
3.43	ITT	SHELL	Summary of All Cardiovascular Events Reported by the Investigator		SAC
Laboratory: Chemistry					
3.44	ITT	LB1	Summary of Changes from Baseline in Chemistry Data	Include Baseline values.	SAC
3.45	ITT	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
Laboratory: Haematology					
3.46	ITT	LB1	Summary of Changes From Baseline in Haematology Data	Include Baseline values	SAC
3.47	ITT	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

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Hepatobiliary (Liver)					
3.48	ITT	LIVER10	Summary of Subjects Meeting Emergent Hepatobiliary Laboratory Abnormality Criteria		SAC
ECGs					
3.49	ITT	EG1	Summary of ECG Findings		SAC
3.50	ITT	EG2	Summary of Change from Baseline in ECG Values by Visit	Include Baseline values	SAC
3.51	ITT	SHELL	Summary of Actual and Change From Baseline QTc(F) Values by Category (msec)		SAC
3.52	ITT	SHELL	Summary of Actual and Change From Baseline QTc(B) Values by Category (msec)		
Vital Signs					
3.53	ITT	VS1	Summary of Change From Baseline in Vital Signs by Visit	Include Baseline values	SAC
Immunogenicity					
3.54	ITT	SHELL	Summary of ADA Assay Results	See format of Other Assessments Table 8.01 (MEA115588 'final' reporting effort)	SAC
3.55	ITT	SHELL	Summary of Treatment Emergent ADA Assay Results		SAC
3.56	ITT	SHELL	Summary of NAb Assay Results	See format of Other Assessments Table 8.02 (MEA115588 'final' reporting effort)	SAC

10.13.1.6. Safety Figures

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Laboratory					
3.1	ITT	LIVER9	Scatter Plot of Maximum Post-Baseline vs. Baseline for ALT		SAC
3.2	ITT	LIVER9	Scatter Plot of Maximum Post-Baseline ALT vs. Maximum Post-Baseline Total Bilirubin		SAC

10.13.1.7. ICH Listings

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.	ASE	ES7	Listing of Reasons for Screening Failure or Run-In Failure		SAC
2.	ASE	IE3	Listing of Failed Inclusion/Exclusion/Continuation criteria		SAC
3.	ITT	ES2	Listing of Reasons for Premature Study Withdrawal		SAC
4.	ITT	ES2	Listing of Reasons for Premature Discontinuation of Study Treatment		SAC
Demographics					
5.	ITT	DM2	Listing of Demographic Characteristics		SAC
6.	ITT	DM9	Listing of Race		SAC
Medication Use					
7.	ITT	CM6	Relationship Between ATC Level 1, Ingredient and Verbatim Text		SAC
Protocol Deviations					
8.	ITT	DV2	Listing of Important Protocol Deviations	Listing also includes Per-Protocol analysis population exclusions	SAC
Efficacy					

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
9.	ITT	SHELL	Listing of ACQ-5 Data		SAC
10.	ITT	SHELL	Listing of Exacerbations	See format of Efficacy Listing 6.01 (MEA115588 'final' reporting effort)	SAC
Exposure					
11.	ITT	EX3	Listing of Exposure Data		SAC
Adverse Events					
12.	ASE	AE8	Listing of All Adverse Events		SAC
13.	ASE	AE7	Listings of Subject Numbers for Individual Adverse Events		SAC
14.	ASE	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		SAC
Serious and Other Significant AEs					
15.	ASE	AE8	Listing of all Fatal Adverse Events		SAC
16.	ASE	AE8	Listing of Non-Fatal Serious Adverse Events		SAC
17.	ASE	AE14	Listing of Reasons for Considering as a Serious Adverse Event		SAC
18.	ITT	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment		SAC

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events of Special Interest					
19.	ITT	SHELL	Listing of AEs meeting Anaphylaxis Criteria	See format of Safety Listing 7.10 (MEA115588 'final' reporting effort)	SAC
20.	ITT	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
21.	ITT	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
22.	ITT	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
23.	ITT	SHELL	Listing of Opportunistic Infections	See format of Safety Listing 7.10 (MEA115588 'final' reporting effort)	SAC
24.	ITT	SHELL	Listing of Malignancies	See format of Safety Listing 2.03 (mid_mepo_iss 'iss_nda' reporting effort)	SAC
25.	ITT	SHELL	Listing of Serious Cardiac, Vascular and Thromboembolic (CVT) AEs	See format of Safety Listing 7.10 (MEA115588 'final' reporting effort)	SAC
26.	ITT	SHELL	Listing of Serious Ischemic AEs	See format of Safety Listing 7.10 (MEA115588 'final' reporting effort)	SAC
Cardiovascular Events					

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
27.	ITT	SHELL	Listing of Investigator Reported Cardiovascular Events: Arrhythmias	See format of Safety Listing 7.11 (MEA115588 'final' reporting effort)	SAC
28.	ITT	SHELL	Listing of Investigator Reported Cardiovascular Events: Congestive Heart Failure	See format of Safety Listing 7.12 (MEA115588 'final' reporting effort)	SAC
29.	ITT	SHELL	Listing of Investigator Reported Cardiovascular Events: Cerebrovascular Events/Stroke	See format of Safety Listing 7.13 (MEA115588 'final' reporting effort)	SAC
30.	ITT	SHELL	Listing of Investigator Reported Cardiovascular Events: Deep venous Thrombosis/Pulmonary Embolism	See format of Safety Listing 7.14 (MEA115588 'final' reporting effort)	SAC
31.	ITT	SHELL	Listing of Investigator Reported Cardiovascular Events: Myocardial Infarction/Unstable Angina	See format of Safety Listing 7.15 (MEA115588 'final' reporting effort)	SAC
32.	ITT	SHELL	Listing of Investigator Reported Cardiovascular Events: Peripheral Arterial Thrombosis Embolism	See format of Safety Listing 7.16 (MEA115588 'final' reporting effort)	SAC
33.	ITT	SHELL	Listing of Investigator Reported Cardiovascular Events: Pulmonary Hypertension	See format of Safety Listing 7.17 (MEA115588 'final' reporting effort)	SAC
34.	ITT	SHELL	Listing of Investigator Reported Cardiovascular Events: Revascularisation	See format of Safety Listing 7.18 (MEA115588 'final' reporting effort)	SAC
35.	ITT	SHELL	Listing of Investigator Reported Cardiovascular Events: Valvulopathy	See format of Safety Listing 7.19 (MEA115588 'final' reporting effort)	SAC
36.	ITT	SHELL	Listing of Investigator Reported Cardiovascular Events: All Cause Deaths	See format of Safety Listing 7.20 (MEA115588 'final' reporting effort)	SAC

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Hepatobiliary (Liver)					
37.	ITT	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting		SAC
38.	ITT	LB5	Chemistry Results for Subjects Meeting Liver Monitoring/Stopping Event Criteria		SAC
39.	ITT	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events		SAC
40.	ITT	SU2	Listing of Substance Use for Subjects with Liver Stopping Events	See format of Safety Listing 7.22 (MEA112997 'final' reporting effort)	SAC
41.	ITT	LIVER13	Listing of Subjects Meeting Hepatobiliary Laboratory Criteria Post-Baseline		SAC
All Laboratory					
42.	ITT	LB5	Listing of Laboratory Data for Subjects with Abnormalities of Potential Clinical Concern		SAC
ECG					
43.	ITT	EG6	Listing of ECG Findings for Abnormal Interpretations		SAC
Immunogenicity					
44.	ITT	SHELL	Listing of Immunogenicity Results	See format of Other Assessments Listing 8.01 (MEA115588 'final' reporting effort)	SAC

10.14. Appendix 14: Example Mock Shells for Data Displays

The data display shells are contained in separate documents which are available on request.