Division: World Wide Development
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Title:	Reporting and Analysis Plan for MEA115666: A multi-centre, open-label, long term safety study of mepolizumab in asthmatic subjects who participated in the MEA112997 trial.

Compound Number: SB-240563

Effective Date: 06-APR-2017

Reporting and Analysis Plan Amendment Number: 01

Description: This study will provide long term safety and immunogenicity data when mepolizumab is administered subcutaneously (SC) to subjects with severe, refractory asthma with a history of eosinophilic inflammation. Additionally, this study will inform on the safety and immunogenicity profile when mepolizumab therapy is reinstituted in subjects following a cessation in drug therapy.

Safety will be assessed by adverse events, clinical laboratory samples, ECGs, immunogenicity and vital signs.

Additional assessments are included to evaluate the effects of mepolizumab on a range of clinical markers of asthma control.

Subject: Severe refractory asthma, mepolizumab, eosinophils, SB-240563, extension study, safety

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ABBREVIATIONS

ACQ	Asthma Control Questionnaire
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine transaminase
ASE	All Subjects Enrolled
AT	As Treated
ATC	Anatomical Therapeutic Chemical
CEC	Clinical Endpoint Committee
CI	Confidence Interval
CS	Corticosteroid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Emergency Department
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GSK	GlaxoSmithKline
IDMC	Independent Data Monitoring Committee
IgE	Immunoglobulin E
IM	Intramuscular
IV	Intravenous
LFT	Liver function test
LLQ	Lower Limit of Quantification
MDP1	Mepolizumab Drug Product 1
MDP2	Mepolizumab Drug Product 2
MedDRA	Medicinal dictionary for regulatory activities
mg	Milligram
mL	Millilitres
N	Number of subjects in the treatment group
n	Number of subjects with non-missing values
NAb	Neutralising antibody
NHANES	National Health and Nutrition Examination Survey
OCS	Oral corticosteroids
OLE	Open label extension (study)
PI	Principal Investigator
PT	Preferred Term
QTc(B)	QT interval corrected by Bazett's method
QTc(F)	QT interval corrected by Fridericia's method
RAP	Reporting and Analysis Plan
RUCAM	Roussel Uclaf Causality Assessment Method
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SDAC	Statistical Data Analysis Centre
SOC	System Organ Class

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1. INTRODUCTION

The purpose of the data analyses outlined in this Reporting and Analysis Plan (RAP) is to evaluate the safety, immunogenicity and effectiveness of treatment with 100mg mepolizumab administered subcutaneously (SC) every 4 weeks in subjects with severe, uncontrolled refractory asthma.

This RAP is based on Section 8 (Data Analysis and Statistical Considerations) of the MEA115666 study protocol issued 06-Mar-2013 (GlaxoSmithKline Document Number 2012N139436_02) and is intended for use by the Statistics & Programming Department. The data analyses produced will be used in a Clinical Study Report.

1.1. Revision Chronology

RAP Section	Amendment Details
Original Reporting and Analysis Plan Effective date: 20-AUG-2013	
Reporting and Analysis Plan Amendment 1 Effective date: 06-APR-2017	
Amendments • Inserted additional outputs to summarise the Adverse Events of Special Interests as agreed within the Program Safety Analysis Plan (PSAP) • Inserted additional table of protocol deviations • Clarified that the most frequent on-treatment AEs will be defined as AEs with frequency ≥3% and not ≥2% • Inserted additional tables and listings of subjects with emergent hepatobiliary laboratory abnormalities and an additional listing of all clinical chemistry results for subjects who meet the liver event criteria • Removed a listing of urinanalysis results as no such data is collected in this study	

2. STUDY OBJECTIVE(S) AND ENDPOINT(S)

2.1. Study Objective(s)

2.1.1. Primary Objective

The primary objective of this study is to describe the long-term safety profile of mepolizumab.

2.1.2. Secondary Objectives

- To provide long-term treatment with mepolizumab to subjects who participated in MEA112997.
- To evaluate the effects of mepolizumab on a range of clinical markers of asthma control.

2.2. Study Endpoint(s)

2.2.1. Primary Endpoint

- Adverse Events (AEs) including both systemic (i.e. allergic/IgE-mediated and non-allergic) and local site reactions.

2.2.2. Secondary Endpoints

- Frequency of positive anti-mepolizumab binding antibodies and neutralising antibodies
- Annualised rate of exacerbations
- Asthma Control Questionnaire (ACQ) score
- Forced expiratory volume in 1 second (FEV_1) as measured by clinic spirometry
- Number of withdrawals due to lack of efficacy
- Number of withdrawals due to adverse events
- Number of hospitalizations due to adverse events including asthma exacerbations
- Frequency of both systemic (i.e., allergic/IgE-mediated and non-allergic) and local site reactions
- 12-Lead Electrocardiogram (ECG) to derive the following endpoints:
    - Mean change from baseline in the QTc(F) (QT interval corrected by Fridericia's method)
    - Mean change from baseline in QTc(B) (QT interval corrected by Bazett's method)
    - Maximum change from baseline for QTc(F) and QTc(B).
- Vital signs
- Clinical Laboratory Parameters

2.3. Statistical Hypotheses

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

3. STUDY DESIGN

This is a multi-centre, open-label, long term, safety study of 100mg mepolizumab administered subcutaneously in addition to standard of care in subjects with severe, refractory asthma and a history of eosinophilic inflammation. Subjects who participated in the MEA112997 trial will be offered the opportunity to consent for this study. All subjects will have experienced a gap of at least 10 months since receiving their last double-blind study medication in MEA112997.

At Visit 1 subjects will undergo an initial screening to assess their eligibility to participate in this study. This screening will include: informed consent, vital signs, update of medical history, immunogenicity status based on MEA112997 data, smoking status, prior monoclonal antibody use, and exacerbations post completion of MEA112997. Subjects meeting the Visit 1 eligibility criteria will enter the run-in period. The purpose of the run-in period is to allow for receipt and review of lab results and the ECG over-read. Visit 2 will mark the end of the run-in period.

Those subjects meeting all the inclusion criteria and none of the exclusion criteria will receive their first mepolizumab dose at Visit 2. Subjects will continue to receive mepolizumab SC injections approximately every 4 weeks until either:

- The risk/benefit profile for the subject is no longer positive in the opinion of the investigator **or**
- the subject's physician withdraws the subject **or**
- the subject withdraws consent **or**
- the sponsor discontinues development of mepolizumab **or**
- the sponsor discontinues the study in the relevant participating country **or**
- mepolizumab becomes commercially available in the relevant participating country

During the trial the vial strength used when dosing will be changed for most subjects, however this will depend on the timing of regulatory approval. The 100mg dose of mepolizumab will be reconstituted from a vial of 250mg/vial strength up until such time that the 100mg/vial strength is available at the site. Once the 100mg/vial strength is available at the site, all subjects will be dosed with 100mg mepolizumab reconstituted from the 100mg/vial strength at their next treatment visit and for the remainder of the study. This change of vial strength will be when subjects are transitioned onto the new drug product. Hereafter, the 250mg/vial strength will be referred to as mepolizumab drug product 1 (MDP1) and the 100mg/vial strength (to which subjects will transition) will be referred to as mepolizumab drug product 2 (MDP2). In the case that MDP2 is not approved for use by ethics/regulatory at a local site/country subjects will continue to be dosed with MDP1.

Subjects will remain on standard of care asthma therapy, which may be adjusted during the study, at the discretion of their physician. The use of Xolair (omalizumab) or any other monoclonal antibody will not be permitted during the course of the study.

Subjects will be monitored in the clinic approximately every 4 weeks to assess adverse events and asthma status. The Asthma Control Questionnaire-5 (ACQ) will be used to assist the investigator in assessing the subject's asthma status along with spirometry at regular intervals. Exacerbations will also be reviewed at each clinic visit. As some subjects may have previously received placebo while participating in the MEA112997 trial and are naive to mepolizumab, safety lab monitoring will be more frequent at the start of the study. Appropriate safety labs will be drawn prior to starting treatment and then at week 4, 8, 12, 24, 36 and 48. Thereafter, these will be collected every 24 weeks. Labs will also be obtained at 12 weeks after discontinuing mepolizumab. Subjects

discontinuing mepolizumab treatment should be monitored for exacerbation of their asthma.

Serum samples for anti-mepolizumab antibody measurements will be obtained from all subjects at Weeks 0, 4, 24 and 48 of the initial year, week 24 and 48 for every additional year, as well as at the Follow-up Visit. Any anti-mepolizumab antibody positive sample will be tested for neutralising antibody.

A maximum of two additional anti-mepolizumab antibody samples will be obtained; one immediately prior to the first dose and the other prior to the second dose with MDP2. If the first or second dose coincides with a visit where an immunogenicity sample is already required, it is not necessary to obtain an additional sample.

4. PLANNED ANALYSES

4.1. Interim Analyses

At a date agreed by the study team a data look will be performed on a subset of the data. The aim of the data look is solely to ensure that all of the required tables, figures and listings are being produced and formatted correctly, such that the output produced at the planned analysis date is correct and complete.

Interim analyses will be performed as needed in order to provide open-label safety data to inform the risk-benefit assessment of mepolizumab in severe asthma. Specifically, an interim analysis will be performed to support the initial regulatory filing of mepolizumab. A second interim will also be performed to support any possible safety updates following these submissions.

At each interim a ‘cut’ will be made in the data, where any data collected beyond a pre-specified cut-off date will not be included within the datasets to be reported. See Section 10, Section 11, Section 12, Section 13 and Section 14 for details of all planned analyses at these interims.

This analysis will be performed by the study statistics and programming team and not by the SDAC described below who solely support the phase III programme IDMC. The safety results from this interim analysis will be reviewed by the internal GSK mepolizumab safety review team.

Access to the results from this interim analysis will not be confidential. Specifically the results may be provided to the study team, GSK governance boards, external investigators and to regulatory authorities.

4.1.1. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be utilised in this study to ensure external objective review of safety issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The IDMC will review cardiovascular adverse events and all cause mortality from the following studies

in the Mepolizumab Severe Asthma Phase III Program: MEA115575; MEA115588; MEA115666 (this study); MEA115661.

The unblinded statistical analyses will be performed by an independent Statistical Data Analysis Centre (SDAC) at Duke University, North Carolina. Unblinded results will not be made available to the study team: The SDAC will communicate directly with the IDMC, and IDMC recommendations will be made to a primary contact who is external to the mepolizumab study team(s) at GSK. See IDMC Charter (available on request).

Stopping guidelines will be based on comparing event rates between mepolizumab and placebo in the two double-blind trials MEA115588 and MEA115575. The two open label studies do not include any comparator data and therefore are not part of the formal stopping guidelines.

Two event rates will be considered:

a) SAEs (including deaths) adjudicated to be cardiovascular events in nature;

b) all cause mortality.

Analysis will be performed based on a meta-analysis of the two studies. For the purposes of the analysis, the two mepolizumab treatment arms (75mg IV and 100mg SC) in study MEA115588 will be combined to produce an overall event rate for mepolizumab in that study. Event rates will be compared between mepolizumab and placebo using the Peto odds ratio test. An estimate and 99% CI will be produced for the odds ratio for experiencing an event on mepolizumab compared to placebo.

Non-binding statistical stopping guidelines of $p<0.01$ two-sided will be used for a) the analysis of SAEs deemed cardiovascular in nature and b) analysis of all cause mortality. Occurrence of either of these flags would signal further examination of available data by the IDMC, with consideration of altering the conduct of either of the studies or terminating either of the studies.

This statistical analysis will be conducted once 8 subjects in the two double blind studies have experienced SAEs adjudicated to be cardiovascular in nature. The timings of further statistical analyses after the first analysis will be determined by the IDMC.

There are no circumstances under which IDMC review of the data would lead to a recommendation to stop for efficacy of mepolizumab. Therefore no adjustment to the final alpha level for efficacy will be made based on the safety stopping guidelines.

For full details of the analyses to be provided to the IDMC by the SDAC see the IDMC statistical analysis plan (available on request).

5. SAMPLE SIZE CONSIDERATIONS

5.1. Sample Size Assumptions

There is no sample size calculation for this study. The sample size will be determined by the number of available subjects who were randomised into the MEA112997 trial and are eligible for the current study based on inclusion and exclusion criteria.

6. ANALYSIS POPULATIONS

The following analysis populations will be derived as required:

All Subjects Enrolled Population

The All Subjects Enrolled (ASE) population will comprise all subjects for whom a record exists on the study database. This population will be used for summarising pre-treatment SAEs, listing AEs and summarising reasons for screen and run-in failures.

As Treated Population

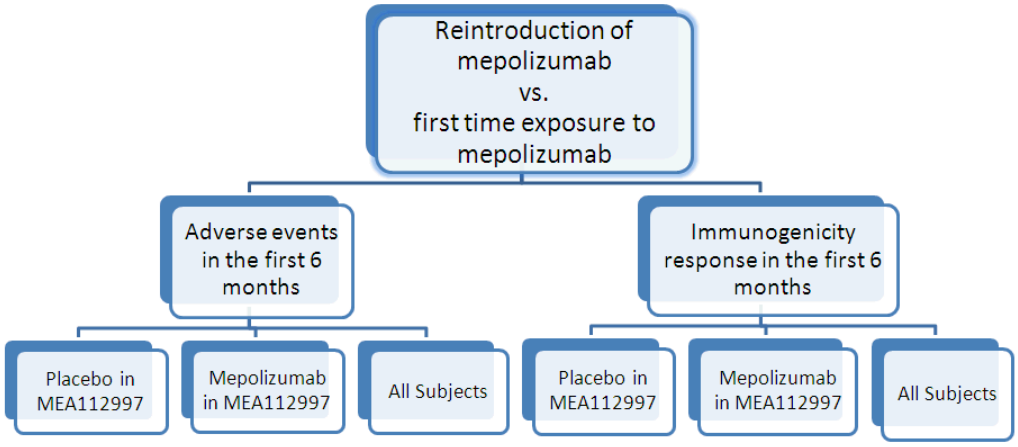
The As Treated (AT) population will consist of all subjects who received at least one dose of open label mepolizumab. This population will be the primary population for all summaries of efficacy and safety measures.

7. TREATMENT COMPARISONS

Due to this study having a single treatment arm, statistical analyses of treatment effect will not be performed. However, there are two comparisons which are of interest:

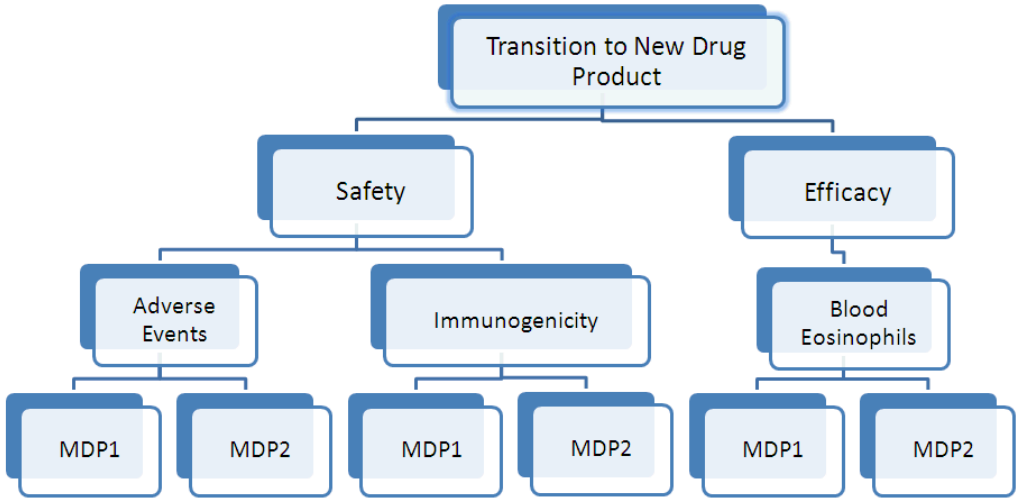
1) Reintroduction of mepolizumab vs. first time exposure: Adverse events and immunogenicity data collected during the first 6 months of treatment within MEA115666 will be summarised by treatment assigned within MEA112997. This is to assess whether subjects present differing responses to treatment dependant on whether they are being reintroduced to mepolizumab or this is their first time exposed to the drug (See Figure 1 and Table 1).

Figure 1 Presentation of Data According to Subject's Former Treatment



2) Change in drug product: Adverse events, immunogenicity and blood eosinophil data will be compared before and after the change in drug product of mepolizumab to investigate whether there is a difference on the safety or efficacy profile following the transition to the new drug product (See Figure 2).

Figure 2 Presentation of Data by Drug Product



7.1. Data Display Treatment and Other Sub-group Descriptors

In the data displays the treatment groups will be identified as described in Table 1. All subjects will be presented within the single treatment group of 'Mepolizumab 100mg SC'.

Table 1 Treatment Group Identifiers

Treatment Group	Descriptor
Mepolizumab 100mg SC every 4 weeks	Mepolizumab 100mg SC

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Programming will be performed in a HARP environment using SAS Version 9 or a later release.

Summary tables will include N, the number of subjects in the treatment group, and n, the number of subjects with non-missing values.

8.1. Multicentre Studies

Centres will be grouped into regions. The following regions are defined:

- USA
- European Union (France, Germany, Poland, Romania, UK)
- Europe Non-EU (Russia, Ukraine)
- South America (Argentina, Chile)
- Rest of World (Australia, Canada, Korea)

The variable CENTREID will be used to identify investigators.

8.2. Other Strata and Covariates

A covariate for region as described above will be included in all model-based analyses. Terms for baseline disease severity (as baseline % predicted pre-bronchodilator FEV_1), the annualised rate of exacerbations in the interval between the MEA112997 trial and the screening visit of this study (as an ordinal variable: 0.0-<1.0, 1.0-<2.0, 2.0-<3.0, 3.0-<4.0, ≥4, See Section 9.2.3) and time on-treatment (as an offset variable) will also be included when estimating the annualised rate of exacerbations.

If there are insufficient subjects in each region or exacerbation rate category for the statistical procedures to converge satisfactorily, further combining of these covariates will be considered.

8.3. Examination of Subgroups

Tabulations of adverse events, immunogenicity and blood eosinophil data will also be reproduced by drug product administered in order to investigate whether there is a differential effect of the two drug products used within the trial (See Section 12 and Section 11.5).

The annualised rate of exacerbations will also be estimated according to blood eosinophil level of ≥150/μL or <150/μL at baseline within MEA115666.

8.4. Multiple Comparisons and Multiplicity

Not applicable.

9. DATA HANDLING CONVENTIONS

Details of key definitions and data handling conventions are detailed below as appropriate.

9.1. Withdrawal and Missing Data

9.1.1. Screening and Enrollment

A subject is considered a Screen Failure if he/she has been assigned a subject identifier but does not continue in the study beyond Visit 1 (Screening). A subject is considered a Run-in Failure if he/she is not a Screen Failure and entered the run-in period, but was not dosed with mepolizumab.

9.1.2. Missing Data

The primary reason for withdrawal will be recorded in the electronic case report form (eCRF) and any data collected up until the point of withdrawal will be used in the data analyses. No imputation will be performed if a subject drops out of the study for any reason, or is lost to follow-up, and their response is unknown.

9.2. Derived and Transformed Data

9.2.1. Definition of Baseline and Change from Baseline

The baseline values for each assessment will be the Visit 2 pre-dose assessment. If a value is missing at Visit 2 then the value recorded at Visit 1 (Screening) will be used as the baseline.

For ECG, clinical chemistry and haematology assessments not scheduled for collection at Visit 2, the baseline value will be that recorded at Visit 1 (Screening).

Generally change from baseline will be defined as the difference between the value of the endpoint at the time point of interest and the baseline value. However, if stated below, a change from baseline analysis may be performed on the ratio scale and change from baseline will be the ratio: time point of interest value/baseline value.

9.2.2. Exacerbations within MEA115666

Exacerbations of asthma will be defined as worsening of asthma which requires use of systemic corticosteroids[1] and/or hospitalisation and/or Emergency Department (ED) visits.

[1]For all subjects, IV 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.

The on-treatment collection period for exacerbations will be defined as being from Visit 2 until either the date of the data collection cut-off or the date of withdrawal inclusive (but no greater than 4 weeks post last study dose received), See Section 9.3.1. For consistency, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

It should be noted that exacerbations recorded in the eCRF will not be verified using eDiary data to confirm that the exacerbation was associated with changes in peak flow, rescue medication use, nocturnal awakening due to asthma symptoms requiring rescue medication use or symptoms. However, 96% of exacerbations captured within MEA112997 met the protocol-defined exacerbation criteria, and only in 4% of the cases were the site/PI not able to provide any objective data to justify the use of corticosteroids.

9.2.3. Annualised Rate of Exacerbations in the Interval Between Studies

The annualised rate of exacerbations in the gap between the MEA112997 trial and the screening visit of this study will be calculated as:

For those subjects that completed the study:

$$\frac{\text{Total Number of Exacerbations Since the Completion of MEA112997}}{\left(\left(\text{Date of Screening MEA115666}\right) - \left(\text{Visit 16 (Week 52) date}\right)\right)/365.25}$$

For those subjects that withdrew from the trial early:

$$\frac{\text{Total Number of Exacerbations Since the Completion of MEA112997}}{\left(\left(\text{Date of Screening MEA115666}\right) - \left(\text{Date of withdrawal}\right)\right)/365.25}$$

This rate will be derived and then categorised as explained in Section 8.2. A value of 365.25 represents the average number of days in a year.

It should be noted that the number of exacerbations reported between the completion of MEA112997 and screening of MEA115666 is self-reported and not subject to verification.

9.2.4. Percent Predicted FEV_1

The predicted normal FEV_1 is based on the NHANES III equations [Hankinson, 1999] and [Hankinson, 2010]. If a subject is recorded as having Hispanic or Latino ethnicity then the Mexican-American equation will be used (irrespective of race). Otherwise, if a subject is recorded as being African-American/African Heritage race, then the African-American equation will be used, similarly if a subject is recorded as being of Asian race, then the Asian equation will be used. Otherwise the Caucasian equation is used.

9.2.5. 12-Lead ECG

'Maximum post-baseline' QTc(F) and QTc(B) values will be derived as the maximum value recorded at any scheduled or unscheduled visit during the treatment period.

9.2.6. Log Transformed Data

Where log-transformed data are used, then summary statistics for these endpoints will include geometric mean, and a measure of spread (SD or SE) on the natural log scale.

Values of zero will be imputed as 0.005 for that measure prior to the log transformation.

9.3. Assessment Windows

Clinic visits are scheduled to take place as specified in the protocol. Measurements outside visit windows will not be excluded from analyses on any population.

If a subject withdraws at a scheduled visit, and these data were scheduled to be collected at that visit, the data will be summarised and analysed (as appropriate) together with data from subjects who did not withdraw.

If a subject withdraws at a scheduled visit at which these data were **not** scheduled to be collected, or if a subject withdraws between scheduled visits, data will be slotted to the next visit.

9.3.1. On-Treatment Exacerbations

In order to model the annualised rate of exacerbations, the reporting period for exacerbations will be as follows:

For subjects remaining in the study:
(Data collection cut-off date) – (Visit 2 date) + 1.

For early withdrawals:
(Date of withdrawal) – (Visit 2 date) + 1.

The on-treatment collection period for exacerbations will be defined as being from Visit 2 until either the date of the data collection cut-off or the date of withdrawal inclusive (but no greater than 4 weeks post last study dose received).

9.3.2. On-Treatment Phase

The on-treatment phase for any purpose except the classification of exacerbations is defined as being from the day of the first administration to the day of the last administration of study treatment + another 28 days inclusive (but no greater than the data collection cut-off date).

i.e. time on-treatment will otherwise be defined as follows:

For all subjects:
(Date of last administration) – (Date of first administration) + 29
but no greater than the data collection cut-off date.

This on-treatment phase will be divided into two periods partitioned at the date and time of receiving the new drug product. This transition will occur when a subject switches from dosing with MDP1 to be dosed with MDP2 for the remainder of the study.

9.3.2.1. Mepolizumab Drug Product 1 Period

For those subjects that have transitioned onto MDP2, the mepolizumab drug product 1 period starts on the first day of dosing with MDP1, and ends the minute prior to the first dose of MDP2.

For those subjects that have not transitioned onto MDP2, the mepolizumab drug product 1 period is defined as being from the day of the first administration using MDP1 to the day of the last administration using MDP1 + another 28 days inclusive (but no greater than the data collection cut-off date).

i.e. time within the mepolizumab drug product 1 period will be defined as:

(Date of first MDP2 administration) – (Date of first MDP1 administration) + 1
for those subjects that have transitioned onto MDP2 **or**

(Date of last MDP1 administration) – (Date of first MDP1 administration) + 29
(but no greater than the data collection cut-off date) for those subjects that have not transitioned onto MDP2.

9.3.2.2. Mepolizumab Drug Product 2 Period

The mepolizumab drug product 2 period is defined as being from the date and time of the first administration of MDP2 to the day of the last administration using MDP2 + another 28 days (but no greater than the data collection cut-off date).

i.e. time within the mepolizumab drug product 2 period will be defined as:

(Date of last MDP2 administration) – (Date of first MDP2 administration) + 28
(but no greater than the data collection cut-off date)

9.4. Values of Potential Clinical Importance

Haematological and clinical chemistry data from subjects who have values outside the normal range and values of potential clinical concern will be listed. Graphical displays of liver function test results will be produced as described in Section 12.9 to identify any liver function tests results which may be of clinical concern. See attachment: Section 18.3 for reference values of potential clinical concern.

9.5. Adverse Events

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

Any SAEs for screen failures or run-in failures will be classified as pre-treatment SAEs.

The most frequent on-treatment AEs will be defined as AEs with frequency ≥3% (prior to rounding).

When presenting summaries of adverse events by drug product, the onset date and time of each event will be used to deem in which drug product period the event occurred. For the definitions of the two drug product periods, see Section 9.3.2.1 and Section 9.3.2.2. When presenting the data in this way, if the AE onset date or time is missing or partial then the most conservative approach possible will be taken.

9.5.1. Exposure Adjusted Adverse Events

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

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

10. STUDY POPULATION

10.1. Disposition of Subjects

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

The proportion of screen failures, the proportion who reported each reason for screen failure, the proportion of run-in failures and the proportion who reported each reason for run-in failure will be presented for the ASE population.

The proportion of subjects in the AT population who has withdrawn from the study, and reported each reason for withdrawal, will be presented. A Kaplan-Meier plot showing the percentage of subjects withdrawing from the study over time will be produced for the AT Population.

The proportion of subjects in the AT population at each centre and within each country and region will be presented. Subject number in MEA115666, treatment received in MEA115666, subject number in MEA112997 and treatment assigned in MEA112997 and will be listed for each centre in the AT population.

10.2. Protocol Deviations

The proportion of subjects in the AT population who failed each inclusion, exclusion or Visit 2 criterion will be presented. Protocol deviations will be summarised and listed for the AT Population.

10.3. Demographic and Baseline Characteristics

10.3.1. Demography and Race

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

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

10.3.2. Medical Conditions

An update in each subject's medical history since completing the medical history form in the MEA112997 trial will be collected at Visit 1 (Screening). If a subject reports no change in medical history, the respective subject's medical history information will be copied over from the MEA112997 trial.

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

10.3.3. Cardiovascular Assessment

A summary of the baseline cardiovascular assessment will be presented. The proportion of subjects who report a family history of medical conditions that may indicate predisposition towards cardiovascular conditions will be summarised.

10.3.4. Since Completion of MEA112997

The number of days and number of exacerbations experienced between the completion of MEA112997 and Visit 1 (Screening) in MEA115666 will be summarised. The completion date of MEA112997 will be considered as the Visit 16 (Week 52) date for

those subjects who completed the study, and will be considered as the date of withdrawal for those subjects that withdrew from the trial prematurely.

10.3.5. Baseline Lung Function Tests

The following Baseline (Visit 2) clinic lung function results will be summarised:

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

10.4. Treatment Compliance

A summary of treatment compliance is not applicable to this study; however number of treatments received is summarised in the Extent of Exposure Section 12.1.

10.5. Concomitant Medications

The proportion of subjects reporting each concomitant medication will be presented. Multi-ingredient medications will be presented according to their combination ATC classification rather than the classifications of the ingredients. Summaries will be split into asthma and non-asthma concomitant medications, as well as into those taken pre-treatment, during treatment and post-treatment (as described in Section 9.3). Asthma medication outputs will not display the ATC grouping.

Classification of a medication as pre-, on- or post-treatment will be made with reference to the study treatment start and stop dates and the medication start date. If the medication start date is missing or partial then the medication will be considered on-treatment unless there is evidence to the contrary (e.g. the month of the start date is present and is less than the month of the first dose of study medication). Medications with a start date of up to 4 weeks after the last dose of treatment will be considered on-treatment. Medications with a start date after this period will be considered post-treatment.

Pre- and on-treatment respiratory medications will be summarised separately.

A medication will be summarised in every period (pre/during/post) in which it was taken, so a medication that was started in the run-in and stopped during active treatment will appear in both the pre-treatment and the during treatment tables.

A listing of the relationship between ATC level 1, ingredient and verbatim term will be produced together with listings of all asthma and non-asthma concomitant medications.

11. EFFICACY ANALYSES

Efficacy data will be summarised using appropriate measures (means/geometric means, standard deviations, medians and ranges for continuous variables and frequencies and

percentages for categorical variables). Unless otherwise stated, analyses will be conducted only for the AT Population.

11.1. Annualised Rate of Exacerbations

The frequency of exacerbations of asthma collected during the on-treatment phase (See Section 9.3.1) will be summarised for the AT population. For consistency, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation (See Section 9.2.2).

The annualised rate of exacerbations will be estimated using a negative binomial generalised linear model with a log link-function. The covariates listed in Section 8.2 will be used in the model. The estimated mean rate per year and 95% confidence interval will be presented. (The estimates of the mean rates should be presented using the observed marginals of the sample covariates).

The annualised rate of exacerbations will also be estimated according to blood eosinophil level of ≥150/µL or <150/µL at baseline within MEA115666.

11.2. Time to First Exacerbation

Summaries and graphs of the Kaplan-Meier estimates of the proportion of subjects with an exacerbation over time will be produced.

11.3. Asthma Control Questionnaire Score

Asthma Control Questionnaire (ACQ) score (absolute value and changes from baseline) will be summarised by visit.

11.4. FEV_1 Measured by Clinic Spirometry

Pre-bronchodilator FEV_1 (absolute value and changes from baseline (mL)) will be summarised by visit.

11.5. Blood Eosinophils

Blood eosinophil count and ratio to baseline will be summarised by visit. Blood eosinophil count and ratio to baseline will be also be summarised by drug product and visit in a separate table. For the definitions of the two drug product periods, see Section 9.3.2.1 and Section 9.3.2.2.

Blood eosinophil counts collected whilst receiving the two drug products will be further compared by summarising the last sample to be collected prior to the first dose of MDP2 and the first sample collected following the first dose with MDP2. This particular table will only include those subjects that have a blood eosinophil sample collected from both drug product periods.

Values of zero cells will be imputed as 0.005 prior to log transformation. Blood eosinophil data will also be listed.

12. SAFETY ANALYSES

All safety summaries and listings will be produced for the AT population, with the exception of the table of pre-treatment SAEs and relationship between system organ class, preferred term and verbatim term which will be reported for the ASE population. Similarly, listings of subject numbers for individual AEs, all AEs, fatal AEs and non-fatal SAEs will be reported for the ASE population.

12.1. Extent of Exposure

The number of treatments administered and the number of days on-treatment will be summarised and listed. The listing of exposure will also contain information of the drug product administered at each dosing visit. For definition of on-treatment, see Section 9.3.2.

The number of treatments administered and the number of days on-treatment will also be summarised by drug product. For the definitions of the two drug product periods, see Section 9.3.2.1 and Section 9.3.2.2.

12.2. Adverse Events

Adverse events will be summarised by preferred term. Numbers will be presented for the whole population. Additionally, events experienced during the first 6 months of treatment within MEA115666 will be presented by treatment assigned within MEA112997.

AEs occurring during pre-treatment, on-treatment and post-treatment phase will be summarised separately.

The number and percentage of subjects experiencing at least one AE of any type, AEs within each body system and AEs within each preferred term will be summarised.

All AEs and SAEs will be summarised by drug product. For the definitions of the two drug product periods, see Section 9.3.2.1 and Section 9.3.2.2.

Exposure adjusted rates of AEs will be presented by drug product to account for any differences in the length of exposure to the two different drug products within the trial. For the definition of exposure adjusted AEs, see Section 9.5.1.

The following summary tables will be produced:

- Overview of all Adverse Events
- Summary of all Adverse Events (on-treatment and post-treatment)
- Summary of drug related Adverse Events (on-treatment)
- Relationship of all Adverse Event SOCs, PTs, and Verbatim Text
- Summary of Most Frequent (≥ 3% Incidence prior to rounding) Adverse Events (on-treatment)

- Summary of Number of Subjects and Occurrences of Common On-Treatment Non-Serious Adverse Events by System Organ Class
- Summary of all Adverse Events Experienced During the First 6 Months of Treatment by Treatment Assigned within MEA112997 (on-treatment)
- Summary of all AEs by drug product (on-treatment)
- Summary of Exposure Adjusted AEs by drug product
- Summary of On-Treatment Adverse Events by Highest Anti Drug Antibody Result At Any Time Post Baseline (See Section 12.12 for further details about Immunogenicity)

The following listings will be produced:

- Listing of Subject Numbers for Individual Adverse Events
- Listing of all Adverse Events

12.3. Adverse Events of Special Interest

Adverse events of special interest (AESIs) are adverse events associated with the identified and potential risks of exposure to mepolizumab. Details regarding these risks and the methods by which each AESI will be identified are provided in the Program Safety Analysis Plan (PSAP).

AESIs of 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. Events considered by the investigator to represent systemic reactions will be required to be assessed against Sampson's diagnostic criteria for anaphylaxis [Sampson, 2006].

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 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 reactions 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/local site reaction will be provided.

The following summary tables will be produced:

- Summary of Adverse Events Of Special Interest: Events Meeting the Criteria for Anaphylaxis (On-Treatment)
- Summary of Adverse Events Of Special Interest: Systemic (Allergic/Hypersensitivity and Non-Allergic) Reactions (On-Treatment)
- Summary of Adverse Events Of Special Interest: Systemic (Allergic/Hypersensitivity) Reactions (On-Treatment)
- Summary of Adverse Events Of Special Interest: Systemic (Non-Allergic) Reactions (On-Treatment)
- Summary of adverse events Experienced on Day of Dosing
- Summary of Adverse Events Of Special Interest: Local Injection Site Reactions (On-Treatment)
- Summary of Adverse Events Of Special Interest: Opportunistic Infections (On-Treatment)
- Summary of Adverse Events Of Special Interest: Malignancies (On-Treatment)
- Summary of Adverse Events Of Special Interest: Serious Cardiac, Vascular and Thromboembolic Events (On-Treatment)
- Summary of Adverse Events Of Special Interest: Serious Ischemic Events (On-Treatment)

The following summary profile tables will be produced:

- Summary Profile of Adverse Events Of Special Interest: Events Meeting the Criteria for Anaphylaxis (On-Treatment)
- Summary Profile of Adverse Events Of Special Interest: Systemic (Allergic/Hypersensitivity and non-Allergic) Reactions (On-Treatment)
- Summary Profile of Adverse Events Of Special Interest: Systemic (Allergic/Hypersensitivity) Reactions (On-Treatment)
- Summary Profile of Adverse Events Of Special Interest: Systemic (Non-Allergic) Reactions (On-Treatment)

- Summary Profile of Adverse Events Of Special Interest: Local Injection Site Reactions (On-Treatment)
- Summary Profile of Adverse Events Of Special Interest: Opportunistic Infections (On-Treatment)
- Summary Profile of Adverse Events Of Special Interest: Malignancies (On-Treatment)
- Summary Profile of Adverse Events Of Special Interest: Serious Cardiac, Vascular and Thromboembolic Events (On-Treatment)
- (This summary will report the events falling into the cardiac disorders and vascular disorders SOCs, plus additional thromboembolic events from other SOCs [e.g., stroke is categorized under the Nervous System SOC] identified by the Safety Review Team)
- Summary Profile of Adverse Events Of Special Interest: Serious Ischemic Events (On-Treatment)

The following listings will be produced:

- Listing of Adverse Events Of Special Interest: Events Meeting the Criteria for Anaphylaxis
- Listing of Adverse Events Of Special Interest: Systemic (Allergic/Hypersensitivity) Reactions
- Listing of Adverse Events Of Special Interest: Systemic (Non-Allergic) Reactions
- Listing of Adverse Events Experienced on Day of Dosing
- Listing of Adverse Events Experienced by Subjects With Investigator Reported Systemic (Allergic/Hypersensitivity and Non-Allergic) Reactions
- Listing of Adverse Events Of Special Interest: Local Injection Site Reactions
- Listing of Adverse Events Experienced by Subjects With Local Injection Site Reactions
- Listing of Adverse Events Of Special Interest: Opportunistic Infections
- Listing of Adverse Events Of Special Interest: Malignancies
- Listing of Adverse Events Of Special Interest: Serious Cardiac, Vascular and Thromboembolic Events
- Listing of Adverse Events Of Special Interest: Serious Ischemic Events

12.4. Deaths and Serious Adverse Events

The following summary tables will be produced:

- Summary of Serious Adverse Events (pre-treatment, on-treatment and post-treatment)
- Summary of Number of Subjects and Occurrences of Serious Adverse Events by System Organ Class and Preferred Term

- Summary of Serious Adverse Events by drug product (on-treatment)
- Summary of Exposure Adjusted Serious Adverse Events by drug product
- Summary of Fatal Events (any period)
- Summary of all Non-Fatal Serious Adverse Events (on-treatment and post-treatment)

The following listings will be produced:

- Listing of Fatal Adverse Events
- Listing of all Non-Fatal Serious Adverse Events

12.5. Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal from the Study and Other Significant Adverse Events

The following summary tables will be produced:

- Summary of Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study (pre-treatment and on/post-treatment)
- Summary of Adverse Events Leading to Interruption of Study Drug (on-treatment)

The following listings will be produced:

- Listing of Adverse Events Leading to Permanent Discontinuation of Study Drug and/or Withdrawal from the Study

12.6. Cardiovascular Events of Interest

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

The following cardiovascular event listings will be produced for both CEC adjudicated events and all investigator reported events. Arrhythmias, pulmonary hypertension, revascularisation and valvulopathy events will not be adjudicated by the CEC so these event listings will only be produced for investigator reported events. Adjudicated investigator reported events that are not considered by the CEC to be cardiovascular in nature will be identified with a footnote in the relevant investigator reported event listings/summaries.

- Arrhythmias (Investigator reported only)
- Congestive Heart Failure
- Cerebrovascular Events/Strokes
- Deep venous Thrombosis/ Pulmonary Embolism
- Myocardial Infarction /Unstable Angina
- Peripheral Arterial Thrombosis Embolism

- Pulmonary Hypertension (Investigator reported only)
- Revascularisation (Investigator reported only)
- Valvulopathy (Investigator reported only)
- Deaths (all cause)

12.7. Pregnancies (as applicable)

Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE and included in summaries and listings of AEs/SAEs as described above in Section 12.2.

12.8. Clinical Laboratory Evaluations

The actual values and change from baseline values for clinical chemistry and haematology will be summarised, in separate tables. Summaries of the data outside the normal range and the changes from baseline relative to the normal range will also be produced, including 'any time post-baseline', which will include laboratory assessments taken at scheduled, unscheduled and Early Withdrawal visits and will report the most extreme value(s). Data from subjects who have values outside the normal range will be listed. The normal ranges will also be included in this listing. Summaries of values of potential clinical concern will be produced. Data from subjects who have values of potential clinical concern will be listed and the ranges of potential clinical concern will be included in this listing.

A trellis display of maximum post-dose liver function test (LFT) versus baseline LFT and a box plot of maximum LFTs will be produced.

12.9. Liver Events

Subjects with emergent hepatobiliary laboratory abnormalities (for example ALT>=3x Upper Limit of Normal) will be summarised and listed.

Liver event information will be summarised and listed for all subjects who report a liver event, to include:

- The information captured on the Liver Event Assessment Form which is used to calculate the Roussel Uclaf Causality Assessment Method (RUCAM) score.
- The size of the biopsy and the recorded outcomes for the liver biopsy.
- The recorded outcomes for the liver imaging assessment.
- All clinical chemistry results for subjects with Liver Event Criteria

Information on alcohol use for subjects who report a liver event will be included in the listing of substance use. Medical conditions reported at the time of the liver event will be included in the listing of medical conditions (see Section 10.3.2).

12.10. Vital Signs

Pre-dose systolic blood pressure, diastolic blood pressure and pulse rate including change from baseline on all visits will be summarised and listed.

12.11. 12-lead ECG

Actual and change from baseline (for post-baseline timepoints) values for QTc(F), QTc(B) and heart rate will be summarised by visit. ECG results will also be listed. Abnormal findings and interpretations will be listed separately.

Individual maximum QTc(F) and QTc(B) values will also be summarised 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 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.

12.12. Immunogenicity

Two types of antibody assay will be performed, i.e. an immunogenicity status anti-drug antibody (ADA) assay and neutralising antibody (NAb) assay. For the ADA assay, a screening assessment will be performed which produces a result of positive or negative. For samples with a positive screening result, a confirmation assay will be carried out, which also produces a result of positive or negative. For samples with a positive confirmation result, a titre value will also be obtained to quantify the degree of binding. Subjects will be viewed as positive for the ADA assay if the confirmation assay is positive.

For subjects who have a positive confirmation result for the ADA assay, a neutralising assay will be performed, which again produces a result of positive or negative.

A table will be produced summarising results for the ADA assay in the AT Population by visit. The table will include the number and proportion of subjects in each results category (see below) for each visit. ADA confirmatory assay results will be categorised as follows:

1. Negative
2. Positive

with the table also summarising the minimum, maximum and median titre values collected for subjects with positive ADA confirmatory assays.

Additionally, results for the ADA assay for the AT Population during the first 6 months of treatment within MEA115666 will be summarised by treatment assigned within MEA112997 and visit.

These two tables will also summarise the highest ADA assay confirmatory result obtained for each subject. If a subject had both Negative and Positive confirmatory results, they will be included in the Positive category.

A table will also be produced summarising results for the ADA assay in the AT Population by drug product and visit. For the definitions of the two drug product periods, see Section 9.3.2.1 and Section 9.3.2.2. This table will also summarise the highest ADA assay confirmatory result obtained for each subject whilst receiving each drug product. If a subject had both Negative and Positive confirmatory results, they will be included in the Positive category.

A table will also be produced summarising results for the NAb assay in the AT Population by visit. Neutralising assay results will be categorised as follows:

1. Negative
2. Positive

Additionally, results for the NAb assay for the AT Population during the first 6 months of treatment within MEA115666 will be summarised by treatment assigned within MEA112997 and visit.

These two tables will also summarise the highest neutralising assay confirmatory result obtained for each subject. If a subject had both Negative and Positive results, they will be included in the Positive category.

A table will also be produced summarising results for the NAb assay in the AT Population by drug product and visit. For the definitions of the two drug product periods, see Section 9.3.2.1 and Section 9.3.2.2. This table will also summarise the highest neutralising assay confirmatory result obtained for each subject whilst receiving each drug product. If a subject had both Negative and Positive results, they will be included in the Positive category.

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

13. HEALTH OUTCOMES ANALYSES

13.1. Resource Utilisation Measures

Healthcare resource use due to an exacerbation will be summarised for the AT population.

14. CLINICAL PHARMACOLOGY DATA ANALYSES

Not applicable to this study.

15. BIOMARKER DATA ANALYSIS

Not applicable to this study.

16. PHARMACOGENETIC DATA ANALYSES

Not applicable to this study.

17. REFERENCES

GlaxoSmithKline Document Number 2012N139436_02 Study ID MEA115666. A multi-centre, open-label, long term safety study of mepolizumab in asthmatic subjects who participated in the MEA112997 trial. Report Date 06-MAR-2013.

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Hankinson JL, Odencrantz JR, Fedan KB. Spirometric Reference Values from a Sample of the General US Population. *American Journal of Respiratory and Critical Care.* 1999;159:179-187.

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

18. ATTACHMENTS

18.1. Table of Contents for Data Display Specifications

18.1.1. Study Population Tables

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5.01	Summary of Subject Populations	ASE
5.02	Summary of Reasons for Screen Failure	ASE
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5.04	Listing of Subjects with Inclusion, Exclusion and Visit 2 Criteria Deviations	ASE
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18.2. Data Display Specifications

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

18.3. Laboratory Potential Clinical Concern Values

Table 2 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)

Table 3 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	

Division: World Wide Development
Retention Category: GRS019
Information Type: Reporting and Analysis Plan

Title:	Reporting and Analysis Plan for MEA115666: A multi-centre, open-label, long term safety study of mepolizumab in asthmatic subjects who participated in the MEA112997 trial.

Compound Number: SB-240563

Effective Date: 20-AUG-2013

Description: This study will provide long term safety and immunogenicity data when mepolizumab is administered subcutaneously (SC) to subjects with severe, refractory asthma with a history of eosinophilic inflammation. Additionally, this study will inform on the safety and immunogenicity profile when mepolizumab therapy is reinstituted in subjects following a cessation in drug therapy.

Safety will be assessed by adverse events, clinical laboratory samples, ECGs, immunogenicity and vital signs.

Additional assessments are included to evaluate the effects of mepolizumab on a range of clinical markers of asthma control.

Subject: Severe refractory asthma, mepolizumab, eosinophils, SB-240563, extension study, safety

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ABBREVIATIONS

ACQ	Asthma Control Questionnaire
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine transaminase
ASE	All Subjects Enrolled
AT	As Treated
ATC	Anatomical Therapeutic Chemical
CEC	Clinical Endpoint Committee
CI	Confidence Interval
CS	Corticosteroid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Emergency Department
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GSK	GlaxoSmithKline
IDMC	Independent Data Monitoring Committee
IgE	Immunoglobulin E
IM	Intramuscular
IV	Intravenous
LFT	Liver function test
LLQ	Lower Limit of Quantification
MDP1	Mepolizumab Drug Product 1
MDP2	Mepolizumab Drug Product 2
MedDRA	Medicinal dictionary for regulatory activities
mg	Milligram
mL	Millilitres
N	Number of subjects in the treatment group
n	Number of subjects with non-missing values
NAb	Neutralising antibody
NHANES	National Health and Nutrition Examination Survey
OCS	Oral corticosteroids
OLE	Open label extension (study)
PI	Principal Investigator
PT	Preferred Term
QTc(B)	QT interval corrected by Bazett's method
QTc(F)	QT interval corrected by Fridericia's method
RAP	Reporting and Analysis Plan
RUCAM	Roussel Uclaf Causality Assessment Method
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SDAC	Statistical Data Analysis Centre
SOC	System Organ Class

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1. INTRODUCTION

The purpose of the data analyses outlined in this Reporting and Analysis Plan (RAP) is to evaluate the safety, immunogenicity and effectiveness of treatment with 100mg mepolizumab administered subcutaneously (SC) every 4 weeks in subjects with severe, uncontrolled refractory asthma.

This RAP is based on Section 8 (Data Analysis and Statistical Considerations) of the MEA115666 study protocol issued 06-Mar-2013 (GlaxoSmithKline Document Number 2012N139436_02) and is intended for use by the Statistics & Programming Department. The data analyses produced will be used in a Clinical Study Report.

2. STUDY OBJECTIVE(S) AND ENDPOINT(S)

2.1. Study Objective(s)

2.1.1. Primary Objective

The primary objective of this study is to describe the long-term safety profile of mepolizumab.

2.1.2. Secondary Objectives

- To provide long-term treatment with mepolizumab to subjects who participated in MEA112997.
- To evaluate the effects of mepolizumab on a range of clinical markers of asthma control.

2.2. Study Endpoint(s)

2.2.1. Primary Endpoint

- Adverse Events (AEs) including both systemic (i.e. allergic/IgE-mediated and non-allergic) and local site reactions.

2.2.2. Secondary Endpoints

- Frequency of positive anti-mepolizumab binding antibodies and neutralising antibodies
- Annualised rate of exacerbations
- Asthma Control Questionnaire (ACQ) score
- Forced expiratory volume in 1 second (FEV_1) as measured by clinic spirometry
- Number of withdrawals due to lack of efficacy
- Number of withdrawals due to adverse events
- Number of hospitalizations due to adverse events including asthma exacerbations
- Frequency of both systemic (i.e., allergic/IgE-mediated and non-allergic) and local site reactions
- 12-Lead Electrocardiogram (ECG) to derive the following endpoints:

- Mean change from baseline in the QTc(F) (QT interval corrected by Fridericia's method)
- Mean change from baseline in QTc(B) (QT interval corrected by Bazett's method)
- Maximum change from baseline for QTc(F) and QTc(B).

- Vital signs
- Clinical Laboratory Parameters

2.3. Statistical Hypotheses

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

3. STUDY DESIGN

This is a multi-centre, open-label, long term, safety study of 100mg mepolizumab administered subcutaneously in addition to standard of care in subjects with severe, refractory asthma and a history of eosinophilic inflammation. Subjects who participated in the MEA112997 trial will be offered the opportunity to consent for this study. All subjects will have experienced a gap of at least 10 months since receiving their last double-blind study medication in MEA112997.

At Visit 1 subjects will undergo an initial screening to assess their eligibility to participate in this study. This screening will include: informed consent, vital signs, update of medical history, immunogenicity status based on MEA112997 data, smoking status, prior monoclonal antibody use, and exacerbations post completion of MEA112997. Subjects meeting the Visit 1 eligibility criteria will enter the run-in period. The purpose of the run-in period is to allow for receipt and review of lab results and the ECG over-read. Visit 2 will mark the end of the run-in period.

Those subjects meeting all the inclusion criteria and none of the exclusion criteria will receive their first mepolizumab dose at Visit 2. Subjects will continue to receive mepolizumab SC injections approximately every 4 weeks until either:

- The risk/benefit profile for the subject is no longer positive in the opinion of the investigator **or**
- the subject's physician withdraws the subject **or**
- the subject withdraws consent **or**
- the sponsor discontinues development of mepolizumab **or**
- the sponsor discontinues the study in the relevant participating country **or**
- mepolizumab becomes commercially available in the relevant participating country

During the trail the vial strength used when dosing will be changed for most subjects, however this will depend on the timing of regulatory approval. The 100mg dose of mepolizumab will be reconstituted from a vial of 250mg/vial strength up until such time that the 100mg/vial strength is available at the site. Once the 100mg/vial strength is

available at the site, all subjects will be dosed with 100mg mepolizumab reconstituted from the 100mg/vial strength at their next treatment visit and for the remainder of the study. This change of vial strength will be when subjects are transitioned onto the new drug product. Hereafter, the 250mg/vial strength will be referred to as mepolizumab drug product 1 (MDP1) and the 100mg/vial strength (to which subjects will transition) will be referred to as mepolizumab drug product 2 (MDP2). In the case that MDP2 is not approved for use by ethics/regulatory at a local site/country subjects will continue to be dosed with MDP1.

Subjects will remain on standard of care asthma therapy, which may be adjusted during the study, at the discretion of their physician. The use of Xolair (omalizumab) or any other monoclonal antibody will not be permitted during the course of the study.

Subjects will be monitored in the clinic approximately every 4 weeks to assess adverse events and asthma status. The Asthma Control Questionnaire-5 (ACQ) will be used to assist the investigator in assessing the subject's asthma status along with spirometry at regular intervals. Exacerbations will also be reviewed at each clinic visit. As some subjects may have previously received placebo while participating in the MEA112997 trial and are naive to mepolizumab, safety lab monitoring will be more frequent at the start of the study. Appropriate safety labs will be drawn prior to starting treatment and then at week 4, 8, 12, 24, 36 and 48. Thereafter, these will be collected every 24 weeks. Labs will also be obtained at 12 weeks after discontinuing mepolizumab. Subjects discontinuing mepolizumab treatment should be monitored for exacerbation of their asthma.

Serum samples for anti-mepolizumab antibody measurements will be obtained from all subjects at Weeks 0, 4, 24 and 48 of the initial year, week 24 and 48 for every additional year, as well as at the Follow-up Visit. Any anti-mepolizumab antibody positive sample will be tested for neutralising antibody.

A maximum of two additional anti-mepolizumab antibody samples will be obtained; one immediately prior to the first dose and the other prior to the second dose with MDP2. If the first or second dose coincides with a visit where an immunogenicity sample is already required, it is not necessary to obtain an additional sample.

4. PLANNED ANALYSES

4.1. Interim Analyses

At a date agreed by the study team a data look will be performed on a subset of the data. The aim of the data look is solely to ensure that all of the required tables, figures and listings are being produced and formatted correctly, such that the output produced at the planned analysis date is correct and complete.

Interim analyses will be performed as needed in order to provide open-label safety data to inform the risk-benefit assessment of mepolizumab in severe asthma. Specifically, an interim analysis will be performed to support the initial regulatory filing of mepolizumab. A second interim will also be performed to support any possible safety updates following these submissions.

At each interim a 'cut' will be made in the data, where any data collected beyond a pre-specified cut-off date will not be included within the datasets to be reported. See Section 10, Section 11, Section 12, Section 13 and Section 14 for details of all planned analyses at these interims.

This analysis will be performed by the study statistics and programming team and not by the SDAC described below who solely support the phase III programme IDMC. The safety results from this interim analysis will be reviewed by the internal GSK mepolizumab safety review team.

Access to the results from this interim analysis will not be confidential. Specifically the results may be provided to the study team, GSK governance boards, external investigators and to regulatory authorities.

4.1.1. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be utilised in this study to ensure external objective review of safety issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The IDMC will review cardiovascular adverse events and all cause mortality from the following studies in the Mepolizumab Severe Asthma Phase III Program: MEA115575; MEA115588; MEA115666 (this study); MEA115661.

The unblinded statistical analyses will be performed by an independent Statistical Data Analysis Centre (SDAC) at Duke University, North Carolina. Unblinded results will not be made available to the study team: The SDAC will communicate directly with the IDMC, and IDMC recommendations will be made to a primary contact who is external to the mepolizumab study team(s) at GSK. See IDMC Charter (available on request).

Stopping guidelines will be based on comparing event rates between mepolizumab and placebo in the two double-blind trials MEA115588 and MEA115575. The two open label studies do not include any comparator data and therefore are not part of the formal stopping guidelines.

Two event rates will be considered:

a) SAEs (including deaths) adjudicated to be cardiovascular events in nature;

b) all cause mortality.

Analysis will be performed based on a meta-analysis of the two studies. For the purposes of the analysis, the two mepolizumab treatment arms (75mg IV and 100mg SC) in study MEA115588 will be combined to produce an overall event rate for mepolizumab in that study. Event rates will be compared between mepolizumab and placebo using the Peto odds ratio test. An estimate and 99% CI will be produced for the odds ratio for experiencing an event on mepolizumab compared to placebo.

Non-binding statistical stopping guidelines of $p<0.01$ two-sided will be used for a) the analysis of SAEs deemed cardiovascular in nature and b) analysis of all cause mortality.

Occurrence of either of these flags would signal further examination of available data by the IDMC, with consideration of altering the conduct of either of the studies or terminating either of the studies.

This statistical analysis will be conducted once 8 subjects in the two double blind studies have experienced SAEs adjudicated to be cardiovascular in nature. The timings of further statistical analyses after the first analysis will be determined by the IDMC.

There are no circumstances under which IDMC review of the data would lead to a recommendation to stop for efficacy of mepolizumab. Therefore no adjustment to the final alpha level for efficacy will be made based on the safety stopping guidelines.

For full details of the analyses to be provided to the IDMC by the SDAC see the IDMC statistical analysis plan (available on request).

5. SAMPLE SIZE CONSIDERATIONS

5.1. Sample Size Assumptions

There is no sample size calculation for this study. The sample size will be determined by the number of available subjects who were randomised into the MEA112997 trial and are eligible for the current study based on inclusion and exclusion criteria.

6. ANALYSIS POPULATIONS

The following analysis populations will be derived as required:

All Subjects Enrolled Population

The All Subjects Enrolled (ASE) population will comprise all subjects for whom a record exists on the study database. This population will be used for summarising pre-treatment SAEs, listing AEs and summarising reasons for screen and run-in failures.

As Treated Population

The As Treated (AT) population will consist of all subjects who received at least one dose of open label mepolizumab. This population will be the primary population for all summaries of efficacy and safety measures.

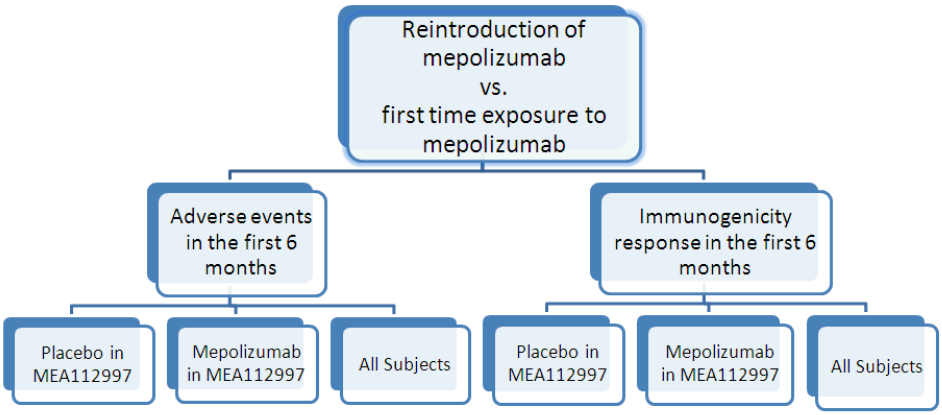
7. TREATMENT COMPARISONS

Due to this study having a single treatment arm, statistical analyses of treatment effect will not be performed. However, there are two comparisons which are of interest:

1) Reintroduction of mepolizumab vs. first time exposure: Adverse events and immunogenicity data collected during the first 6 months of treatment within MEA115666 will be summarised by treatment assigned within MEA112997. This is to assess whether subjects present differing responses to treatment dependant

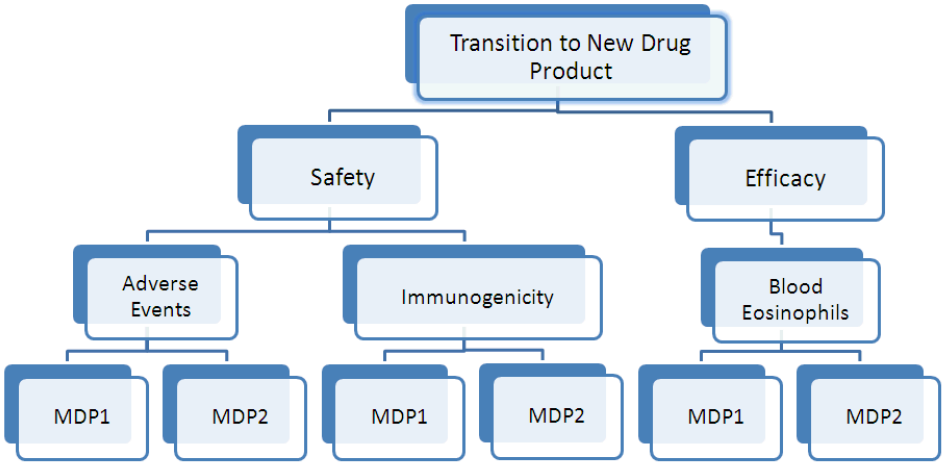
on whether they are being reintroduced to mepolizumab or this is their first time exposed to the drug (See Figure 1 and Table 1).

Figure 1 Presentation of Data According to Subject's Former Treatment



2) Change in drug product: Adverse events, immunogenicity and blood eosinophil data will be compared before and after the change in drug product of mepolizumab to investigate whether there is a difference on the safety or efficacy profile following the transition to the new drug product (See Figure 2).

Figure 2 Presentation of Data by Drug Product



7.1. Data Display Treatment and Other Sub-group Descriptors

In the data displays the treatment groups will be identified as described in Table 1. All subjects will be presented within the single treatment group of 'Mepolizumab 100mg SC'.

Table 1 Treatment Group Identifiers

Treatment Group	Descriptor
Mepolizumab 100mg SC every 4 weeks	Mepolizumab 100mg SC

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Programming will be performed in a HARP environment using SAS Version 9 or a later release.

Summary tables will include N, the number of subjects in the treatment group, and n, the number of subjects with non-missing values.

8.1. Multicentre Studies

Centres will be grouped into regions. The following regions are defined:

- USA
- European Union (France, Germany, Poland, Romania, UK)
- Europe Non-EU (Russia, Ukraine)
- South America (Argentina, Chile)
- Rest of World (Australia, Canada, Korea)

The variable CENTREID will be used to identify investigators.

8.2. Other Strata and Covariates

A covariate for region as described above will be included in all model-based analyses. Terms for baseline disease severity (as baseline % predicted pre-bronchodilator FEV_1), the annualised rate of exacerbations in the interval between the MEA112997 trial and the screening visit of this study (as an ordinal variable: 0.0-<1.0, 1.0-<2.0, 2.0-<3.0, 3.0-<4.0, ≥4, See Section 9.2.3) and time on-treatment (as an offset variable) will also be included when estimating the annualised rate of exacerbations.

If there are insufficient subjects in each region or exacerbation rate category for the statistical procedures to converge satisfactorily, further combining of these covariates will be considered.

8.3. Examination of Subgroups

Tabulations of adverse events, immunogenicity and blood eosinophil data will also be reproduced by drug product administered in order to investigate whether there is a differential effect of the two drug products used within the trial (See Section 12 and Section 11.6).

The annualised rate of exacerbations will also be estimated according to blood eosinophil level of ≥150/μL or <150/μL at baseline within MEA115666.

8.4. Multiple Comparisons and Multiplicity

Not applicable.

9. DATA HANDLING CONVENTIONS

Details of key definitions and data handling conventions are detailed below as appropriate.

9.1. Withdrawal and Missing Data

9.1.1. Screening and Enrollment

A subject is considered a Screen Failure if he/she has been assigned a subject identifier but does not continue in the study beyond Visit 1 (Screening). A subject is considered a Run-in Failure if he/she is not a Screen Failure and entered the run-in period, but was not dosed with mepolizumab.

9.1.2. Missing Data

The primary reason for withdrawal will be recorded in the electronic case report form (eCRF) and any data collected up until the point of withdrawal will be used in the data analyses. No imputation will be performed if a subject drops out of the study for any reason, or is lost to follow-up, and their response is unknown.

9.2. Derived and Transformed Data

9.2.1. Definition of Baseline and Change from Baseline

The baseline values for each assessment will be the Visit 2 pre-dose assessment. If a value is missing at Visit 2 then the value recorded at Visit 1 (Screening) will be used as the baseline.

For ECG, clinical chemistry and haematology assessments not scheduled for collection at Visit 2, the baseline value will be that recorded at Visit 1 (Screening).

Generally change from baseline will be defined as the difference between the value of the endpoint at the time point of interest and the baseline value. However, if stated below, a

change from baseline analysis may be performed on the ratio scale and change from baseline will be the ratio: time point of interest value/baseline value.

9.2.2. Exacerbations within MEA115666

Exacerbations of asthma will be defined as worsening of asthma which requires use of systemic corticosteroids[1] and/or hospitalisation and/or Emergency Department (ED) visits.

[1]*For all subjects, IV 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.*

The on-treatment collection period for exacerbations will be defined as being from Visit 2 until either the date of the data collection cut-off or the date of withdrawal inclusive (but no greater than 4 weeks post last study dose received), See Section 9.3.1. For consistency, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

It should be noted that exacerbations recorded in the eCRF will not be verified using eDiary data to confirm that the exacerbation was associated with changes in peak flow, rescue medication use, nocturnal awakening due to asthma symptoms requiring rescue medication use or symptoms. However, 96% of exacerbations captured within MEA112997 met the protocol-defined exacerbation criteria, and only in 4% of the cases were the site/PI not able to provide any objective data to justify the use of corticosteroids.

9.2.3. Annualised Rate of Exacerbations in the Interval Between Studies

The annualised rate of exacerbations in the gap between the MEA112997 trial and the screening visit of this study will be calculated as:

For those subjects that completed the study:

$$\frac{\text{Total Number of Exacerbations Since the Completion of MEA112997}}{\big((\text{Date of Screening MEA115666}) - (\text{Visit 16 (Week 52) date})\big)/365.25}$$

For those subjects that withdrew from the trial early:

$$\frac{\text{Total Number of Exacerbations Since the Completion of MEA112997}}{\big((\text{Date of Screening MEA115666}) - (\text{Date of withdrawal})\big)/365.25}$$

This rate will be derived and then categorised as explained in Section 8.2. A value of 365.25 represents the average number of days in a year.

It should be noted that the number of exacerbations reported between the completion of MEA112997 and screening of MEA115666 is self-reported and not subject to verification.

9.2.4. Percent Predicted FEV_1

The predicted normal FEV_1 is based on the NHANES III equations [Hankinson, 1999] and [Hankinson, 2010]. If a subject is recorded as having Hispanic or Latino ethnicity then the Mexican-American equation will be used (irrespective of race). Otherwise, if a subject is recorded as being African-American/African Heritage race, then the African-American equation will be used, similarly if a subject is recorded as being of Asian race, then the Asian equation will be used. Otherwise the Caucasian equation is used.

9.2.5. 12-Lead ECG

'Maximum post-baseline' QTc(F) and QTc(B) values will be derived as the maximum value recorded at any scheduled or unscheduled visit during the treatment period.

9.2.6. Log Transformed Data

Where log-transformed data are used, then summary statistics for these endpoints will include geometric mean, and a measure of spread (SD or SE) on the natural log scale.

Values of zero will be imputed as half the lower limit of quantification for that measure (LLQ/2) prior to the log transformation.

9.3. Assessment Windows

Clinic visits are scheduled to take place as specified in the protocol. Measurements outside visit windows will not be excluded from analyses on any population.

If a subject withdraws at a scheduled visit, and these data were scheduled to be collected at that visit, the data will be summarised and analysed (as appropriate) together with data from subjects who did not withdraw.

If a subject withdraws at a scheduled visit at which these data were **not** scheduled to be collected, or if a subject withdraws between scheduled visits, data will be slotted to the next visit.

9.3.1. On-Treatment Exacerbations

In order to model the annualised rate of exacerbations, the reporting period for exacerbations will be as follows:

For subjects remaining in the study:
(Data collection cut-off date) – (Visit 2 date) + 1.

For early withdrawals:
(Date of withdrawal) – (Visit 2 date) + 1.

The on-treatment collection period for exacerbations will be defined as being from Visit 2 until either the date of the data collection cut-off or the date of withdrawal inclusive (but no greater than 4 weeks post last study dose received).

9.3.2. On-Treatment Phase

The on-treatment phase for any purpose except the classification of exacerbations is defined as being from the day of the first administration to the day of the last administration of study treatment + another 28 days inclusive (but no greater than the data collection cut-off date).

i.e. time on-treatment will otherwise be defined as follows:

For all subjects:
(Date of last administration) – (Date of first administration) + 29
but no greater than the data collection cut-off date.

This on-treatment phase will be divided into two periods partitioned at the date and time of receiving the new drug product. This transition will occur when a subject switches from dosing with MDP1 to be dosed with MDP2 for the remainder of the study.

9.3.2.1. Mepolizumab Drug Product 1 Period

For those subjects that have transitioned onto MDP2, the mepolizumab drug product 1 period starts on the first day of dosing with MDP1, and ends the minute prior to the first dose of MDP2.

For those subjects that have not transitioned onto MDP2, the mepolizumab drug product 1 period is defined as being from the day of the first administration using MDP1 to the day of the last administration using MDP1 + another 28 days inclusive (but no greater than the data collection cut-off date).

i.e. time within the mepolizumab drug product 1 period will be defined as:

(Date of first MDP2 administration) – (Date of first MDP1 administration) + 1
for those subjects that have transitioned onto MDP2 **or**

(Date of last MDP1 administration) – (Date of first MDP1 administration) + 29
(but no greater than the data collection cut-off date) for those subjects that have not transitioned onto MDP2.

9.3.2.2. Mepolizumab Drug Product 2 Period

The mepolizumab drug product 2 period is defined as being from the date and time of the first administration of MDP2 to the day of the last administration using MDP2 + another 28 days (but no greater than the data collection cut-off date).

i.e. time within the mepolizumab drug product 2 period will be defined as:

(Date of last MDP2 administration) – (Date of first MDP2 administration) + 28
(but no greater than the data collection cut-off date)

9.4. Values of Potential Clinical Importance

Haematological and clinical chemistry data from subjects who have values outside the normal range and values of potential clinical concern will be listed. Graphical displays of liver function test results will be produced as described in Section 12.8 to identify any liver function tests results which may be of clinical concern. See attachment: Section 18.3 for reference values of potential clinical concern.

9.5. Adverse Events

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

Any SAEs for screen failures or run-in failures will be classified as pre-treatment SAEs.

The most frequent on-treatment AEs will be defined as AEs with frequency ≥2%.

When presenting summaries of adverse events by drug product, the onset date and time of each event will be used to deem in which drug product period the event occurred. For the definitions of the two drug product periods, see Section 9.3.2.1 and Section 9.3.2.2. When presenting the data in this way, if the AE onset date or time is missing or partial then the most conservative approach possible will be taken.

9.5.1. Exposure Adjusted Adverse Events

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

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

10. STUDY POPULATION

10.1. Disposition of Subjects

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

The proportion of screen failures, the proportion who reported each reason for screen failure, the proportion of run-in failures and the proportion who reported each reason for run-in failure will be presented for the ASE population.

The proportion of subjects in the AT population who has withdrawn from the study, and reported each reason for withdrawal, will be presented. A Kaplan-Meier plot showing the percentage of subjects withdrawing from the study over time will be produced for the AT Population.

Summaries and graphs of the Kaplan-Meier estimates of the proportion of subjects withdrawn due to lack of efficacy over time will be produced.

Summaries and graphs of the Kaplan-Meier estimates of the proportion of subjects withdrawn due to adverse events over time will be produced.

The proportion of subjects in the AT population at each centre and within each country and region will be presented. Subject number in MEA115666, treatment received in MEA115666, subject number in MEA112997 and treatment assigned in MEA112997 and will be listed for each centre in the AT population.

10.2. Protocol Deviations

The proportion of subjects in the AT population who failed each inclusion, exclusion or Visit 2 criterion will be presented. Protocol deviations will be listed for the AT Population.

10.3. Demographic and Baseline Characteristics

10.3.1. Demography and Race

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

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

10.3.2. Medical Conditions

An update in each subject's medical history since completing the medical history form in the MEA112997 trial will be collected at Visit 1 (Screening). If a subject reports no change in medical history, the respective subject's medical history information will be copied over from the MEA112997 trial.

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

10.3.3. Cardiovascular Assessment

A summary of the baseline cardiovascular assessment will be presented. The proportion of subjects who report a family history of medical conditions that may indicate predisposition towards cardiovascular conditions will be summarised.

10.3.4. Since Completion of MEA112997

The number of days and number of exacerbations experienced between the completion of MEA112997 and Visit 1 (Screening) in MEA115666 will be summarised. The completion date of MEA112997 will be considered as the Visit 16 (Week 52) date for those subjects who completed the study, and will be considered as the date of withdrawal for those subjects that withdrew from the trial prematurely.

10.3.5. Baseline Lung Function Tests

The following Baseline (Visit 2) clinic lung function results will be summarised:

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

10.4. Treatment Compliance

A summary of treatment compliance is not applicable to this study; however number of treatments received is summarised in the Extent of Exposure Section 12.1.

10.5. Concomitant Medications

The proportion of subjects reporting each concomitant medication will be presented. Multi-ingredient medications will be presented according to their combination ATC classification rather than the classifications of the ingredients. Summaries will be split into asthma and non-asthma concomitant medications, as well as into those taken pre-treatment, during treatment and post-treatment (as described in Section 9.3). Asthma medication outputs will not display the ATC grouping.

Classification of a medication as pre-, on- or post-treatment will be made with reference to the study treatment start and stop dates and the medication start date. If the medication start date is missing or partial then the medication will be considered on-treatment unless there is evidence to the contrary (e.g. the month of the start date is present and is less than the month of the first dose of study medication). Medications with a start date of up to 4 weeks after the last dose of treatment will be considered on-treatment. Medications with a start date after this period will be considered post-treatment.

Pre- and on-treatment respiratory medications will be summarised separately.

A medication will be summarised in every period (pre/during/post) in which it was taken, so a medication that was started in the run-in and stopped during active treatment will appear in both the pre-treatment and the during treatment tables.

A listing of the relationship between ATC level 1, ingredient and verbatim term will be produced together with listings of all asthma and non-asthma concomitant medications.

11. EFFICACY ANALYSES

Efficacy data will be summarised using appropriate measures (means/geometric means, standard deviations, medians and ranges for continuous variables and frequencies and percentages for categorical variables). Unless otherwise stated, analyses will be conducted only for the AT Population.

11.1. Annualised Rate of Exacerbations

The frequency of exacerbations of asthma collected during the on-treatment phase (See Section 9.3.1) will be summarised for the AT population. For consistency, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation (See Section 9.2.2).

The annualised rate of exacerbations will be estimated using a negative binomial generalised linear model with a log link-function. The covariates listed in Section 8.2 will be used in the model. The estimated mean rate per year and 95% confidence interval will be presented. (The estimates of the mean rates should be presented using the observed marginals of the sample covariates).

The annualised rate of exacerbations will also be estimated according to blood eosinophil level of ≥150/μL or <150/μL at baseline within MEA115666.

11.2. Time to First Exacerbation

Summaries and graphs of the Kaplan-Meier estimates of the proportion of subjects with an exacerbation over time will be produced.

11.3. Hospitalisations Due to Exacerbations or Adverse Events

Within a single table, the number of hospitalizations due to exacerbations and the number of hospitalizations due to adverse events will be summarized.

11.4. Asthma Control Questionnaire Score

Asthma Control Questionnaire (ACQ) score (absolute value and changes from baseline) will be summarised by visit (withdrawals will be presented as a separate category).

11.5. FEV_1 Measured by Clinic Spirometry

Pre-bronchodilator FEV_1 (absolute value and changes from baseline (mL)) will be summarised by visit.

11.6. Blood Eosinophils

Blood eosinophil count and ratio to baseline will be summarised by visit. Blood eosinophil count and ratio to baseline will be also be summarised by drug product and visit in a separate table. For the definitions of the two drug product periods, see Section 9.3.2.1 and Section 9.3.2.2.

Blood eosinophil counts collected whilst receiving the two drug products will be further compared by summarising the last sample to be collected prior to the first dose of MDP2 and the first sample collected following the first dose with MDP2. This particular table will only include those subjects that have a blood eosinophil sample collected from both drug product periods.

Values below the lower limit of quantification will be imputed as half the lower limit of quantification prior to summarising. Data will be log-transformed prior to summarising.

Blood eosinophil data will also be listed.

12. SAFETY ANALYSES

All safety summaries and listings will be produced for the AT population, with the exception of the table of pre-treatment SAEs and relationship between system organ class, preferred term and verbatim term which will be reported for the ASE population. Similarly, listings of subject numbers for individual AEs, all AEs, fatal AEs and non-fatal SAEs will be reported for the ASE population.

12.1. Extent of Exposure

The number of treatments administered and the number of days on-treatment will be summarised and listed. The listing of exposure will also contain information of the drug product administered at each dosing visit. For definition of on-treatment, see Section 9.3.2.

The number of treatments administered and the number of days on-treatment will also be summarised by drug product. For the definitions of the two drug product periods, see Section 9.3.2.1 and Section 9.3.2.2.

12.2. Adverse Events

Adverse events will be summarised by preferred term. Numbers will be presented for the whole population. Additionally, events experienced during the first 6 months of treatment within MEA115666 will be presented by treatment assigned within MEA112997.

AEs occurring during pre-treatment, on-treatment and post-treatment phase will be summarised separately.

The number and percentage of subjects experiencing at least one AE of any type, AEs within each body system and AEs within each preferred term will be summarised.

All AEs and SAEs will be summarised by drug product. For the definitions of the two drug product periods, see Section 9.3.2.1 and Section 9.3.2.2.

Exposure adjusted rates of AEs will be presented by drug product to account for any differences in the length of exposure to the two different drug products within the trial. For the definition of exposure adjusted AEs, see Section 9.5.1.

- Overview of all Adverse Events

The following summary tables will be produced:

- Summary of all Adverse Events (on-treatment and post-treatment)
- Summary of drug related Adverse Events (on-treatment)
- Relationship of all Adverse Event SOCs, PTs, and Verbatim Text
- Summary of Most Frequent (≥ 2% Incidence) Adverse Events (on-treatment)
- Summary of all Adverse Events Experienced During the First 6 Months of Treatment by Treatment Assigned within MEA112997 (on-treatment)
- Summary of all AEs by drug product (on-treatment)
- Summary of Exposure Adjusted AEs by drug product

The following listings will be produced:

- Listing of Subject Numbers for Individual Adverse Events
- Listing of all Adverse Events

12.3. Deaths and Serious Adverse Events

The following summary tables will be produced:

- Summary of Serious Adverse Events (pre-treatment, on-treatment and post-treatment)
- Summary of Serious Adverse Events by drug product (on-treatment)
- Summary of Exposure Adjusted Serious Adverse Events by drug product
- Summary of Fatal Events (any period)

The following listings will be produced:

- Listing of Fatal Adverse Events
- Listing of all Non-Fatal Serious Adverse Events

12.4. Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal from the Study and Other Significant Adverse Events

Systemic or local site injection reactions will be summarised.

The following summary tables will be produced:

- Summary of Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study (pre-treatment and on-treatment)
- Summary of Adverse Events Leading to Interruption of Study Drug (on-treatment)
- Summary of AEs defined by the investigator as being systemic (non-allergic or allergic/hypersensitivity) reactions (on-treatment)
- Summary of AEs defined by the investigator as being local injection site reactions (on-treatment)
- Summary of symptoms associated with AEs defined by the investigator as being systemic (non-allergic or allergic/hypersensitivity) reactions (on-treatment)
- Summary of symptoms associated with AEs defined by the investigator as being local injection site reactions (on-treatment)
- Summary of Serious Cardiac, Vascular and Thromboembolic Adverse Events (on-treatment) (This summary will report the events falling into the cardiac disorders and vascular disorders SOCs, plus additional thromboembolic events from other SOCs [e.g., stroke is categorized under the Nervous System SOC] identified by the Safety Review Team).

The following listings will be produced:

- Listing of Adverse Events Leading to Permanent Discontinuation of Study Drug and/or Withdrawal from the Study (pre-treatment and on-treatment)
- Listing of Adverse Events (with symptoms) defined by the investigator as being systemic (non-allergic or allergic/hypersensitivity) reactions (on-treatment)
- Listing of Adverse Events (with symptoms) defined by the investigator as being local injection site reactions (on-treatment)
- Listing of All Anaphylaxis Reaction Events
- Listing of Opportunistic Infections (as defined by the Safety Review Team)

12.5. Cardiovascular Events of Interest

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

The following cardiovascular event listings will be produced for both CEC adjudicated events and all investigator reported events. Arrhythmias, pulmonary hypertension, revascularisation and valvulopathy events will not be adjudicated by the CEC so these event listings will only be produced for investigator reported events. Adjudicated investigator reported events that are not considered by the CEC to be cardiovascular in nature will be identified with a footnote in the relevant investigator reported event listings/summaries.

- Arrhythmias (Investigator reported only)
- Congestive Heart Failure
- Cerebrovascular Events/Strokes
- Deep venous Thrombosis/ Pulmonary Embolism
- Myocardial Infarction /Unstable Angina
- Peripheral Arterial Thrombosis Embolism
- Pulmonary Hypertension (Investigator reported only)
- Revascularisation (Investigator reported only)
- Valvulopathy (Investigator reported only)
- Deaths (all cause)

12.6. Pregnancies (as applicable)

Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE and included in summaries and listings of AEs/SAEs as described above in Section 12.2.

12.7. Clinical Laboratory Evaluations

The actual values and change from baseline values for clinical chemistry and haematology will be summarised, in separate tables. Summaries of the data outside the normal range and the changes from baseline relative to the normal range will also be produced, including ‘any time post-baseline’, which will include laboratory assessments taken at scheduled, unscheduled and Early Withdrawal visits and will report the most extreme value(s). Data from subjects who have values outside the normal range will be listed. The normal ranges will also be included in this listing. Summaries of values of

potential clinical concern will be produced. Data from subjects who have values of potential clinical concern will be listed and the ranges of potential clinical concern will be included in this listing.

A trellis display of maximum post-dose liver function test (LFT) versus baseline LFT and a box plot of maximum LFTs will be produced.

12.8. Liver Events

Liver event information will be summarised and listed for all subjects who report a liver event, to include:

- The information captured on the Liver Event Assessment Form which is used to calculate the Roussel Uclaf Causality Assessment Method (RUCAM) score.
- The time from the start of study treatment to the liver event and the time from the most recent study treatment to the liver event.
- The size of the biopsy and the recorded outcomes for the liver biopsy.
- The recorded outcomes for the liver imaging assessment.

Information on alcohol use for subjects who report a liver event will be included in the listing of substance use. Medical conditions reported at the time of the liver event will be included in the listing of medical conditions (see Section 10.3.2).

12.9. Vital Signs

Pre-dose systolic blood pressure, diastolic blood pressure and pulse rate including change from baseline on all visits will be summarised and listed.

12.10. 12-lead ECG

Actual and change from baseline (for post-baseline timepoints) values for QTc(F), QTc(B) and heart rate will be summarised by visit. ECG results will also be listed. Abnormal findings and interpretations will be listed separately.

Individual maximum QTc(F) and QTc(B) values will also be summarised 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 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.

12.11. Immunogenicity

Two types of antibody assay will be performed, i.e. an immunogenicity status anti-drug antibody (ADA) assay and neutralising antibody (NAb) assay. For the ADA assay, a screening assessment will be performed which produces a result of positive or negative. For samples with a positive screening result, a confirmation assay will be carried out, which also produces a result of positive or negative. For samples with a positive confirmation result, a titre value will also be obtained to quantify the degree of binding. Subjects will be viewed as positive for the ADA assay if the confirmation assay is positive.

For subjects who have a positive confirmation result for the ADA assay, a neutralising assay will be performed, which again produces a result of positive or negative.

A table will be produced summarising results for the ADA assay in the AT Population by visit. The table will include the number and proportion of subjects in each results category (see below) for each visit. ADA confirmatory assay results will be categorised as follows:

1. Negative
2. Positive (any titre result)
   - Positive (titre result ≤ Q1)
   - Positive (titre result > Q1 - ≤Q2)
   - Positive (titre result > Q2 - ≤Q3)
   - Positive (titre result > Q3)

where Q1 – Q4 represents quartiles of all titre values observed in the study.

Additionally, results for the ADA assay for the AT Population during the first 6 months of treatment within MEA115666 will be summarised by treatment assigned within MEA112997 and visit.

These two tables will also summarise the highest ADA assay confirmatory result obtained for each subject. If a subject had both Negative and Positive confirmatory results, they will be included in the Positive category. If a subject had titre results that fall into multiple titre result categories, they will be included in the highest category.

A table will also be produced summarising results for the ADA assay in the AT Population by drug product and visit. For the definitions of the two drug product periods,

see Section 9.3.2.1 and Section 9.3.2.2. This table will also summarise the highest ADA assay confirmatory result obtained for each subject whilst receiving each drug product. If a subject had both Negative and Positive confirmatory results, they will be included in the Positive category. If a subject had titre results that fall into multiple titre result categories, they will be included in the highest category.

A table will also be produced summarising results for the NAb assay in the AT Population by visit. Neutralising assay results will be categorised as follows:

1. Negative
2. Positive

Additionally, results for the NAb assay for the AT Population during the first 6 months of treatment within MEA115666 will be summarised by treatment assigned within MEA112997 and visit.

These two tables will also summarise the highest neutralising assay confirmatory result obtained for each subject. If a subject had both Negative and Positive results, they will be included in the Positive category.

A table will also be produced summarising results for the NAb assay in the AT Population by drug product and visit. For the definitions of the two drug product periods, see Section 9.3.2.1 and Section 9.3.2.2. This table will also summarise the highest neutralising assay confirmatory result obtained for each subject whilst receiving each drug product. If a subject had both Negative and Positive results, they will be included in the Positive category.

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

13. HEALTH OUTCOMES ANALYSES

13.1. Resource Utilisation Measures

Healthcare resource use due to an exacerbation will be summarised for the AT population.

14. CLINICAL PHARMACOLOGY DATA ANALYSES

Not applicable to this study.

15. BIOMARKER DATA ANALYSIS

Not applicable to this study.

16. PHARMACOGENETIC DATA ANALYSES

Not applicable to this study.

17. REFERENCES

GlaxoSmithKline Document Number 2012N139436_02 Study ID MEA115666. A multi-centre, open-label, long term safety study of mepolizumab in asthmatic subjects who participated in the MEA112997 trial. Report Date 06-MAR-2013.

Hankinson JL, Kawut SM, Shahar E, Smith LJ, Stukovsky KH, Barr RG. Performance of American Thoracic Society-Recommended Spirometry Reference Values in a Multiethnic Sample of Adults. *Chest.* 2010;137/1:138-145.

Hankinson JL, Odencrantz JR, Fedan KB. Spirometric Reference Values from a Sample of the General US Population. *American Journal of Respiratory and Critical Care.* 1999;159:179-187.

18. ATTACHMENTS

18.1. Table of Contents for Data Display Specifications

18.1.1. Study Population Tables

Number	Title	Pop
5.01	Summary of Subject Populations	ASE
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5.03	Summary of Reasons for Run-in Failure	ASE
5.04	Summary of Attendance at Each Clinic Visit	AT
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5.04	Listing of Subjects with Inclusion, Exclusion and Visit 2 Criteria Deviations	AT
5.05	Listing of Protocol Deviations	AT
5.06	Listing of Demographic Characteristics	AT
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Number	Title	Pop
5.08	Listing of Medical Conditions	AT
5.09	Listing of Cardiovascular Assessment	AT
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6.08	Summary of Asthma Control Questionnaire (ACQ) score	AT
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7.06	Summary of Drug-Related Adverse Events (On-Treatment)	AT
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7.38	Summary of Haematology Changes from Baseline Relative to the Normal Range	AT
7.39	Summary of Haematology Data Outside the Reference Range (Potential Clinical Concern)	AT
7.40	Summary of Haematology Changes from Baseline Relative to the Reference Range (Potential Clinical Concern)	AT
7.41	Summary of Liver Events Assessment	AT

Number	Title	Pop
7.42	Summary of Time On-Treatment Before Liver Event	AT
7.43	Summary of Vital Signs	AT
7.44	Summary of Change from Baseline in Vital Signs	AT
7.45	Summary of ECG findings	AT
7.46	Summary of ECG Values	AT
7.47	Summary of Change From Baseline in ECG Values	AT
7.48	Frequency of Maximum QTc(F) Interval (msec)	AT
7.49	Frequency of Maximum QTc(B) Interval (msec)	AT
7.50	Summary of ADA Assay Results	AT
7.51	Summary of NAb Assay Results	AT
7.52	Summary of ADA Assay Results During First 6 Months of Treatment by Treatment Assigned within MEA112997	AT
7.53	Summary of NAb Assay Results During First 6 Months of Treatment by Treatment Assigned within MEA112997	AT
7.54	Summary of ADA Assay Results by Drug Product	AT
7.55	Summary of NAb Assay Results by Drug Product	AT

18.1.8. Safety Figures

Number	Title	Pop
7.01	Display of AE Incidence Rates	AT
7.02	Trellis Display of Maximum Post-Baseline LFT Values Versus Baseline LFT Values	AT
7.03	Box Plot of Maximum Post-Baseline Liver Function Tests	AT

18.1.9. Safety Listings

Number	Title	Pop
7.01	Listing of Exposure Data	AT
7.02	Listing of Subject Numbers for Individual Adverse Events	ASE
7.03	Listing of All Adverse Events	ASE
7.04	Listing of Fatal Adverse Events	ASE
7.05	Listing of Non-Fatal Serious Adverse Events	ASE

Number	Title	Pop
7.06	Listing of Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from the Study	AT
7.07	Listing of Adverse Events Defined by the Investigator as a Systemic (ie, Allergic/IgE-mediated and Non-allergic) Reaction	AT
7.08	Listing of Adverse Events Defined by the Investigator as a Local Injection Site Reaction	AT
7.09	Listing of Opportunistic Infections	AT
7.10	Listing of Investigator Reported Cardiovascular Events: Arrhythmias	AT
7.11	Listing of Investigator Reported Cardiovascular Events: Congestive Heart Failure	AT
7.12	Listing of Investigator Reported Cardiovascular Events: Cerebrovascular Events/Stroke	AT
7.13	Listing of Investigator Reported Cardiovascular Events: Deep venous Thrombosis/ Pulmonary Embolism	AT
7.14	Listing of Investigator Reported Cardiovascular Events: Myocardial Infarction /Unstable Angina	AT
7.15	Listing of Investigator Reported Cardiovascular Events: Peripheral Arterial Thrombosis Embolism	AT
7.16	Listing of Investigator Reported Cardiovascular Events: Pulmonary Hypertension	AT
7.17	Listing of Investigator Reported Cardiovascular Events: Revascularisation	AT
7.18	Listing of Investigator Reported Cardiovascular Events: Valvulopathy	AT
7.19	Listing of Investigator Reported Events: All Cause Deaths	AT
7.20	Listing of CEC Adjudicated Cardiovascular Events: Congestive Heart Failure	AT
7.21	Listing of CEC Adjudicated Cardiovascular Events: Cerebrovascular Events/Stroke	AT
7.22	Listing of CEC Adjudicated Cardiovascular Events: Deep venous Thrombosis/ Pulmonary Embolism	AT
7.23	Listing of CEC Adjudicated Cardiovascular Events: Myocardial Infarction /Unstable Angina	AT
7.24	Listing of CEC Adjudicated Cardiovascular Events: Peripheral Arterial Thrombosis Embolism	AT
7.25	Listing of CEC Adjudicated Events: All Cause Deaths	AT
7.26	Listing of Chemistry Data for Subjects with at Least One Value Outside the Normal Range	AT

Number	Title	Pop
7.27	Listing of Haematology Data for Subjects with at Least One Value Outside the Normal Range	AT
7.28	Listing of Urinalysis Data	AT
7.29	Listing of Liver Event Information for RUCAM Score	AT
7.30	Listing of Liver Event Results and Time of Event Relative to Treatment	AT
7.31	Listing of Liver Biopsy Details	AT
7.32	Listing of Liver Imaging Details	AT
7.33	Listing of Alcohol Intake at Onset of Liver Event	AT
7.34	Listing of Vital Signs	AT
7.35	Listing of ECG Values	AT
7.36	Listing of ECG Findings for Abnormal Interpretations	AT
7.37	Listing of Immunogenicity Results	AT

18.1.10. Health Outcomes Tables

Number	Title	Pop
8.01	Summary of Unscheduled Healthcare Resource Use Associated with an Exacerbation	AT

18.2. Data Display Specifications

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

18.3. Laboratory Potential Clinical Concern Values

Table 2 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)

Table 3 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	