Statistical Analysis Plan	
Study Code	D3250C00037
Edition Number	Final 2.0
Date	16 July 2020

A Multicenter, Open-label, Safety Extension Study with Benralizumab (MEDI-563) for Asthmatic Adults on Inhaled Corticosteroid Plus Long-acting β2 Agonist (MELTEMI)

TABLE OF CONTENTS PAGE

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	Anti-drug antibodies
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AZDD	AstraZeneca drug dictionary
BMI	Body mass index
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DAE	AEs causing discontinuation of investigational product
eCRF	Electronic Case Report Form
EOT	End of treatment
ED	Emergency department
FAS	Full analysis set
FU	Follow-up
GGT	Gamma-glutamyltransferase
ICS	Inhaled corticosteroids
IP	Investigational product
IPD	Investigational product discontinuation
LABA	Long-acting β_2 agonists
MedDRA	Medical Dictionary for Regulatory Activities
OCS	Oral corticosteroids
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SI	Standard International
SOC	System organ class

Abbreviation or special term	Explanation
TBL	Total bilirubin
ULN	Upper limit of normal
WBDC	Web based data capture

AMENDMENT HISTORY

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
	30/June/2016	Initial Approved SAP Edition 1.0		
Other: IPD criteria	05/July/2020	Add maintenance of high-dose ICS criterion, and safety related IPD		To further clarify the IPD related to both efficacy and safety.
Other: COVID-19 protocol deviation	05/July/2020	Add summary and listing for patients who have protocol deviation due to COVID-19 pandemic		Consistent with FDA guidance of displaying COVID-19 pandemic effects on clinical trials.
Other: Window definition for Vital signs	05/July/2020	Add a restriction of records to be summarised for vital signs, i.e., only within 14 days of scheduled visit records will be summarised		Due to patients off-schedule visits, original web based data capture has visit records that are beyond scheduled time points.
Other: On-treatment period definition	05/July/2020	Add additional restriction of on-treatment period to be within 30 days of last dose		To further clarify the definition of on-treatment period.
Other: Definition of patient-level exacerbation rate calculation	05/July/2020	Remove the definition of patient level exacerbation rate calculation formula		Removed parameter that is not planned to be summarized.
Other: ADA response	05/July/2020	Additional ADA response criteria		To explore ADA responses other than negative/positive status.
Other: Compliance	05/July/2020	Removed treatment compliance summary		Removed due to the study being a long term safety follow-up study, while some dose delays or missed doses are expected.
Statistical analysis method	05/July/2020	Remove reference to global ADA summary template		Corresponding analysis methods are directly added into the current document

Other: baseline ADA data source	05/July/2020	Baseline ADA information will be obtained directly from the predecessor study BORA		To clarify data source
Other: exclusion of ADA sample records	05/July/2020	ADA records that collect on the same day of dosing but after, or within 3 days of dosing after will be excluded from all ADA analyses		Due to ADA sample responses being affected by study treatment dosing, ADA samples collected close to study treatment need to be excluded.
Statistical analysis method	05/July/2020	Add healthcare encounter summary		Add analysis associated with healthcare encounter endpoint.
Other: inclusion of by-visit presentation rule	16/July/2020	Add a rule for not displaying visit summaries where less than 20 patients and less than 1/3 treated patients in any of the treatment group exist.		Consistent with Astrazeneca general guidance in presentation and analysis of clinical safety data

1. STUDY DETAILS

This statistical analysis plan (SAP) outlines the analyses to be generated for the global clinical study report (CSR).

1.1 Study objectives

1.1.1 Primary objective

Objective	Endpoint
• To assess the safety and tolerability of 2 dosing regimens of benralizumab for adult patients	• AEs/SAEs • Laboratory assessments

1.1.2 Secondary objectives

Objective	Endpoint
• To evaluate the effect of 2 dosing regimens of benralizumab on asthma exacerbations, and asthma-related hospitalizations and emergency room visits	• Asthma exacerbations • Asthma-related hospitalizations and emergency room visits.
• To evaluate the pharmacodynamics and immunogenicity of 2 dosing regimens of benralizumab for adult patients	• Eosinophil levels • Anti-drug antibodies (ADA)

1.2 Study design

This is a multicenter, open-label, safety extension study to evaluate the safety and tolerability of a fixed 30 mg dose of benralizumab (MEDI-563) administered subcutaneously (SC) in asthmatic adults. Patients who complete at least 16 and not more than 40 weeks in Study D3250C00021 (BORA) are eligible to enroll into this study.

The 16-week treatment period in BORA allows patients on placebo in the predecessor studies to receive at least the 3 monthly doses (“loading doses”) of benralizumab within BORA before transition into this open label study and continuing with either the every 4 week (Q4W) or every 8 week (Q8W) dosing regimen.

Patients transitioning to this open label study will need to complete BORA end of treatment (EOT) assessments and sign an informed consent for this study, after which their treatment allocation will be unblinded. Patients will then receive their first dose of benralizumab for this study and their subsequent visits will be scheduled accordingly.

Patients will remain on the same dosing regimen as they had received during the preceding BORA: Patients previously randomized to the 4 week (Q4W) regimen of benralizumab in BORA will continue injections of active drug every 4 weeks in this study; Patients previously randomized to the 8 week (Q8W) regimen in BORA will continue to receive active drug every 8 weeks in this study.

Patients must remain on a medium- to high-dose inhaled corticosteroids plus long-acting β_2 agonists (ICS-LABA) therapy, throughout the treatment period. Any changes in ICS-LABA therapies or other background therapies must be documented in the appropriate eCRF.

Patients will be allowed to remain in this study until benralizumab is commercially available in their local market or the candidate drug is withdrawn from the approval process in the local market. For countries in which a marketing application is not submitted, patients will receive their last dose of benralizumab in December 2018, with EOT and follow-up (FU) visits in Q1 2019.

1.3 Number of subjects

Adult patients who have completed at least 16 weeks in BORA may be eligible to transition into this study after the requirement for approximately 1200 patients who will go on to complete BORA has been met. This safety extension study will enroll approximately 700-1000 patients worldwide.

All analyses will be descriptive only. The study is not designed to power the statistical testing of any null hypothesis.

2. ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 Full analysis set

All patients who received at least 1 dose of investigational product (IP) within the current study will be included in the full analysis set (FAS). Patients will be classified according to the treatment to which they were assigned originally in BORA.

2.2 Violations and deviations

Patients who do not meet eligibility criteria but are still dosed will not be excluded from the analyses. There is no intent to perform a per-protocol analysis for this study. In addition, a separate listing of COVID related disruptions (protocol deviations and issues) that pertaining to individual patients will be provided. Total number of patients affected will be summarized.

2.2.1 Important protocol deviations

The important protocol deviations are important in that they may significantly affect the assessments of the safety endpoint.

The final list of protocol deviation will be finalized and documented prior to database lock. Only important protocol deviations will be listed and tabulated in the Clinical Study Report (CSR). The following categories of protocol deviations will be reviewed by medical advisors and statisticians prior to database lock to determine those which are considered important deviations as outlined above.

- Patients who do not meet the inclusion criteria
- Patients who meet any of the exclusion criteria
- Concomitant use of disallowed medications (to be identified through programming). Patients who use one or more disallowed medication (for any reason, unless otherwise specified) during the open label treatment period will be classed as protocol deviators.
- Patients who were not maintaining ICS dose
- Patients who received the incorrect study dose or administered through other than subcutaneous route
- Patients who developed withdrawal criteria during the study but were not withdrawn
- Patients who had safety related violations (case by case basis)

2.3 Visit window definitions

For the exacerbation-related analyses, no windows will be applied. For all vital signs, the visit recorded in web based data capture (WBDC) will be used. However, the post-baseline assessment closest to the scheduled visit date but within 14 days before or after (calculated from day of first dosing) is summarised due to patients' off-schedule visits during this long-term follow-up study.

For other endpoints that present visit-based data (i.e., hematology laboratory tests, chemistry laboratory tests, and ADA), the variables will be summarized based on the scheduled days with adjusted analysis-defined visit windows. The adjusted analysis-defined windows will be based on the collection schedule listed in the protocol and variables will be windowed to the closest scheduled visit for that variable. All collected assessments before the EOT or IPD visit will be allocated to a particular visit as described in Table 1 below. Assessments collected at EOT/IPD visit and follow-up visit will be summarized separately.

Table 1 Visit windows*

Adjusted Defined Windows Visit	Scheduled Study Day	Maximum Windows
Week 0 Day 1	1	Study Day=1

Week 16	113	99 ≤Study Days≤126
Week 32	225	211≤Study Days≤238
Week 48	337	323≤Study Days≤350
Week 72	505	491≤Study Days≤518
Week 96	673	659≤Study Days≤686
Week 120	841	827≤Study Days≤854
Week 144	1009	995≤Study Days≤1022
Week 168	1177	1163≤Study Days≤1190
Week 192	1345	1331≤Study Days≤1358

* Medication may become commercially available before Week 192, in which case the window definition may stop at earlier week.

For assignment of data to adjusted analysis-defined visit windows, study day will be defined as follows:

(Date of assessment – date of first IP dose) + 1

By this definition, the day of Visit 1 will be study day 1 and the planned date of Week 16 (Visit 5 for Q4W regimen or Visit 3 for Q8W regimen) will be study day 113 (=112+1), for example.

If multiple assessments are recorded within a single adjusted visit window, please refer to the rules below.

- If there are two or more observations within the same visit window, then the non-missing one closest to the scheduled visit will be used in the analysis.
- If two observations are equidistant from the scheduled visit, then the non-missing observation with the earlier collection date will be used in the analysis.
- If two observations are collected on the same day then the non-missing one with the earlier collection time will be included in the analysis.

If an adjusted visit window does not contain any observations, then the data will remain missing.

For overall analyses not based on any particular study visit, all data will be listed and/or analyzed, including any repeat or unscheduled visits, unless otherwise specified.

2.4 Baseline and change from baseline

In general, the last non-missing observation prior to the first dose of the IP for this study will serve as the baseline assessment. The baseline observation is not a pre-treatment observation as each patient was on IP in the predecessor study. Change from baseline will be calculated as

the post baseline assessment value minus the baseline assessment value. Percent change from baseline is computed as ((*visit value – baseline value*)/*baseline value*) × 100%. If either value is missing, then the change from baseline will be missing.

Complete medical, surgical, and asthma history must be re-recorded for this study and will not be integrated from BORA for the CSR. Ongoing non-serious AEs including non-serious exacerbation at the end of the predecessor study will be considered concurrent medical history at the discretion of the Investigator. All concurrent medications taken by the patient at the time of entry into this study and the relevant condition for which treatment is being given are also to be re-entered for this study.

Baseline ADA status resides in the predecessor database, i.e., Study D3250C00021 (BORA) and will not be copied into current study database. Thus, baseline will be obtained from BORA final assessment and used as the baseline status for the patient.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Primary outcome variables

The following safety data are collected: reported AEs/SAEs, hematology laboratory tests, clinical chemistry laboratory tests, and vital signs. Change from baseline at each post-treatment time point where scheduled assessments were made will be calculated for relevant measurements.

3.1.1 Adverse events

Adverse event (AE) and serious adverse event (SAE) are defined at Section 7.1 of the Clinical study protocol (CSP).

All AEs, including SAEs, will be collected from the time the patient signs the informed consent at Visit 1 throughout the study.

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

AE data will be categorized according to their onset date into the following study periods:

- AEs in the on-study period are defined as those with onset between day of the first dose of study treatment and end of study (i.e., EOT visit or follow-up visit, whichever occurs later).

- AEs in the on-treatment period are defined as those with onset between day of the first study treatment and scheduled EOT visit for patients who complete study treatment or scheduled IPD visit for those patients who prematurely discontinue study treatment visit, inclusive. In the event that the EOT or IPD visit is beyond the protocol defined visit window, AEs with onset after the last dose of study treatment

date + 28 days + 7 days (visit window) will be excluded from the on-treatment period and instead assigned to the post-treatment period.

- AEs in the post-treatment period are defined as those with onset after the on-treatment period defined above.

AE on-study period is a combined period of on-treatment period and post-treatment period (when applicable).

For instances where a patient attends the safety follow-up visit only, but does not attend an earlier IPD visit or EOT visit, adverse events occurring on or after the day of the first dose of study treatment and on or before the last dose of study medication + 28 days will be assigned to the on-treatment period, while AEs with onset date after this time will be assigned to the post-treatment period.

If an AE has a missing onset date then unless the stop date of the AE indicates otherwise, this will be considered an on treatment event. Similarly, if an AE has a partial onset date, then unless the partial onset date or the stop date indicates otherwise, this will be considered an on-treatment AE.

3.1.2 Laboratory variables

Blood samples for determination of clinical chemistry and hematology parameters will be taken at the times detailed in the CSP, and will be assessed in a central laboratory. The parameters outlined in Section 5.2.1 of the CSP will be collected.

In summaries, listings and figures, lab results and normal ranges will be presented in the International System (SI) unit. Eosinophils data will be presented in both SI and conventional units (cells/µL) in summaries.

Changes in hematology and clinical chemistry variables between baseline and each subsequent post-baseline assessment will be calculated. For values recorded with a leading greater than or less than (‘>’, ‘<’) symbol, the reported numeric value will be used for analysis and the value with the symbol will be included in the listings, unless otherwise specified. For example, a value of <0.01 will be analyzed as 0.01 and listed as <0.01.

Absolute values will be compared to the relevant reference range and classified as low (below range), normal (within range or on limits) or high (above range). The central laboratory reference ranges will be used for laboratory variables. All absolute values falling outside the reference ranges will be flagged.

For the purposes of hematology and clinical chemistry shift tables, baseline will be defined as the latest non-missing assessment prior to the first IP dose date, and maximum or minimum value post-baseline will be calculated over the entire post-baseline period including any unscheduled assessments.

For the liver function tests: Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline phosphatase, Gamma-GT (GGT) and total bilirubin (TBL), the multiple of the central laboratory upper limit of the normal (ULN) range will be calculated for each data point.

Multiple = Value / ULN

For example, if the ALT value was 72 IU/L (ULN 36) then the multiple would be 2.

Patients who meet any of the following criteria at any point during the study will be flagged:

- AST ≥ 3x ULN
- ALT ≥ 3x ULN
- BILI ≥ 2xULN

3.2 Variables of other assessments

3.2.1 Asthma exacerbations

An asthma exacerbation is defined by a worsening of asthma requiring the use of systemic corticosteroids (or an increase in oral steroid dose for those already on systemic corticosteroids) and/or an in-patient hospitalization, and/or an emergency department (ED) visit.

In order to calculate the number of exacerbations experienced by a patient during the study, the following rule will be applied.

The start of an exacerbation is defined as the start date of systemic corticosteroids or start date of a temporary increase in a stable oral corticosteroid background dose, or start date of hospital/ER admission, whichever occurs earlier. The end date is defined as the last day of systemic corticosteroids or the last day of a temporary increase in a stable oral corticosteroid background dose, or the date of discharge from a hospital/ER, whichever occurs later.

Additional systemic corticosteroids treatment or temporary increase in oral steroid dose for those already on systemic corticosteroids, an in-patient hospitalization or an emergency department visit due to asthma should not be regarded as a new exacerbation. In order to be counted as a new exacerbation it must be preceded by at least 7 days in which neither criterion is fulfilled.

For the production of summary statistics, the on-study annual exacerbation rate in each treatment group will be calculated using the time-based approach.

*Annual Exacerbation Rate = 365.25*Total Number of Exacerbations within the treatment group /Total duration of follow-up for all patients within the treatment group (days)*

3.2.2 Asthma-related health care utilization

Information on health care utilization such as in-patient hospitalizations, number of days in the hospital, and number of emergency department (ED) visits will be collected at each visit and recorded in the appropriate eCRF module.

Asthma-related hospitalization and ED visit information will be collected with a recall period of 'since the previous visit'.

3.2.3 Pharmacodynamics

Blood eosinophil levels will be determined by complete white blood count with differential at a central lab according to the schedule of assessments in the protocol

3.2.4 Vital signs

Pre-dose vital signs (pulse, systolic blood pressure, diastolic blood pressure, respiration rate, and body temperature) will be obtained in accordance with schedule provided in the protocol.

Changes in vital signs variables from baseline to each visit, baseline to maximum post-baseline and baseline to minimum post-baseline value will be calculated. The change from baseline is defined as the post-baseline visit value minus the baseline visit value. There will be no imputation for missing values.

Absolute values will be compared to the relevant reference ranges and classified as low (below range), normal (within range or on limits) or high (above range). All values falling outside the reference ranges (see Table 2) will be flagged.

Table 2 Vital signs reference ranges

Parameter	Standard Units	Lower Limit	Upper Limit
Diastolic Blood Pressure (DBP)	mmHg	60	120
Systolic Blood Pressure (SBP)	mmHg	100	160
Pulse Rate	Beats/min	40	120
Respiratory Rate	Breaths/min	8	28
Body Temperature	Celsius	36.5	38

3.2.5 Immunogenicity variables

Serum samples for ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titre) and ADA data will be collected at scheduled visits shown in the CSP. ADA result from each sample will be reported as either positive or negative. If the sample is positive, the ADA titre will be reported as well. In addition, the presence of neutralizing antibodies (nAb) will be tested in all ADA-positive samples using a ligand binding assay. The nAb results will be reported as positive or negative.

Assessments at both scheduled and unscheduled visits that are analysed will be included in all the summaries of ADA results across visits according to the windowing algorithm described in Section 2.3. ADA results from samples collected post-dose on the same day or within +3 days of the dosing will be excluded from all analyses.

The number and percentage of patients in the study who meet the criteria of the following ADA categories in each treatment group will be presented, together with descriptive statistics of the ADA titres.

- ADA positive at any time
- ADA positive at baseline only
- ADA positive at post baseline only
- ADA positive at both baseline and post baseline
- ADA persistently positive, defined as at least 2 post baseline ADA positive measurements with at least 16 weeks (112 days) between the first and last positive measurement or an ADA positive result at the last available assessment
- ADA transiently positive, defined as at least one post baseline ADA positive and not fulfilling the conditions for persistently positive
- nAb positive

4. ANALYSIS METHODS

4.1 General principles

The analysis of the primary and secondary endpoints will include all data captured during the study, unless the patient withdraws consent, and assent, where applicable, to study participation, regardless of whether study treatment was prematurely discontinued or delayed, and/or irrespective of protocol adherence.

Summary data will be presented in tabular format by treatment groups. Categorical data will be summarized by the number and percentage of patients in each category. Continuous variables for parametric data will be summarized by descriptive statistics including n, mean, standard deviation, median, minimum value and maximum value. For descriptive summaries by visit, when fewer than 20 patients and less than 1/3 of treated patients remain in any of the treatment group, the descriptive summaries will cease from that visit on.

There will be no hypothesis testing conducted.

The data analyses will be conducted using the SAS® System (version 9.4 or higher) (SAS Institute Inc., Cary, NC).

4.2 Analysis methods

All analyses will be conducted for the full analysis set.

4.2.1 Patient disposition

The number and percentage of patients within each treatment group will be presented by the following categories: received treatment, completed treatment, discontinued treatment (and reason), discontinued treatment but completed study follow-up, completed study, and withdrawn from study (and reason). The number and percentage of patients started from predecessor studies D3250C00017, D3250C00018, and study D3250C00020 will be presented.

The number of patients by country and center will be summarized by treatment group.

4.2.2 Demography data and patient characteristics

Demography data such as age, gender, ethnicity and race will be summarized by treatment groups and overall. Age will be derived from the date of informed consent-date of birth, rounded down to the nearest integer. For patients in country where date of birth is not recorded the age as recorded in the eCRF will be used.

Various baseline and disease characteristics will also be summarized by treatment groups and overall. These will include medical, surgical and respiratory disease histories, asthma duration, age at onset of asthma, the use of maintenance asthma medications, maintenance ICS medications and maintenance oral corticosteroids (yes/no), the number of exacerbations in the previous 12 months, and the number of exacerbations requiring hospitalizations in the previous 12 months.

Medical and surgical histories will be summarized by MedDRA PT within MedDRA SOC.

4.2.3 Concomitant medications

The number and percentage of patients who take concomitant medications, and those who take disallowed concomitant medications during the study, will be presented by treatment groups and overall. Concomitant medications will be classified according to WHODRUG B3. The summary table will present data by generic term within ATC code.

4.2.4 Study treatments

4.2.4.1 Exposure

Exposure to investigational product will be calculated in days as:

Last dose date of IP - first dose date of IP+1

and will be summarized by treatment groups.

The number of doses received will also be summarized by treatment group.

4.2.5 Analysis methods for primary safety variables

4.2.5.1 Adverse events (AEs)

Adverse events will be summarized separately for each benralizumab treatment group (30 mg Q4W and 30 mg Q8W) for the on-study, on-treatment, and post-treatment periods, as defined in Section 3.1.1. All AEs will be listed for each patient, regardless of treatment period.

A summary table by benralizumab treatment group will be produced showing the number and percentage of patients with at least 1 AE in any of the following categories: AEs, serious adverse events (SAEs), deaths due to AE, and AEs leading to discontinuation of investigational product (DAEs). The total number of AEs in the different AE categories in terms of AE counts will also be presented (i.e., accounting for multiple occurrences of the same event in a patient).

AEs, AEs with outcome of death, SAEs and DAEs will be summarized by System Organ Class (SOC) and Preferred Term (PT) assigned to the event by MedDRA. For each PT, the number and percentage of patients reporting at least one occurrence will be presented, i.e. for a patient multiple occurrences of an AE will only be counted once.

AEs (by PT) will be summarized by causality and maximum intensity. If a patient reports multiple occurrences of the same AE, the maximum intensity will be taken as the highest recorded maximum intensity (the order being mild, moderate, and severe). SAEs, DAEs, and deaths will also be summarized in separate tables.

A summary of the most common (i.e. frequency of >= 3%) AEs will be presented by PT.

Adverse events of injection site reactions (high level term of injection site reaction) and hypersensitivity (standardized MedDRA PTs (preferred term) of hypersensitivity) will be summarized by PT for the on-study, on-treatment, and post-treatment periods.

The rate of AEs per person-years at risk, calculated as (number of patients reporting AE)/(total duration of study period for which patients at risk of AE), will also be reported for the on-study and on-treatment periods. The total period at risk for each patient will be defined as the period from first dose of study treatment to the date of the EOT or IPD visit for the on-treatment period and as the period from first dose of study treatment to the follow-up visit for the on-study period. Rates will typically be expressed in terms of number of patients who had events per 100 patient-years.

Separate listings of patients with AEs, SAEs, death due to AEs, or DAEs will be presented if applicable.

4.2.5.2 Laboratory data

All continuous laboratory parameters will be summarized by absolute value, together with the corresponding changes from baseline, at each visit by treatment groups. The summary statistics presented will be the mean, SD, median, minimum, and maximum.

A shift table will be produced for each laboratory parameter to display low, normal, and high values. The shift tables will present baseline and maximum/minimum post-baseline value, as applicable for each parameter.

Shift plots showing each individual patient's laboratory value at baseline and at maximum/minimum will also be produced for each continuous laboratory variable. If any laboratory variables show any unusual features (high or low values or a general shift in the data points) at other time points then shift plots of these data may be produced.

Data for patients who have post-baseline values outside the central laboratory reference range will be presented in listings.

Maximum post-baseline total bilirubin elevations by maximum post-baseline ALT and AST will be presented, expressed as multiples of ULN. Total bilirubin will be presented in multiples of the following ULN ≤1.5, >1.5-2, >2, and AST and ALT will be presented in multiples of the following ULN ≤1, >1-3, >3-5, >5-10, >10.

Maximum post-baseline total bilirubin will be presented (<2 and ≥2 xULN) and plotted against maximum post-baseline ALT (<3, ≥3 - <5, ≥5-<10, and ≥10 xULN), expressed as multiples of ULN. This will be repeated to show maximum post-baseline total bilirubin against maximum post-baseline AST.

Data for patients with ALT or AST ≥3x ULN, and bilirubin ≥2x ULN will be presented, which will include all visits for this subset of patients. A line plot of liver biochemistry test results (including ALP, ALT, AST, total bilirubin, and GGT) over time will also be presented for this subset of patients. Any data outside the central laboratory reference ranges will be explicitly noted on the listings that are produced.

4.2.6 Analysis methods for secondary safety variables

4.2.6.1 Asthma exacerbations and asthma-related health care utilization

Asthma exacerbation summary statistics will be presented by the treatment groups. The number of asthma exacerbations, number of patients with at least one exacerbation, number of exacerbations per patient, duration of exacerbation, annual exacerbation rate, number of exacerbations requiring hospitalization, and number of exacerbations requiring ED visits will be summarized for the study duration.

In addition, the number and percentage of patients with asthma specific resource utilization will be presented by treatment group.

4.2.6.2 Blood eosinophil level

Absolute eosinophil counts along with their absolute changes from baseline and percentage changes from baseline will be summarized using descriptive statistics for each visit by treatment groups.

4.2.6.3 Vital Signs

Summaries of vital signs will be presented for each treatment group. Baseline to maximum post-baseline and baseline to minimum post-baseline value shift tables will be generated for each parameter and will include patients with both baseline and post-baseline data. All recorded vital signs data will be listed.

4.2.6.4 Analysis method for immunogenicity variables

ADA and nAb responses will be summarized by treatment groups. The responses are described as in section 3.2.5.

In addition, ADA titres will be summarized at each visit by treatment group. Persistently positive ADA titres will be summarized by median maximum titre. Cumulative number and percentage of patients with positive ADA will be summarized.

The number and percentage of nAb positive at each visit will be summarized as well.

Furthermore, the subgroup analyses of eosinophils count and adverse events by ADA status: positive and negative, and by ADA persistently positive, ADA positive with maximum titre > median of maximum titres.

5. INTERIM ANALYSES

No interim analysis planned for this study.

6. CHANGES OF ANALYSIS FROM PROTOCOL

There is no change of analysis from protocol.

7. REFERENCES

Not applicable.

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d3250c00037-sap-ed-2		
Document Title:	Statistical Analysis Plan Edition 2	
Document ID:	Doc ID-003269482	
Version Label:	2.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
20-Jul-2020 13:40 UTC	Redacted	Content Approval
20-Jul-2020 14:17 UTC	Redacted	Content Approval
20-Jul-2020 16:27 UTC	Redacted	Author Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.