AstraZeneca

Statistical Analysis Plan

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A Multicentre, Double-blind, Randomised, Parallel Group, Phase 3 Safety Extension Study to Evaluate the Safety and Tolerability of Benralizumab (MEDI-563) in Asthmatic Adults and Adolescents on Inhaled Corticosteroid Plus Long-acting β_2 Agonist (BORA)

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K&L Study Statistician Redacted

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AstraZeneca Global Product Statistician

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ-6	Asthma Control Questionnaire 6
ADA	Anti-drug antibodies
AE	Adverse event
AQLQ(S)+12	Standardised Asthma Quality of Life Questionnaire for 12 Years and Older
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AZDRUG	AstraZeneca drug dictionary
BD	Bronchodilator
BMI	Body mass index
CI	Confidence interval
CSP	Clinical study protocol
CSR	Clinical study report
DAE	AEs causing discontinuation of investigational product
ECG	Electrocardiogram
ED	Emergency department
EOT	End of treatment
eCRF	Electronic case report form
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels
EU	European Union
FEV_1	Forced expiratory volume in 1 second
FU	Follow-up
GGT	Gamma-glutamyltransferase
ICS	Inhaled corticosteroids
IP	Investigational product
IPD	Premature Investigational Product Discontinuation
IV	Intravenous
LABA	Long-acting β_2 agonists

Abbreviation or special term	**Explanation**
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
nAb	Neutralising antibodies
OCS	Oral corticosteroids
PK	Pharmacokinetic(s)
PRO	Patient reported outcome
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SI	Standard International
SOC	System organ class
TBL	Total bilirubin
TBNK	T cell, B cell and Natural Killer cell
ULN	Upper limit of normal
WBDC	Web-based data capture
WPAI+CIQ	Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions

AMENDMENT HISTORY

Date	Brief description of change
14 March 2017	• Remove the redundant descriptions in Study design section • Full analysis population is to be used for all non-PK parameters • Further clarification of baseline selection • Remove the redundant item on the list of protocol deviation • Exacerbation rate is to be calculated separately for on-treatment period, and post-treatment period to investigate whether the underlying exacerbation rate changes with withdrawal of treatment • Annual rate of health care encounters is to be calculated separately for on-treatment period, and post-treatment period to evaluate whether the underlying health care encounters change with withdrawal of treatment • Adverse events occurrence period definitions for on-treatment, post treatment, and on-study periods, are further clarified • Drug Dictionary is updated to WHODRUG • Addition of Japanese interim analyses to facilitate regulatory reporting requirements in Japan • Clarify the analyses for the clinical study report will follow two phases including Adult Completion Analysis and Adolescent Completion Analysis • Adjustment of analysis visit window according to collection schedule according to the rules specified in final pivotal studies' analysis • ADA analyses are expanded according to global ADA analysis plan and the nature of study design

11 December 2017	Amended to reflect the following updates (minor updates are not listed): • Add Double-blinded to the study title to be consistent with the final protocol amendment • Drug Dictionary is updated to AZDRUG due to the timeline change in drug dictionary migration • Add the rationale to remove data from SIROCCO centre Redacted (centre Redacted in BORA) in summary • Define anomalies in the plasma concentrations and clarify how these patients will be reported • Clarify the baseline definition, especially for pre-/post-BD FEV1 • Update the AE on-treatment period for analysis of adolescent data during the adult completion analysis • Change the threshold of most common AEs from frequency of ≥3% in any treatment group to ≥5% in any treatment group to count for the small group of adolescent patients • Clarify the rule that derived scores will be set to missing if any item in the questionnaire is missing only apply to ACQ-6 and AQLQ(s)+12. Further clarify for AQLQ(s)+12, the total score and all domains will be set to missing if any item is missing • Update the hybrid LOCF will not be applied to adolescents' data for adult completion analysis given that adolescent patients' EOT visit is Week 108, and adolescents do not have a scheduled AQLQ(S)+12 assessment in BORA at the Week 56 time point (coinciding with the adult EOT visit) • Update the ADA response categories: replace ADA persistently positive with ADA newly persistently positive; further clarify ADA transiently ADA positive definition; Rename prolonged lowered ADA to decrease in titre and further clarify the definition • Update the analyses of efficacy, PROs and healthcare resource utilisation analyse to clarify data for patients from Study 20

Date	Brief description of change
	(ZONDA) will not be separated by the patients with predecessor baseline blood eosinophil count ≥300/μL and <300/μL • Update the section of analysis method for immunogenicity variables to clarify AEs/SAEs tables by ADA subgroup, and add a summary table including ADA response by predecessor studies' ADA status. Update also includes 4 new figures • Clarify the shift tables from baseline to maximum post-baseline Common Terminology Criteria for Adverse Events (CTCAE) grade • Remove median time and its corresponding 95% confidence interval from Kaplan-Meier plot for the time to the first exacerbation due to anticipated low exacerbation rates after being treated with benralizumab, thus median survival time will not be estimable • Update Appendix A for safety lab' visit window for selective chemistry labs: Calcium, Chloride, CO2, Glucose, Phosphorus, Potassium, Sodium, Total cholesterol and Uric acid which have different assessment schedules • Clarify that Appendix A for PK data is for unscheduled PK samples • Update Appendix B Partial and missing date imputation to keep consistency within this study • Update data analyses will be conducted using the SAS® System 9.4 instead of 9.2

1. STUDY DETAILS

1.1 Study objectives

Following are the study primary and secondary objectives (per protocol amendment v3.0).

Primary Objectives

Objective	Endpoint
1. To assess the safety and tolerability of 2 dosing regimens of benralizumab for adult patients during the 56-week treatment period and through the follow-up period (16 weeks from day of last dose). 2. To assess the safety and tolerability of 2 dosing regimens of benralizumab for adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose).	• AEs/SAEs • Laboratory variables • Physical examination

Secondary Objectives

Objective	Endpoint
1. To evaluate the effect of 2 dosing regimens of benralizumab on asthma exacerbations in adult patients during the 56-week treatment period and through the follow-up period (16 weeks from day of last dose). 2. To evaluate the effect of 2 dosing regimens of benralizumab on asthma exacerbations in adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose).	• Annual asthma exacerbation rate, where an asthma exacerbation is defined by a worsening of asthma requiring the use of systemic corticosteroids for at least 3 days, and/or an in-patient hospitalisation, and/or an emergency department or urgent care visit.

Secondary Objectives

Objective	Endpoint
1. To evaluate the effect of 2 dosing regimens of benralizumab on health care utilisation and work and productivity loss for adult patients during the 56-week treatment period and through the follow-up period (16 weeks from day of last dose) 2. To evaluate the effect of 2 dosing regimens of benralizumab on health care utilisation and work and productivity loss for adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)	• WPAI+CIQ • Hospitalisations, emergency department (ED) visits, urgent care visits and all other outpatient visits due to asthma
1. To assess the effect of 2 dosing regimens of benralizumab on asthma related and general health-related quality of life for adult patients during the 56-week treatment period and through the follow-up period (16 weeks from day of last dose) 2. To assess the effect of 2 dosing regimens of benralizumab on asthma related and general health-related quality of life for adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)	• AQLQ(S)+12 • EQ-5D-5L
1. To assess the effect 2 dosing regimens of benralizumab on asthma control for adult patients during the 56-week treatment period and through the follow-up period (16 weeks from day of last dose) 2. To assess the effect 2 dosing regimens of benralizumab on asthma control for adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)	• ACQ-6

Objective	Endpoint
1. To evaluate the pharmacokinetics and immunogenicity of 2 dosing regimens of benralizumab for adult patients during the 56-week treatment period and through the follow-up period (16 weeks from day of last dose) 2. To evaluate the pharmacokinetics and immunogenicity of 2 dosing regimens of benralizumab for adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)	• PK parameters • Anti-drug antibodies (ADA)
1. To assess the effect of 2 dosing regimens of benralizumab on pulmonary function for adult patients during the 56-week treatment period (16 weeks from day of last dose) 2. To assess the effect of 2 dosing regimens of benralizumab on pulmonary function for adolescent patients during the 108-week treatment period (16 weeks from day of last dose)	• Pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 at the study centre
1. To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels for adult patients during the 56-week treatment period and through follow-up period (16 weeks from day of last dose) 2. To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels for adolescent patients during the 108-week treatment period and through the follow-up period (16 weeks from day of last dose)	• Blood eosinophils

1.2 Study design

This is a double-blind, randomised, parallel group, extension study designed to evaluate the safety and tolerability of a fixed 30 mg dose of benralizumab administered subcutaneously (SC). Patients who complete 1 of the predecessor studies D3250C00017 (SIROCCO), D3250C00018 (CALIMA), or D3250C00020 (ZONDA) on investigational product (IP) may

be eligible to enrol into this study. Patients who enrol in the study will follow the flow charts as shown in Figure 1, Figure 2, and Figure 3.

After a minimum of 1200 patients have been enrolled in this study, subsequent patients (up to a maximum of 2200 total for the study), who complete a minimum of 16 weeks, and no more than 40 weeks, in this study, will be given the option to transition to an open-label safety extension study, Study D3250C00037 (MELTEMI), which retains patients on the same treatment regimen as in BORA and contains a simplified set of study assessments.

Patients choosing to enter MELTEMI will complete an end-of-treatment (EOT) visit in BORA before transitioning. Adolescent patients, patients from Japan and South Korea, and any patient who chooses not to enter MELTEMI will remain in BORA through IP discontinuation (IPD) or EOT and follow-up (FU).

Once the blind is broken in the predecessor studies, BORA becomes a single-blind design for those patients who had been on active treatment in the predecessor studies. The study will become single-blind for all remaining patients at the time of the Japanese EOT analysis and when all country regulatory required approvals are received for the protocol amendment that details the reporting and unblinding plan. While the Sponsor will be unblinded to regimen for analysis purposes, study conduct and blinding at the site and patient level will remain unchanged.

Figure 1 Adults study flow charts

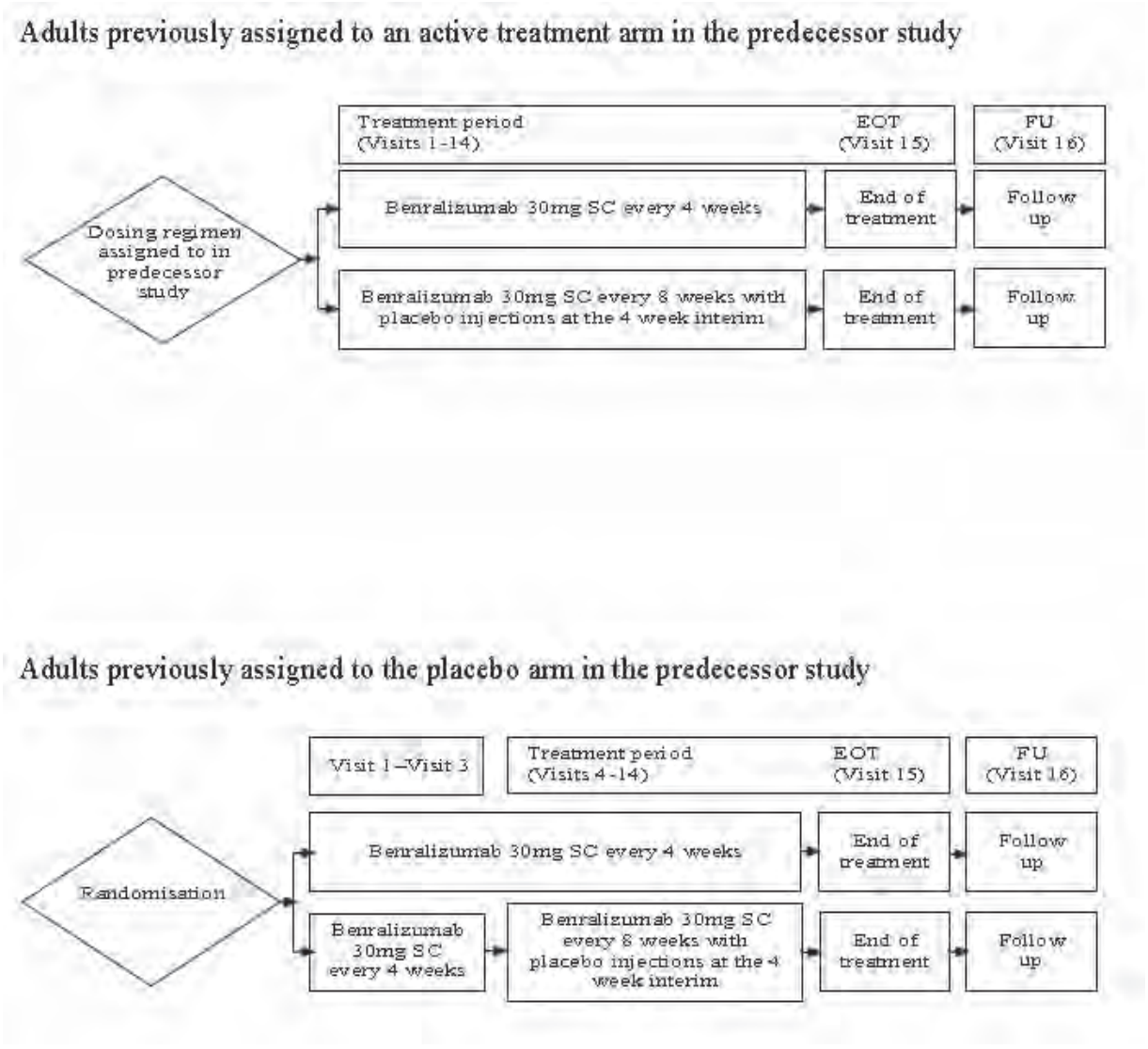
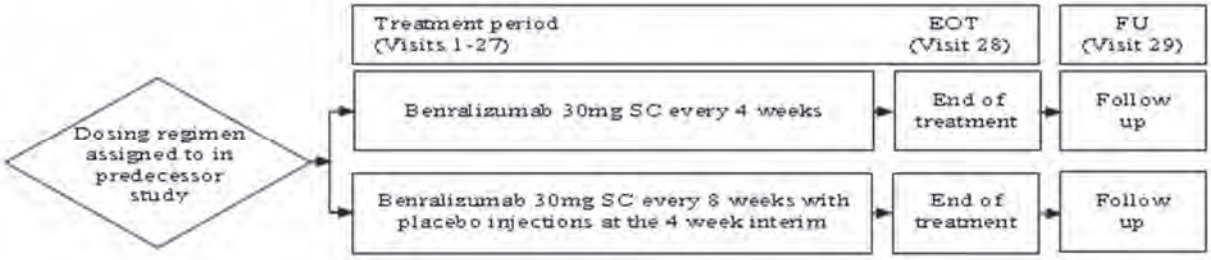


Figure 2 Adolescent study flow charts (outside the EU)

Adolescents outside the EU previously assigned to an active treatment arm in the predecessor study



Adolescents outside the EU previously assigned to the placebo arm in the predecessor study

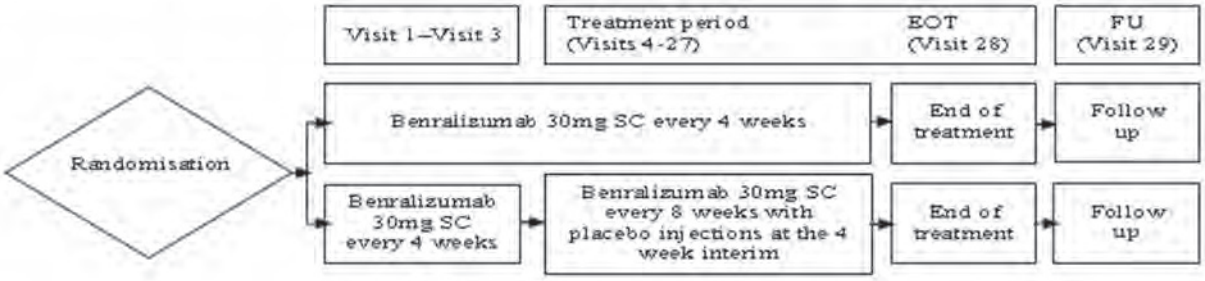
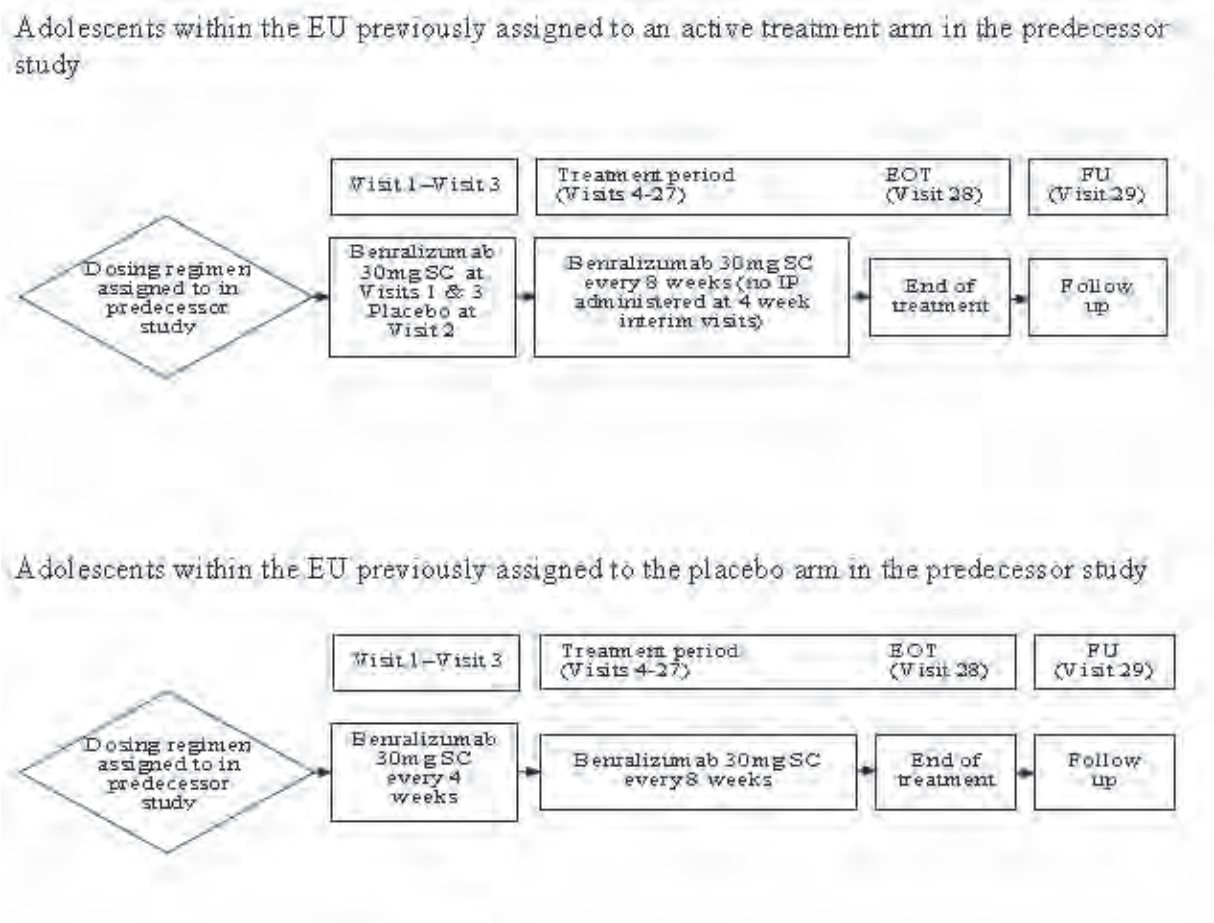


Figure 3 Adolescent study flow charts (within the EU)



1.3 Number of subjects

Patients who complete the double-blind treatment period on IP in 1 of the predecessor studies, SIROCCO, CALIMA, or ZONDA, may be eligible to enrol into BORA. With an estimated rollover rate of >90% from these preceding studies, this safety extension study will enrol approximately 1800 to 2000 patients, up to a maximum of 2200 patients worldwide. The first 1200 adult patients will remain in BORA through IPD or EOT and FU. The remaining 700-1000 adult patients will be asked to transition into the safety extension study, MELTEMI. Adolescent patients and patients from Japan and South Korea will remain in BORA through IPD or EOT and FU.

A minimum of 1200 patients is considered sufficient to address the primary objective of safety and tolerability in the on-treatment and 16-week safety FU period of BORA. The safety extension study, MELTEMI, will allow remaining patients to continue to receive benralizumab until it is available in their local market or until it has been withdrawn from the approval process in their local market. The minimum 16-week treatment period prior to the transition to MELTEMI ensures that any patients previously randomised to placebo have

completed monthly study visits and assessments for the first 3 active doses within BORA before transitioning to MELTEMI.

The study is not designed to power the statistical testing of any null hypothesis.

2. ANALYSIS SETS

As a result of a GCP breach outlined below, all data from the BORA site Redacted in Redacted will be excluded from all analysis sets outlined below, tables and figures. Data from this site will still be included in data listings in BORA.

Following review of anomalous pharmacokinetic (PK) results from the predecessor studies, a for cause audit was conducted at SIROCCO centre Redacted (centre Redacted in BORA). The audit and responses provided by the principal investigator (PI) could not establish a root cause for the anomalous PK results. During the audit, the site staff redacted personal identification data in source documentation making it impossible to reconstruct the study data entered into the database in order to assess the validity of the data reported.

AstraZeneca decided to close the BORA trial at this site and considered this a GCP breach and a report of a potential scientific misconduct was submitted by AstraZeneca to the FDA on 22 November 2016. All 10 subjects at the site withdrew informed consent to be contacted further.

2.1 Definition of analysis sets

In the analysis sets outlined below, data from patients who do not enrol into MELTEMI are the primary data source and are summarised separately from patients who enrol into MELTEMI unless otherwise noted in the following sections. Patients must have provided their informed consent. If no signed informed consent is collected (major protocol deviation), then the patient will be excluded from all analysis sets defined below.

2.1.1 All patients analysis set

This analysis set comprises all patients screened for the study and will be used for reporting of disposition and possible screening failures.

2.1.2 Full analysis set

All patients who received at least one dose of IP will be included in the full analysis set. Patients will be classified according to the treatment they were assigned.

Except for summaries of pharmacokinetic (PK) data, all demographic and baseline characteristics, safety, efficacy, patient reported outcome, healthcare resource utilisation, and anti-drug antibodies (ADA) analyses will be based on this analysis set.

2.1.3 PK analysis set

All patients who received benralizumab, from whom PK blood samples are assumed not to be affected by factors such as protocol violations, and who had at least 1 quantifiable serum PK observation post the first dose will be included in the PK analysis dataset. All PK summaries will be based on this analysis set.

2.2 Violations and deviations

Patients who do not meet eligibility criteria but are randomised will be analysed according to the analysis sets described in Section 2.1. There is no intention to perform a per-protocol analysis in BORA.

2.2.1 Important protocol deviations

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

The final list of protocol deviations will be reviewed, finalised 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:

- 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 treatment period will be classed as protocol deviators
- Patients who received the incorrect study dose regimen
- Patients who developed withdrawal criteria during the study but were not withdrawn

Any patients with anomalies in the plasma concentrations, determined as follows, will be flagged and discussed in the CSR:

- Patients for whom all collected plasma concentration levels are persistently below the LLOQ (3.86 ng/ML) throughout the treatment period
- Patients with plasma concentrations in excess of what is considered to be physiologically possible with dosing (ie concentrations ≥12,000 ng/ML)

A listing will be prepared for these patients highlighting the PK sampling times along with their results from the ADA and eosinophil assessments.

2.3 Adjusted visit window definitions

For the exacerbation-related analyses, no windows will be applied. For local electrocardiogram (ECG), vital signs, Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions (WPAI+CIQ), and post-bronchodilator spirometry, the visit recorded in web-based data capture (WBDC) will be used. For other visit-based data the variables will be summarised based on the collection study days with adjusted visit windows.

The adjusted analysis-defined windows will be based on the collection schedule listed in the protocol, and collected assessments will be windowed to the closest scheduled visit for the variable of interest. Visit windows have been constructed so that every observation collected can be allocated to a particular visit. The adjusted windows are summarised in Table 2 – Table 8 in Appendix A Analysis visit windows

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

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

By this definition, the day of first dose will be Study Day 1 and the planned date of Visit 2 (Week 4) will be Study Day 29 (=28+1), for example.

If multiple readings are recorded within a single adjusted visit window, in general, the following rules will be applied:

- If there are 2 or more observations within the same adjusted visit window, then the non-missing one closest to the scheduled study day will be used in the analysis.
- If 2 or more observations are equidistant from the scheduled study day, then the non-missing observation with the earlier collection date will be used in the analysis.
- If 2 or more 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 the overall analyses that are not based on any particular study visit, all data will be listed and/or analysed, including any repeat or unscheduled visits, unless otherwise specified. For example, for safety summaries, all post-baseline results will be included in the overall analysis up to and including the FU visit.

2.4 Baseline and change from baseline

In general, the last non-missing value on or prior to the first dose of IP in BORA will be used as the baseline. The last evaluable post-dose record from the predecessor studies will also be

considered in the selection of baseline value for BORA study. If there is no assessment present, then the baseline value will not be imputed and will be set as missing. Exceptions for both pre-bronchodilator (pre-BD) and post-bronchodilator (post-BD) FEV_1 as specified below.

For pre-BD FEV_1, the following hierarchy rules will be applied to derive baseline:

- Step 1: Select values with acceptable quality (acceptable or borderline quality grade) on the same date closest to the first IP dose in BORA. If the assessments are on the same day of the first IP dose, only the assessments on or prior to the IP dose are used.
- Step 2: If there are central and local spirometry assessments on the same day, central spirometry assessments will be used.
- Step 3: If there are multiple assessments with different times, the earliest assessment will be used.
- Step 4: If there are multiple assessments with the same date and time, the value recorded in the BORA study database will be used.

For post-BD FEV_1, the baseline will be derived independently from pre-BD FEV1 assessments. With exception from Step 2 to select the highest value within central or local spirometry, the same hierarchy rules as explained above will be applied.

Change from baseline will be calculated as the post-baseline assessment value minus the baseline assessment value. If either value is missing, then the change from baseline value will be missing.

2.5 Prior/Concomitant medications

Medication will be classified as a maintenance asthma medication at baseline if it started prior to or on the date of first dose of IP in BORA and was ongoing after the first dose of IP. Inhaled corticosteroid (ICS) doses will be converted to their Fluticasone Propionate dry powder equivalent in micrograms. Oral corticosteroid (OCS) doses will be converted to their Prednisolone equivalent in milligrams.

An asthma medication will be regarded as prior if it was stopped on or before the date of first dose for the study (medication stop date $\leq$ date of the first dose).

Medication will be regarded as concomitant if the start date is after the date of first dose in BORA, or if it started prior to the date of first dose and was ongoing after the date of first dose. Medications with start date after the on-treatment period (as is defined for adverse events in Section 3.1.1) will not be considered as a concomitant.

Medications recorded in the predecessor studies that were ongoing or stopped after the first dose of BORA are integrated with BORA data for summaries.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Safety outcome variables

The following safety data will be collected: reported AEs, clinical chemistry, haematology, urinalysis, local 12-lead ECG, vital signs, and physical examination. There will be no imputation for missing values for all the safety variables.

Change from baseline to each post-treatment time point where scheduled assessments are performed will be calculated for relevant measurements.

3.1.1 Adverse events

Adverse event (AE) and serious adverse event (SAE) are defined in Section 7.1 of the CSP. All AEs, including SAEs, will be collected from the time the patient signs the informed consent throughout the treatment period and including the follow-up period (Visit 16, Week 68 for adults, and Visit 29, Week 120 for adolescents). Any AEs that are unresolved at follow-up in the study will be followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. If the record was entered in CRF for an ongoing event post-study follow-up visit, study output will list those events and indicates as such.

Adverse events experienced by the patients will be collected throughout the entire study and will be coded by the AstraZeneca designee using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse event data will be categorised according to their onset date into the following study periods:

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

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.

For adolescent data included in the adult completion analyses, only on-treatment AEs will be summarised. AEs will be categorised as having occurred in the on-treatment period if they satisfy one of the following conditions.

For adult completion analysis, the last dose date for an adolescent is defined as the date of last administered dose on or prior to Week 56.

- For patients who received study treatment at Week 56, AEs in the on-treatment period are defined as those with onset between the date of the first BORA study treatment and the Week 56 visit, inclusively.

- For patients who missed Week 56 visit but continued study after Week 56, AEs with onset on or prior to the last dose date of study treatment (as defined above) + 28 days will be assigned to the on-treatment period.
- For patients who discontinued study treatment prior to Week 56 and had IPD visit, AEs with onset on or prior to the IPD visit date or the last dose date (as defined above) + 28 days + 7 days, whichever is earlier, will be included in the on-treatment period.
- For patients who discontinued study treatment prior to Week 56 and had no IPD visit, AEs with onset on or prior to the date of the last dose of study treatment (as defined above) + 28 days will be assigned to the on-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. If an AE has a partial onset date, the handling of partial/missing dates is detailed in Section 8.2.

3.1.1.1 Adjudicated adverse events

An independent adjudication committee is constituted to provide an independent, external, systematic, and unbiased assessment of blinded data to confirm diagnosis of 1) Investigator-reported non-fatal myocardial infarction, non-fatal stroke (hemorrhagic, ischemic, embolic), as well as cardiovascular deaths and 2) Investigator-reported malignancies during the Phase 3 trials. The committee will operate in accordance with an Adjudication Committee Charter/Manual of Operations, which will also provide detail on specific information the committee requires to enable a thorough adjudication.

3.1.2 Laboratory variables

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters will be taken at times detailed in the CSP, and will be assessed in a central laboratory. The parameters outlined in Section 5.2.5, Tables 3 and 4 of the CSP will be collected. Laboratory data is to be reported in SI units. Eosinophils data will be presented in both SI and conventional units (cells/μL) in summaries.

Changes in haematology and clinical chemistry variables between baseline and each subsequent 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 analysed 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 ranges will be used for laboratory variables. All absolute values falling outside the reference ranges will be flagged.

Urinalysis data will be categorised as negative (0), positive (+), or strongly positive (++, +++, or >+++) at each time-point.

For the purposes of haematology, clinical chemistry and urinalysis shift tables, baseline will be defined as the latest non-missing assessment prior to first IP dose date, and maximum or minimum value post-baseline will be calculated over the entire post-baseline period, including the post-treatment 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
- TBL ≥2xULN

In addition to the safety laboratory tests, immunoglobulins and T cell, B cell and NK cell (TBNK) flow cytometry are collected for adolescent patients.

3.1.3 Physical examination

Complete and brief physical examinations will be performed at time points specified in Section 4, Tables 1 (adults) and 2A and 2B (adolescents) of the CSP. What is included in the assessment will be dependent on whether the examination is complete or brief, as described in Section 5.2 of the CSP. For the brief physical examination only information on whether the assessment was performed or not is to be recorded.

Each component of the baseline (Visit 1) complete physical examination will be recorded as normal or abnormal. Each component of the follow-up complete physical examinations will be recorded as normal, same as baseline, or new/aggravated.

Any new finding(s) or aggravated existing finding(s), judged as clinically significant by the Investigator, will be reported as an AE.

3.1.4 Electrocardiograms

Twelve-lead electrocardiogram (ECG) measurements will be recorded in accordance with schedule provided in Tables 1 (adults) and 2A and 2B (adolescents) of the CSP.

The outcome of the overall evaluation is to be recorded as normal/abnormal in the eCRF, with any abnormalities being recorded as not clinically significant or clinically significant.

3.1.5 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 Section 5.2, Tables 1 (adults) and 2A and 2B (adolescents) of the CSP.

Changes in vital signs variables between baseline and each subsequent scheduled assessment will be calculated.

Absolute values will be compared to the relevant reference range (Table 1) and classified as low (below range), normal (within range or on limits) or high (above range). All values (absolute and change) falling outside the reference ranges will be flagged.

Table 1 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
Weight	kg	40	200

Body mass index (BMI) will be calculated from the height and weight as follows:

$$\text{BMI } (kg/m^2) = \text{weight } (kg)/(\text{height } (m))^2$$

3.2 Efficacy outcome variables

3.2.1 Exacerbation

3.2.1.1 Annual exacerbation rate

The analysis is based on exacerbation events reported by the investigator in the eCRF. The exacerbation events will be categorised according to their onset date into on-study, on-treatment and post-treatment periods following the same algorithms used to classify study periods for AEs in Section 3.1.1 above. Similarly, for the analysis of adolescent data at Week 56 visit, only on-treatment exacerbations will be included in the adult completion analysis phase.

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

- Annual Exacerbation Rate (on-treatment)=Total number of on-treatment exacerbations *365.25/Total duration of on-treatment follow-up within the treatment group (days)
- Annual Exacerbation Rate (post-treatment)=Total number of post-treatment exacerbations *365.25/Total duration of post-treatment follow-up within the treatment group (days)
- Annual Exacerbation Rate (on-study)=Total number of on-study exacerbations *365.25/Total duration of on-study follow-up within the treatment group (days)

Where the durations of follow-ups for on-treatment, post-treatment and on-study periods will follow the definitions of corresponding study periods in the AE Section 3.1.1.

3.2.1.2 Time to first asthma exacerbation

Time to first asthma exacerbation will only be calculated for the patients who were randomised to placebo in the predecessor studies with start of exacerbation during the on-treatment period, and is calculated as follows:

Start Date of first asthma exacerbation-date of first dose+1.

The time to first asthma exacerbation for patients who do not experience an asthma exacerbation during the treatment period will be censored at their end of on-treatment period as defined in AE Section of 3.1.1.

3.2.2 Lung function

The absolute and the changes from baseline to each of the post-baseline visits as scheduled in Table 1 (adults) and Tables 2A and 2B (adolescents) of the CSP on pre-BD FEV_1 and post-BD FEV_1 will both be summarised.

3.3 Patient reported outcome variables

All the PROs are collected on paper CRFs. In the calculation of the scores of ACQ-6 and AQLQ(s)+12, if any one of the component values within the questionnaire is missing, then the mean score of ACQ-6, and total score and all 4 domain scores of AQLQ(s)+12 will be considered as missing.

3.3.1 Asthma Control Questionnaire

In the ACQ-6 questionnaire the patients are asked to recall the status of their asthma during the previous week with regards to symptom and bronchodilator use. The questionnaire includes questions on

- Awakened at night by symptoms
- Limitation of normal daily activities
- Waking in the morning with symptoms
- Dyspnoea
- Wheeze
- Daily rescue medication

The questions of the ACQ-6 are measured on a 7-point scale scored from 0 (totally controlled) to 6 (severely uncontrolled). The ACQ-6 score is computed as the un-weighted mean of the responses.

Asthma control responder status (Improved, No change, Deterioration) at EOT (56 weeks for adults and 108 weeks for adolescents) will be categorised according to the following limits (Juniper et al 2005):

- ACQ-6 (End of treatment–baseline) $\leq$ -0.5 $\rightarrow$ Improvement
- -0.5 < ACQ-6 (End of treatment–baseline) < 0.5 $\rightarrow$ No change
- ACQ-6 (End of treatment–baseline) $\geq$ 0.5 $\rightarrow$ Deterioration

In the event of missing EOT ACQ-6 score during deriving responder status at EOT visit, a hybrid last observation carried forward (LOCF) approach will be used such that patients who did not discontinue treatment but have a missing EOT result will have their last observation carried forward while subjects who discontinued treatment will be considered as non-responders. The hybrid LOCF will not be applied to adolescents' data for adult completion analysis given that adolescent patients' EOT visit is Week 108, and adolescents do not have a scheduled AQLQ(S)+12 assessment in BORA at the Week 56 time point (coinciding with the adult EOT visit).

Similarly, asthma control responder status will also be categorised in the same way for other post-baseline visits but the hybrid LOCF will not be applied for any missing non-EOT values.

Asthma control status will be categorised according to their ACQ-6 end-of-treatment score as follows (Juniper et al 2006):

- ACQ-6 (End of treatment) ≤ 0.75 → Well controlled
- 0.75< ACQ-6 (End of treatment) < 1.5 → Partly controlled
- ACQ-6 (End of treatment) ≥ 1.5 → Not well controlled

Similarly, asthma control status for other post-baseline visits will also be categorised the same way. The hybrid LOCF will be used for any missing EOT values as described above.

3.3.2 Standardised Asthma Quality of Life Questionnaire for 12 years and older

The AQLQ(s)+12 is a 32 question health-related quality of life assessment. Respondents are asked to recall their experiences during the previous 2 weeks and to score each of the 32 questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score is calculated as the mean response to all questions. The 4 individual domain scores (4 domains assessing 1) symptoms, 2) activity limitations, 3) emotional function, and 4) environmental stimuli) are the means of the responses to the questions in each of the domains.

Health-related quality of life (HRQoL) responder will be categorised at EOT (56 weeks for adults and 108 weeks for adolescents) according to the following definitions based on the overall score:

- AQLQ(S)+12 (End of treatment–baseline) ≥ 0.5 → Improvement
- -0.5 < AQLQ(S)+12 (End of treatment–baseline) <0.5 → No change
- AQLQ(S)+12 (End of treatment–baseline) ≤ -0.5 → Deterioration

In the event of missing EOT AQLQ(S)+12 overall score, the hybrid (LOCF) approach described above will be used for categorisation of responders. The hybrid LOCF will not be applied to adolescents' data for adult completion analysis given that adolescent patients' EOT visit is Week 108, and adolescents do not have a scheduled AQLQ(S)+12 assessment in BORA at the Week 56 time point (coinciding with the adult EOT visit).

Similarly, HRQoL responder status will also be categorised in the same way for other post-baseline visits but the hybrid LOCF will not be applied for any missing non-EOT values.

3.3.3 Work Productivity and Activity Impairment (WPAI+CIQ)

The 10 questions included in the WPAI+CIQ are as follows:

1 = currently employed (yes/no)

2 = hours missed work due to health problems

3 = hours missed work due to other reasons

4 = hours actually worked

5 = degree health affected productivity while working (0-10 scale, with 0 meaning no effect)

6 = attends class in an academic setting (yes/no)

7 = hours missed class due to health problems

8 = hours actually attended class

9 = degree health affected productivity while attending class (0-10 scale, with 0 meaning no effect)

10 = degree health affected regular activities (other than work or class) (0-10 scale, with 0 meaning no effect)

If the answer to question 1 is 'No, not currently employed', then the patient should skip to question 6. If the answer to question 6 is 'No, not currently attending class', then the patient should skip to question 10.

The WPAI+CIQ provides 4 types of scores: absenteeism (work or class time missed), presenteeism (impairment at work or class/reduced on-the-job effectiveness), work productivity loss (overall work or class impairment/absenteeism plus presenteeism), and activity impairment. WPAI+CIQ outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

For the work related questions, the following calculations should be used to create the variables of interest:

- Number of work hours missed = Q2
- Absenteeism = Q2/(Q2+Q4)
- Presenteeism = Q5/10
- Work Productivity Loss = Q2/(Q2+Q4)+[(1-Q2/(Q2+Q4))x(Q5/10)]
- Activity Impairment = Q10/10

For the class-related questions, the following calculations should be used to create the variables of interest:

- Number of class hours missed = Q7
- Absenteeism = Q7/(Q7+Q8)
- Presenteeism = Q9/10

- Class Productivity Loss = Q7/(Q7+Q8)+[(1-Q7/(Q7+Q8))x(Q9/10)]
- Activity Impairment = Q10/10.

3.3.4 EQ-5D-5L

The EQ-5D-5L questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty. The value of response is 1 corresponding to 'no problems', and 5 corresponding to 'extreme problems'.

The patient will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale, where the patient will be asked to rate current health status on a scale of 0-100, with 0 being the worst imaginable health state.

3.4 Health care resource utilisation due to asthma

Health care resource utilisation due to asthma will be collected by the Investigator/authorised delegate at each visit as specified in the protocol and recorded in the Asthma-related health care event module in the eCRF.

Following are the resource categories utilised for each patient:

- Ambulance transport
- Hospitalisation, intensive care (days in intensive care)
- Hospitalisation, general care (days in general care)
- Emergency room visit
- Visit to specialist
- Visit to primary health care physician
- Other health care visit
- Home visit, physician
- Home visit, other health care
- Telephone call to physician
- Telephone call to nurse

- Spirometry
- Advanced pulmonary function test

The annual rates of health care utilisation by type of health care encounter will be calculated for hospitalisation (combining intensive care and general care), emergency department visits, unscheduled outpatient visits (ie, visit to specialist and/or visit to primary health care physician and/or other health care visit), home visit (combining physician or other health care), telephone calls (to physician or nurse), ambulance transport, clinical tests (spirometry and advanced pulmonary function test), and all of these healthcare encounters combined. The annual rates of health care encounters will be calculated in a manner similar to the calculation of the annual exacerbation rates defined in Section 3.2.1.1 (ie, annual rate for the treatment group) for on-treatment, post-treatment and on-study periods.

3.5 Pharmacokinetic variables

Due to the limited sampling schedule, the PK assessment will be primarily based on the observed steady-state serum trough (pre-dose) concentrations, C_{trough}.

3.6 Immunogenicity variables

ADA assessments will be conducted utilising a tiered approach (screen, confirm, titre). The presence of neutralising antibodies (nAb) will be tested in all ADA-positive samples using a ligand binding assay.

For each patient, the following response variables will be evaluated based on ADA status in predecessor studies and data from the start of the BORA through to the BORA FU visit (Week 68 for adults and Week 120 for adolescents). For adolescents in adult completion analysis phase, the responses variables will be evaluated from the start of the BORA through the Week 56 visit or IPD visit, whichever is earlier.

- ADA positive at any visit (including baseline, post-baseline, unscheduled visits)
- ADA positive at both baseline and at least one post-baseline
- ADA positive at baseline only
- ADA positive at post-baseline only
- ADA newly persistently positive: defined as ADA negative at BORA baseline and 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 stable persistently positive: defined as ADA positive at BORA baseline and at least 2 post-baseline ADA positive measurements with at least 16 weeks (112 days) between the first and last positive measurement.

- ADA transiently positive: defined as having at least one post-baseline ADA positive measurement and not fulfilling the conditions for either newly or stable persistently positive.

- nAb positive

- Newly treatment-induced ADA positive: defined for patients who in predecessor study were not ADA positive any time, but post-baseline in the current study is ADA positive for the first time.

- Decrease in titre: defined as having at least two post-baseline ADA positive results, and a >75% decrease from the maximum post-baseline titre which must be maintained from the time when it first occurred until the last on-treatment period visit. The >75% decrease can include going from a positive to negative titre result (e.g. a change of titer from ≥200 to negative).

- Treatment boosted ADA: at least one of patient's post baseline titres is > 4-fold of the baseline titre.

Treatment-emergent ADA positive (BORA-specific incidence) is defined as either newly treatment-induced ADA positive or treatment boosted ADA as defined above.

4. ANALYSIS METHODS

4.1 General principles

The age group classification for adult and adolescent from the predecessor studies will be used in the BORA subgroup analysis. If the patient's age at the time of enrolment in the previous study was between 12 and 17 years old then he/she was considered as part of the adolescent group even if the patient was 18 years old at the time of entry in to BORA study. If it was between 18 and 75 years old, he/she was considered as part of adult group. Actual age calculated at BORA study entry will be used in descriptive summary of age and listings.

Patients randomised to placebo in the predecessor study will be summarised separately from patients randomised to benralizumab. The presentation of treatment group will combine treatment assigned in both BORA and the predecessor study as follows:

- Benra 30 mg q.4 weeks
  - Predecessor q.4 weeks
  - Predecessor placebo
- Benra 30 mg q.8 weeks

- Predecessor q.8 weeks
- Predecessor placebo

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, regardless of whether study treatment was prematurely discontinued or delayed, and/or irrespective of protocol adherence. Any data collected after a patient is transitioned into the long-term extension study MELTEMI will not be included in the analyses described in this SAP.

Summary data will be presented in tabular format by treatment. Categorical data will be summarised by the number and percentage of patients in each category. Continuous variables for parametric data will be summarised by descriptive statistics including n, mean, standard deviation, median, minimum value and maximum value unless otherwise specified.

All endpoints as describe in previous sections will be summarised descriptively. The study is not a confirmatory study, thus in general no hypothesis testing and/or p-values will be provided. Following are sets of planned groups for the study.

The primary source of data for the clinical study report (CSR) summaries will be based on patients who stayed in the BORA study. The analyses will follow the two phases as described in the protocol amendment. Some selective summaries will be separately presented for the patients who enrolled into MELTEMI study.

4.1.1 Adult completion analysis

This analysis will be conducted when all adult patients within BORA have completed the study, and the final adolescent patient has completed the first 56 weeks of treatment within BORA. At this time, all of the study objectives related to adults will be fully addressed. The CSR will be prepared for the adult completion analysis as detailed below.

Data cutoff for this analysis will be the date when all adult patients within BORA have completed the study, and the final adolescent patient has completed the first 56 weeks of treatment within BORA. The analysis summary tables and figures will include adult data up to and including follow-up visit and adolescent data up to Week 56 visit or IPD visit, whichever is earlier, while all listings will include all adult data up to and including follow-up visit and adolescent data up to the date of data cut-off (therefore may include adolescent data beyond Week 56 that is not included in any analyses).

Summaries will be presented for patients enrolled from studies D3250C00017 and D3250C00018, separately for patients from study D3250C00020. Adult patients and adolescents will be separately summarised as well as combined.

For the analysis of adolescent data in the adult completion analysis, only on-treatment evaluations will be included in the summaries. For example, for summaries of AEs, only on-treatment AEs will be summarised for adolescents.

4.1.2 Adolescent completion analysis

This analysis will be conducted when the final adolescent patient has completed BORA. The analysis will include all data for adolescents up to follow-up visit and will be reported in an addendum report to the CSR.

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

4.2 Analysis methods

4.2.1 Patient disposition

The patients from the predecessor studies that sign the informed consent form will be summarised. The number and percentage of patients throughout the study with respect to completion of treatment, completion of the study and discontinuation from the study will be provided. For adolescent patients, number and percentage of adolescent patients who completed treatment, completed the study and discontinued from the study on or prior to the cut-off date will be presented for the adult completion analysis. Patients who enrolled into MELTEMI will be considered as BORA study completers, but will be identified as a separate category in the disposition summary. In addition, the number and percentage of patients in each analysis set will be presented. These analyses will be summarised for patients with predecessor baseline eosinophil count ≥300/μL and <300/μL.

4.2.2 Demography data and patient characteristics

Demography data such as age, gender, and race will be summarised by treatment group for the FAS. Age at the time of BORA's enrolment will be present. Age group for adult and adolescent will be based on the age group from predecessor studies.

Various baseline characteristics will also be summarised by treatment group based on the full analysis set. These include data (minimum, but not limited to) such as medical, surgical, cardiovascular and respiratory disease histories, weight, height and BMI, history of allergy, FEV_1 (pre and post bronchodilator) at baseline, asthma duration, age at onset of asthma, the use of maintenance oral corticosteroids (yes/no), asthma medications, the number of exacerbations in the previous 12 months, and the number of exacerbations requiring hospitalisations in the previous 12 months. Overall key baseline characteristics, lung function data and respiratory disease characteristics will be summarised for patients with predecessor baseline eosinophil count ≥300/μL and <300/μL.

Medical and surgical histories will be summarised by MedDRA SOC and MedDRA PT.

All demographic and baseline characteristics data including medical, surgical, cardiovascular and respiratory disease histories will be also summarised for the patients who rolled over to MELTEMI study.

4.2.3 Concomitant medication

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 group. Concomitant medications will be classified according to the AstraZeneca Drug Dictionary (AZDRUG). The summary tables will present data by generic term within ATC code.

The number and percentage of patients taking maintenance asthma medications, including ICS/LABA fixed dose combinations, at baseline will be summarised and for those patients taking ICS and OCS at the study baseline, the converted dose will be summarised. The number of patients treated with ICS and OCS at baseline will be summarised separately by ATC code and preferred term, with total daily dose (non-converted) at baseline summarised for each preferred term. A similar summary will be prepared to summarise total daily dose of OCS at baseline. For patients from ZONDA, all OCS taken at baseline regardless of reason for therapy will be included to be consistent with the way the data was reported and analysed in ZONDA.

All above summaries also will be summarised for the patients who rolled over to MELTEMI study.

4.2.4 Exposure

Exposure to the investigational product will be summarised by treatment group for the full analysis set. Summary of exposure will be also summarised for the patients who rolled over to MELTEMI study.

4.2.5 Analysis methods for safety variables

All safety variables will be summarised for the full analysis set.

4.2.5.1 Adverse events

Adverse events (AEs) will be summarised separately by the treatment group for the on-study, on-treatment and post-treatment periods, as defined in Section 3.1.1.

An overall summary table 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 causing discontinuation of the investigational product (DAEs). This summary will also be repeated by baseline blood eosinophil count (<300/µL, ≥300/µL) for the on-study and on-treatment periods. The total number of AEs in the different AE categories in terms of AE counts will also be presented (ie, accounting for multiple occurrences of the same event in a patient).

AEs will be summarised 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, ie, for a patient multiple occurrences of an AE will only be counted once.

A summary of the most common (frequency of ≥5% in any treatment group) AEs will be presented by PT. AEs (by PT) will be summarised 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 summarised in separate tables.

Furthermore, events of interests such as injection site adverse events, hypersensitivity adverse events, adjudicated MACE+, and malignancies will be summarised separately.

The rate of AEs per person-years at risk, calculated as (number of patients reporting AE)/(total period with patients at risk of AE), will be reported for the on-study, post-treatment and on-treatment periods. The total period at risk for each patient within each study period will follow the definitions specified in Sections 3.1.1. Rates will typically be expressed in terms of events per 100 patient-years.

Separate listings of patients with AEs, SAEs, death due to AE, discontinuations due to AEs, as well as events of interest will be presented.

For the patients who rolled over to MELTEMI study, selective AE and SAE tables during study period will be summarised by treatment group. A listing of adjudicated MACE+ and malignancies will be also provided.

4.2.5.2 Laboratory data

All continuous laboratory parameters will be summarised descriptively by absolute value at each visit by treatment group, together with the corresponding changes from baseline. All parameters will be summarised in SI units, with the exception of blood eosinophil counts which will be summarised in both SI and conventional units. Results which are reported from the central laboratory in conventional units will be converted to SI units for reporting.

Central laboratory reference ranges will be used for the identification of abnormalities, and a shift table will be produced for each laboratory parameter to display low, normal, high, and missing 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 post-baseline will 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 treatment-emergent values outside central laboratory reference ranges will be presented. This data presentation will include all visits for this subset of patients.

Maximum post-baseline bilirubin elevations by maximum post-baseline ALT and AST will be presented, expressed as multiples of ULN. 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 x ULN) and plotted against maximum post-baseline ALT (<3, ≥3 - <5, ≥5-<10, and ≥10 x ULN), 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 ≥3 x ULN, and bilirubin ≥2 x 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.

A summary of shifts from baseline to maximum post-baseline Common Terminology Criteria for Adverse Events (CTCAE) grade will be produced for white blood cell counts and its components using CTCAE version 4.03 (June 14, 2010). The summary of shifts from baseline to maximum grade post-baseline will be produced, with results categorised as no grade, grades 1 to 4. White blood cells included in these summaries are: CD4 + T-cells, neutrophils, lymphocytes, and leukocytes. These will be from the CBC reports and will be done by absolute count. B-cells, CD4 + T-cells, CD8 + T-cells, NK cells are measured by flow cytometry. The cell counts by flow cytometry will also be summarised by shifts tables (categorised for the minimum value as low, normal, and high), based on both percentage cells and absolute cell counts.

For urinalysis data, a shift table will be generated to present changes from baseline to maximum post-baseline value for each parameter and will include patients with both baseline and post-baseline data.

Descriptive statistics and change from baseline at each visit will be presented for IgE by treatment group for adolescent patients.

Any data outside the central laboratory normal reference ranges will be explicitly noted on the listings that are produced.

For the patients who rolled over to MELTEMI study, the following safety lab tables will be presented by treatment group:

- Data for patients who have treatment-emergent values outside central laboratory reference ranges

- Data for patients with ALT or AST ≥3 x ULN, and bilirubin ≥2 x ULN

4.2.5.3 Physical examination

Shift tables (normal, abnormal) of baseline versus EOT will be generated, presenting the assessment for each component of the complete physical examination separately.

Listings of abnormal results will be produced.

4.2.5.4 Electrocardiographs

The Investigator's assessment of the 12-lead ECG (normal or abnormal) will be listed for all patients, along with detailing whether any abnormalities were clinically significant or not.

A shift table will be generated to display normal, abnormal – not clinically significant, abnormal – clinically significant, and not done. The table will be presented for baseline and the last post baseline observation.

4.2.5.5 Vital signs

Descriptive statistics and change from baseline for vital signs data will be presented for each treatment group by visit. Baseline to maximum post-baseline and baseline to minimum post-baseline value shift tables will be generated, as applicable 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 Analysis methods for efficacy variables

All efficacy data from SIROCCO and CALIMA will be summarized by treatment for the patients with predecessor baseline blood eosinophil count ≥300/μL and <300/μL. Efficacy data from ZONDA will be summarised for the FAS regardless of predecessor baseline eosinophil counts.

4.2.6.1 Asthma exacerbation

Annual asthma exacerbation rate

The annual asthma exacerbation rate will be summarised descriptively by the treatment group. On-treatment exacerbation, post-treatment exacerbation, as well as on-study exacerbation rates will be summarised separately. All exacerbation incidences will be listed.

Time to the first asthma exacerbation

Time to the first asthma exacerbation will be described using a Kaplan-Meier plot by the treatment group. Note that this calculation will only be displayed for patients who received placebo in the predecessor studies.

4.2.6.2 Pre- and post-bronchodilator FEV_1 measured at the study centre

Summary statistics of the change from baseline in the pre- and post-bronchodilator FEV_1 will be produced for all post-baseline visits by treatment group.

4.2.6.3 Change of eosinophils by visit

Summary statistics of the change and percent change from baseline in blood eosinophil counts will be provided for all post-baseline visit by treatment group.

4.2.7 Analysis methods for patient-reported outcomes

All PROs data from SIROCCO and CALIMA will be summarized by treatment for the patients with predecessor baseline blood eosinophil count ≥300/μL and <300/μL. PROs data from ZONDA will be summarised for the FAS regardless of predecessor baseline eosinophil counts.

4.2.7.1 ACQ-6

The following summaries will be presented by treatment.

- Descriptive summaries on the mean score values and changes from baseline to each post-baseline visit
- Number and percentage of patients in each asthma control status (well controlled, partly controlled, and not controlled) at each visit
- Number and percentage of patients in each asthma control status (well controlled, partly controlled, and not controlled) at each post-baseline visit by baseline control status
- Number and percentage of patients in each asthma responder status (Improved, No change, Deterioration) from baseline to each post-baseline visit
- Number and percentage of patients in each asthma responder status (Improved, No change, Deterioration) at each post-baseline visit by baseline asthma control status (well controlled, partly controlled, and not controlled)

4.2.7.2 AQLQ(S)+12

The following summaries will be presented by treatment group.

- Overall score and 4 domain scores and change from baseline to each post-baseline visit
- HRQoL responder status (Improved, No change, Deterioration) from baseline to each post-baseline visit

4.2.7.3 WPAI+CIQ

The WPAI+CIQ are collected at baseline and Follow-up visit for adults, and baseline and EOT visit for adolescents. The following summaries will be presented by treatment group.

- Number and percentage of patients employed and attending classes
- Number of work hours missed and the number of class hours missed due to asthma
- Summary scores of absenteeism, presenteeism, absenteeism + presenteeism combined (ie work/class productivity loss),
- Activity impairment

4.2.7.4 EQ-5D-5L

The following summaries will be presented by treatment.

- The distribution of responses for each of the 5 dimensions assessed at each visit
- The shift table presenting baseline and last observation post-baseline value by dimension.
- The change from baseline on the visual analogue scale will also be evaluated by treatment group.

4.2.8 Analysis methods for healthcare resource utilisation

The number and percentage of patients with asthma specific resource utilisation (defined in Section 3.4) will be presented by treatment group. In addition, the annual rate of healthcare resource utilisation will be summarised by treatment group for the patients from SIROCCO and CALIMA with predecessor baseline blood eosinophil count ≥300/μL and <300/μL. Data from ZONDA will be summarised for the FAS regardless of predecessor baseline eosinophil counts.

4.2.9 Analysis methods for pharmacokinetic variables

The PK analyses will be performed at or under the guidance of AstraZeneca Research and Development. Benralizumab serum concentrations will be summarised using descriptive statistics at each visit by treatment group using PK analysis set.

4.2.10 Analysis method for immunogenicity variables

Demographic and patient characteristics including age, sex, race, ethnicity group and BMI subgroups (≤35 kg/m^2, >35 kg/m^2) by ADA status (positive, negative) and ADA positive subgroups (stable persistently positive, nAb positive) will be presented by treatment group.

The number and percentage of patients within each ADA response category defined in Section 3.6 will be summarised by treatment group and ADA status in predecessor studies. Anti-drug antibody response and the corresponding titre will be summarised by visits. In addition, the ADA response will be presented cumulatively by visit. A summary of ADA titres over time by ADA status (ADA positive patients at any visit, ADA newly persistently positive, ADA stable persistent positive, and nAb positive patients) will be provided to monitor titre changes over time.

Newly persistently positive ADA response and ADA stable persistently positive by maximum titer quartile subgroups will be presented by treatment group. A table will be presented to list patients in each treatment group with treatment boosted ADA, and repeated for those patients with maximum titer above the 3rd quartile. For each patient, the table will list the titre at study baseline, maximum titre, and the fold-change that is above the 3rd quartile of the maximum titre from baseline. Similar summaries will be provided for patients with decrease in titre

including the baseline titre, maximum titre, post maximum titre that is decreased >75% from the maximum titre, and its percent reduction from the maximum titre.

The relationship among the following parameters with ADA status (positive, negative) and ADA positive subgroups (ADA titre greater than median of the maximum, newly persistently positive, stable persistently positive, nAb positive) will be presented, unless stated otherwise.

- The annual exacerbation rate during on-study period, on-treatment period and post-treatment period
- Change from baseline in pre-BD FEV_1 for each post-baseline visit
- Adverse events (AEs) and serious adverse events (SAEs) by System Organ Class (SOC) and Preferred Term (PT), AEs and SAEs by preferred term, AEs and SAEs by PT and causality, and hypersensitivity events by PT and causality. These summaries will be conducted during on-treatment period. Additional AE summaries may be added as needed, based on review of the pre-specified summaries
- Absolute blood eosinophil counts (cells/μL) for each visit
- Benralizumab serum concentrations for each visit

The following plots will be provided:

- Percentage of Anti-Drug Antibody positive patients by visit
- Anti-Drug antibody titres by visit
- Median blood eosinophil counts profile by (1) treatment groups and ADA subgroup (ADA positive and ADA negative), and (2) by ADA subgroups (ADA positive, ADA negative, newly persistently ADA positive, stable persistently ADA positive, ADA with titer > median of maximum titre, ADA with titer > 3rd quartile of maximum titre) for each treatment group.

Note data from adolescents will not be plotted for the median blood eosinophil counts.

5. INTERIM ANALYSES

An interim analysis was planned for Japanese patients when the final Japanese patient completes his/her EOT visit. The analysis details were prepared in a separate interim analysis plan.

6. CHANGES OF ANALYSIS FROM PROTOCOL

Not applicable.

7. REFERENCES

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Juniper E.F, Svensson K., Mörk A-K, Elisabeth Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med 2005;99:553–58.

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8. APPENDICES

8.1 Appendix A Analysis visit windows

Table 2 Adjusted visit windows for variables with scheduled visits every 4 weeks (eg, EQ-5D-5L)

Analysis Visit	Scheduled study day	Adjusted visit window
Week 0	1	Study Day≤1
Week 4	29	2 ≤Study Days≤42
Week 8	57	43 ≤Study Days≤70
Week 12	85	71 ≤Study Days≤98
Week 16	113	99 ≤Study Days≤126
Week 20	141	127 ≤Study Days≤154
Week 24	169	155≤Study Days≤182
Week 28	197	183≤Study Days≤ 210
Week 32	225	211≤Study Days≤238
Week 36	253	239≤Study Days≤266
Week 40	281	267≤Study Days≤294
Week 44	309	295≤Study Days≤322
Week 48	337	323≤Study Days≤350
Week 52	365	351≤Study Days≤378
Week 56 (EOT for adults)	393	379≤Study Days≤406
Week 68# (FU for adults)	477	407≤Study Days
Week 60*	421	407≤Study Days≤434
Week 64*	449	435≤Study Days≤462
Week 68*	477	463≤Study Days≤490
Week 72*	505	491≤Study Days≤518
Week 76*	533	519≤Study Days≤546
Week 80*	561	547≤Study Days≤574
Week 84*	589	575≤Study Days≤602
Week 88*	617	603≤Study Days≤630
Week 92*	645	631≤Study Days≤658
Week 96*	673	659≤Study Days≤686
Week 100*	701	687≤Study Days≤714

Table 2 **Adjusted visit windows for variables with scheduled visits every 4 weeks (eg, EQ-5D-5L)**

Analysis Visit	Scheduled study day	Adjusted visit window
Week 104*	729	715≤Study Days≤742
Week 108* (EOT for adolescents)	757	743≤Study Days≤770
Week 120* (FU for adolescents)	841	771≤Study Days

Visit for adults only.
* Visits for adolescents only.

Table 3 **Adjusted visit windows for variables with scheduled every 12 weeks visits (eg, ACQ-6 and AQLQ(S)+12)**

Analysis Visit	Scheduled study day	Adjusted visit window
Week 0	1	Study Day≤1
Week 12	85	2≤Study Days≤126
Week 24	169	127≤Study Days≤210
Week 36	253	211≤Study Days≤294
Week 48	337	295≤Study Days≤378
Week 56# (EOT for adults)	393	379≤Study Days≤434
Week 68# (FU for adults)	477	435≤Study Days
Week 60*	421	379≤Study Days≤462
Week 72*	505	463≤Study Days≤546
Week 84*	589	547≤Study Days≤630
Week 96*	673	631≤Study Days≤714
Week 108* (EOT for adolescents)	757	715≤Study Days≤798
Week 120* (FU for adolescents)	841	799≤Study Days

Visit for adult only.
* Visits for adolescents only.

Table 4a Adjusted visit windows for hematology, cell marker, immunology, microbiology tests

Analysis Visit	Scheduled study day	Adjusted visit window
Week 0	1	Study Day≤1
Week 12	85	2 ≤Study Days≤140
Week 28	197	141≤Study Days≤252
Week 44	309	253≤Study Days≤350
Week 56 (EOT for adults)	393	351≤Study Days≤462
Week 68# (FU for adults)	477	463≤Study Days
Week 76*	533	463≤Study Days≤588
Week 92*	645	589≤Study Days≤700
Week 108* (EOT for adolescents)	757	701≤Study Days≤798
Week 120* (FU for adolescents)	841	799≤Study Days

Visit for adult only.
* Visits for adolescents only.

Table 5b Adjusted visit windows for Chemistry laboratory tests - part 1

Analysis Visit	Scheduled study day	Adjusted visit window
Week 0	1	Study Day≤1
Week 12	85	2 ≤Study Days≤140
Week 28	197	141≤Study Days≤252
Week 44	309	253≤Study Days≤350
Week 56 (EOT for adults)	393	351≤Study Days
Week 56 (For adolescents)	393	351≤Study Days≤462
Week 76*	533	463≤Study Days≤588
Week 92*	645	589≤Study Days≤700
Week 108* (EOT for adolescents)	757	701≤Study Days

Apply for chemistry (excluding tests: Calcium, Chloride, CO2, Glucose, Phosphorus, Potassium, Sodium, Total cholesterol and Uric acid) and Urine tests.
Visit for adult only.
* Visits for adolescents only.

Table 6c Adjusted visit windows for chemistry laboratory tests - part2

Analysis Visit	Scheduled study day	Adjusted visit window
Week 0	1	Study Day≤1
Week 12	85	2 ≤Study Days≤238
Week 56 (EOT for adults)	393	239≤Study Days≤574
Week 108* (EOT for adolescents)	757	575≤Study Days

For chemistry labs: Calcium, Chloride, CO2, Glucose, Phosphorus, Potassium, Sodium, Total cholesterol and Uric acid.
* Visits for adolescents only.

Table 7 Adjusted visit windows for PK (unscheduled samples only) and ADA (including nAb)

Analysis Visit	Scheduled study day	Adjusted visit window
Week 0	1	Study Day≤1
Week 8	57	2 ≤Study Days≤84
Week 16	113	85≤Study Days≤154
Week 28	197	155≤Study Days≤252
Week 44	309	253≤Study Days≤336
Week 52	365	337≤Study Days≤385
Week 56# (EOT for adults)	393	386≤Study Days≤434
Week 68# (FU for adults)	477	435≤Study Days
Week 60*	421	386≤Study Days≤476
Week 76*	533	477≤Study Days≤588
Week 92*	645	589≤Study Days≤700
Week 108* (EOT for adolescents)	757	701≤Study Days≤798
Week 120* (FU for adolescents)	841	799≤Study Days

Visit for adult only.
* Visits for adolescents only.
Note that the Week 52 window has a shorter window range (3 weeks) post scheduled study day due to adjustment for adult group having a scheduled EOT visit 4 weeks later.

Table 8 Adjusted visit windows for Pre-BD spirometry

Analysis Visit	Scheduled study day	Adjusted visit window
Week 0	1	Study Day≤1
Week 16	113	2≤Study Days≤168
Week 32	225	169≤Study Days≤280
Week 48	337	281≤Study Days≤385
Week 56# (EOT for adults)	393	386≤Study Days
Week 64*	449	386≤Study Days≤504
Week 80*	561	505≤Study Days≤616
Week 96*	673	617≤Study Days≤728
Week 108* (EOT for adolescents)	757	729≤Study Days

Visit for adult only.
* Visits for adolescents only.
Note that Week 48 window has shorter window range (7 weeks) post scheduled study day due to adjustment for adult group having a scheduled EOT visit 8 weeks later.

8.2 Appendix B Partial and missing date imputation

Dates missing the day or both the day and month of the year will adhere to the following conventions in order to classify on-treatment AEs and to classify prior/concomitant medications.

For AE start date or medication start date:

Partial missing start date:

- Missing day of the month: 1st day of the month
- Missing day and month: Jan. 1st of the year

Completely missing start date:

- If AE end date or medication end date is missing, then impute the start date as the first visit date (Visit 1)
- If AE end date or medication end date is before the first visit date (Visit 1), then impute the start date as the end date
- If AE end date or medication end date is after the first visit date (Visit 1), then impute the start date as the first visit date (Visit 1)
- Otherwise, impute the start date as the first visit date (Visit 1)

For AE end date or medication end date:

Partial missing end date:

- Missing day of the month: Last day of the month
- Missing day and month: Dec. 31st of the year
- Further adjust by selecting the earlier of the imputed date, death date, and post-treatment end date*.

Post-treatment end date* is defined as the last visit date or the discontinuation of study day, whichever is later.

Completely missing end date:

- AE end date will be left as missing
- Medication end date will be imputed as earlier of death date and post-treatment end date (as defined above).