**Statistical Analysis Plan**

| | |
|---|---|
| Study Code | D3250C00025 |
| Edition Number | v2.0 |
| Date | 18 October 2022 |

# An Open-label Study to Evaluate the Pharmacokinetics and Pharmacodynamics and Long-term Safety of Benralizumab Administered Subcutaneously in Children with Severe Eosinophilic Asthma

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| Abbreviation or special term | Explanation |
|---|---|
| ACQ-IA | Interviewer-administered asthma control questionnaire |
| ADA | Anti-drug antibodies |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| Amean | Arithmetic mean |
| AAER | Annualized asthma exacerbation rate |
| AST | Aspartate aminotransferase |
| ATC | Anatomical therapeutic chemical |
| ATS | American thoracic society |
| AUC | Area under concentration time curve from time zero extrapolated to infinity |
| $AUC_{(0-28)}$ | Area under the concentration time curve from time zero to 28 days after dosing |
| BMI | Body mass index |
| CIs | Confidence intervals |
| CL/F | Apparent clearance for parent drug estimated as dose divided by AUC |
| $C_{max}$ | Observed maximum benralizumab concentration |
| CGIC | Clinician global impression of change |
| CRF | Case report form (electronic) |
| CSP | Clinical study protocol |
| CSR | Clinical study report |
| CSRHLD | Corporate clinical study report or higher level document |
| CTMS | Clinical trial management system |
| CV | Coefficient of variation |
| CV% | Coefficient of variation |
| DAE | Adverse event leading to discontinuation of investigational product |
| DBL | Database lock |
| DBP | Diastolic blood pressure |
| DSMB | Drug safety monitoring board |
| DXD | Early discontinuation visit |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| ED | Emergency department |
| EOT | End of treatment |
| ERS | European respiratory society |
| FEV1 | Forced expiratory volume in 1 second |

| Abbreviation or special term | Explanation |
|---|---|
| gCV% | Geometric coefficient of variation |
| GMean | Geometric mean |
| gSD | Geometric standard deviation |
| ICS | Inhaled corticosteroids |
| IP | Investigational product |
| Kg | Kilograms |
| LLOQ | Lower limit of quantification |
| M | Metres |
| Max | Maximum |
| MedDRA | Medical dictionary for regulatory activities |
| Min | Minimum |
| N | Number of patients |
| nAb | Neutralizing antibodies |
| NC | Not calculated |
| NCA | Non-compartmental analysis |
| NQ | Not quantifiable |
| NR | Not reportable |
| NS | No sample |
| OCS | Oral corticosteroids |
| PD | Pharmacodynamic(s) |
| PE | Physical examination |
| PGIC-IA | Interviewer administered patient global impression of change |
| PopPK | Population pharmacokinetics |
| PK | Pharmacokinetic(s) |
| PT | Preferred term |
| Rsq | R-squared (coefficient of determination) |
| SABA | Short-acting β2 agonists |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SBP | Systolic blood pressure |
| SC | Subcutaneous(ly) |
| SD | Standard deviation |
| SOC | System organ class |
| SRC | Safety review committee |
| $t_{1/2}$ | Terminal half-life |
| TBL | Total bilirubin |

| Abbreviation or special term | Explanation |
|---|---|
| $T_{max}$ | Time to reach cmax |
| ULN | Upper limit of normal |
| λz | Terminal rate constant |

# AMENDMENT HISTORY

| Date | Brief description of change |
|---|---|
| 14-Oct-2019 | SAP v1.0 |
| 18-Oct-2022 | 3.1.4. Added further rules on how to handle the overlap in the week 1 and 2 visit windows schedule assessments |
| 18-Oct-2022 | 3.3.2 Added nAb will be tested for all ADA-positive samples |
| | 4.2.8 Added that the nAb results will be reported as positive or negative. |
| | 4.2.8 Added the following summary categories for nAb:<br>- nAb positive at baseline and/or post-baseline (nAb prevalence)<br>- Treatment-induced nAb positive (nAb incidence)<br>4.2.8 Added that for ADA summaries at a single time point (e.g. baseline ADA or by visit) the corresponding titre summary will be based on the titre of the positive sample for that particular visit. |
| | 1 updated CSP version to v5.0 dated 22 February 2022 |
| | 4.2.5.1 and 4.2.5.2 Updated to present PK concentration and parameter descriptive statistics to 2 decimals |
| 18-Oct-2022 | 4.2.5.1 updated that <LLOQ concentrations will be set to zero both at pre-dose and after pre-dose timepoints |
| | 4.2.5.2 updated that All <LLOQ values will be substituted with a value of zero for descriptive statistics<br>Updated that <LLOQ samples will be plotted as LLOQ |

# 1 STUDY DETAILS

This is the statistical analysis plan (SAP) for study D3250C00025. The SAP is based on version 5.0 of the clinical study protocol (CSP) dated 22 February 2022. The SAP expands on the statistical analyses specified in the CSP; any changes with regards to what is already specified in the CSP will be described in Section 6 of this document.

## 1.1 Study objectives

### 1.1.1 Primary objectives

| **Primary Objective:** | **Endpoints/variables:** |
|---|---|
| To evaluate the pharmacokinetics (PK) of benralizumab administered subcutaneously (SC) in children from 6 to 11 years of age with severe eosinophilic asthma | • Clearance<br>• Area under concentration time curve to Day 28 ($AUC_{0-28}$)<br>• Maximum serum concentration ($C_{max}$)<br>• Terminal phase elimination half-life ($t_{1/2}$)<br>• Time to reach $C_{max}$ ($T_{max}$) |
| To evaluate the pharmacodynamics (PD) of benralizumab administered SC in children from 6 to 11 years of age with severe eosinophilic asthma | Change from baseline in peripheral blood eosinophil count at Weeks 4, 8, 12 and 16 (Part A), and Weeks 24 and 48 (Part B). |

### 1.1.2 Secondary objectives

| **Secondary Objective:** | **Endpoints/variables:** |
|---|---|
| To characterize the PK of benralizumab | Body weight-adjusted clearance. |
| To evaluate the immunogenicity of benralizumab | Presence of anti-benralizumab antibodies. |
| To evaluate the effect of benralizumab on pulmonary function | Change from baseline in pre-dose (when applicable), pre-bronchodilator, forced expiratory volume in 1 second ($FEV_1$) measured at Weeks 4, 8, 12, and 16 (Part A), and Weeks 24 and 48 (Part B). |

| | |
|---|---|
| To assess the effect of benralizumab on asthma symptoms and other asthma control metrics | Change from baseline in Interviewer-administered Asthma Control Questionnaire (ACQ-IA) score, measured at screening and Weeks 1, 2, 4, 8, 12, and 16 (Part A), and Weeks 24, 32, 40 and 48, and at follow-up (Part B).<br>Interviewer-administered Patient Global Impression of Change (PGIC-IA), measured at Week 16 (Part A), and Weeks 24, 32 and 48 (Part B).<br>Clinician Global Impression of Change (CGIC), measured at Week 16 (Part A), and Weeks 24, 32 and 48 (Part B) and at the DXD/WD visit. |

### 1.1.3 Safety objectives

| **Safety Objective:** | **Endpoints/variables:** |
|---|---|
| To assess the safety and tolerability of benralizumab | Adverse events (AEs)<br>Vital signs<br>Collection of clinical chemistry/haematology parameters and urinalysis |

### 1.1.4 Exploratory objective

| **Exploratory Objective:** | **Endpoints/variables:** |
|---|---|
| To evaluate exacerbations experienced during treatment period | Annualized asthma exacerbation rate (AAER) |

## 1.2 Study design

This is an open-label, phase 3, parallel group study designed to evaluate the PK and PD, and long-term safety of benralizumab administered SC in 30 children from 6 to 11 years of age in US and Japan with severe eosinophilic asthma. Up to an additional 3 Japanese patients aged 12 to 14 years will be enrolled.

Patients aged 6 to 11 years will be stratified by body weight at screening (< 35 kg / ≥ 35 kg). Patients with a body weight < 35 kg at screening will receive the following regimen of benralizumab: [redacted] mg administered by SC injection at Day 0 and Weeks 4, 8, and 16 (Part A), followed by [redacted] mg at Weeks 24, 32, and 40 (Part B). Patients with a body weight ≥ 35 kg at screening will receive the following regimen of benralizumab: [redacted] mg administered by SC injection at Day 0 and Weeks 4, 8, and 16 (Part A), followed by [redacted] mg at Weeks 24, 32, and

40 (Part B). Japanese patients aged 12 to 14 years will receive [redacted] mg regardless of their body weight, and their visit schedules will be the same as patients aged 6 to 11 years throughout the study.

The study will be conducted in 2 parts, Part A and Part B. Part A will consist of 16 weeks of treatment to evaluate the PK/PD (see Table 1 below for PK assessments timepoints) and safety of benralizumab. Part B will consist of 32 weeks of continued treatment to evaluate the safety of benralizumab. All study data will be summarized together, not separately by study part.

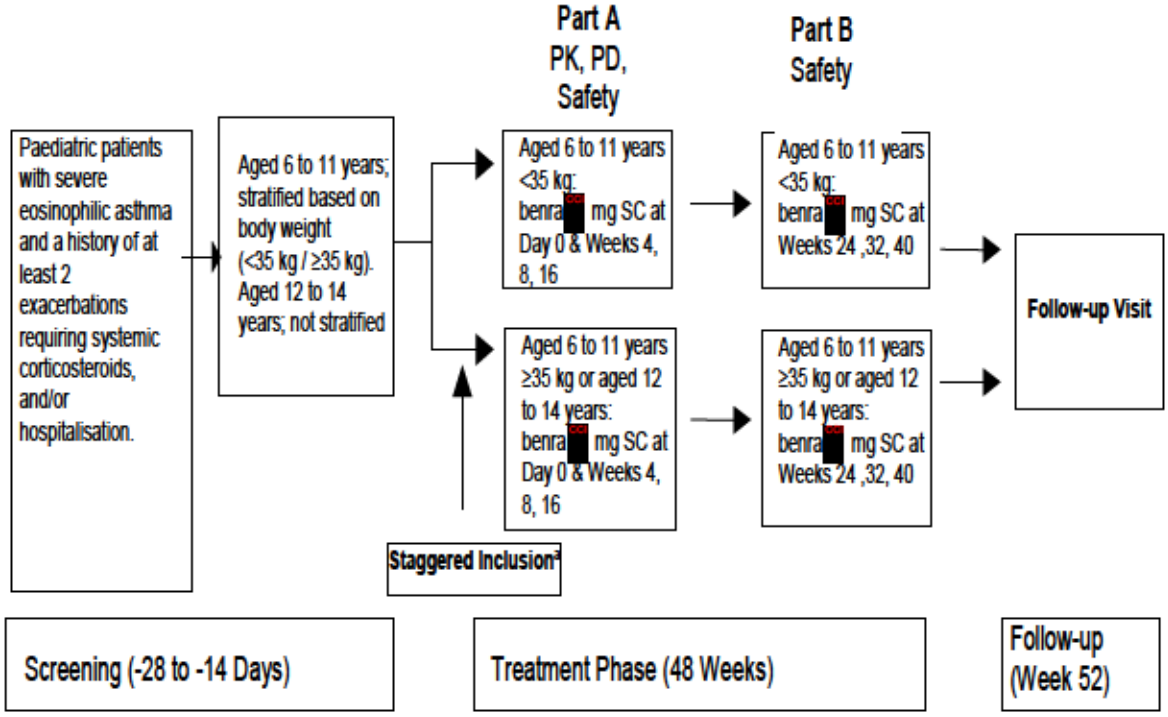
After initial enrolment and confirmation of entry criteria, patients will proceed to a screening period of up to 28 days to allow adequate time for the eligibility criteria to be evaluated. The screening period may be extended if necessary after discussion with the AstraZeneca Study Physician. Patients who meet the eligibility criteria will enter the 48-week treatment period.

Staggered inclusion will occur for patients aged 6 to 11 years in which 4 patients with a body weight < 35 kg and 4 patients with a body weight ≥ 35 kg will complete Part A then progress directly into Part B. Each treatment/weight group will be assessed separately by the Safety Review Committee (SRC) in accordance with the charter, so the treatment/weight groups can progress independently into Part B. After evaluation of all available PK and safety data from the initial 4 evaluable patients in each treatment/weight group, the remaining enrolled patients will enter the treatment phase as in section 1.2 of the CSP. Patients aged 12 to 14 years in Japan may be enrolled in parallel with the staggered inclusion for the first 8 patients aged 6 to 11 years.

An overview of the general study design is shown in Figure 1. The schedule of activities is presented in Table 1 of the CSP.

**Figure 1 Study Design**

May be its my screen but can we make image a little better




[a] After he first 4 patients in each weight group have completed Part A (after evaluation of the PK and safety from Part A in hese patients by the safety review committee), he remaining patients within the weight group will enter the treatment phase.

## 1.3 Number of subjects

The sample size is not based on any formal sample size calculation. A sample size of 30 evaluable patients aged 6 to 11 years will be treated with benralizumab across the 2 combined weight strata, with a minimum of 8 evaluable patients in each weight stratum, was chosen to provide sufficient data across the dosing and weight categories for PK parameter estimations using non-compartmental analysis (NCA). In addition, a cohort of up to 3 Japanese patients aged 12 to 14 years will be enrolled.

# 2 ANALYSIS SETS

## 2.1 Definition of analysis sets

All data (including PD) except for PK data will be analysed using the safety analysis set. PK data will be analysed using the NCA and PK analysis set.

### 2.1.1 Pharmacokinetic (PK) analysis set

This analysis set comprises all patients who received at least 1 dose of benralizumab and from whom PK blood samples are not assumed to be affected by factors such as protocol violations

(Section 2.2 ) and who had at least one quantifiable serum PK observation post first investigational product (IP) dose.

### 2.1.2 Non-compartmental analysis (NCA) set

This analysis set comprises all patients who received the first dose of benralizumab and from whom PK blood samples are not assumed to be affected by factors such as protocol violations (Section 2.2) and who had at least 3 quantifiable serum PK observations post-dose on Days 1, 7, 14, and 28.

### 2.1.3 Safety analysis set

This analysis set comprises all patients who receive at least one dose of benralizumab. All safety and PD analyses will be based on safety analysis set.

## 2.2 Violations and deviations

Important protocol deviations (IPDs) are considered any protocol deviation that may greatly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being. They may include (but not be limited to):

- Patients who were assigned to a study treatment even though they did not meet key entry criteria
- Patients who developed withdrawal criteria during the study but were not withdrawn
- Patients who received the wrong treatment or an incorrect dose
- Patients who received a restricted or prohibited concomitant treatment.

Only IPDs will be listed and tabulated in the clinical study report (CSR). All the IPDs will be identified and documented by the study team prior to database lock.

IQVIA will prepare a separate protocol deviation Analysis Set Plan document to facilitate the identification of all IPDs to be documented prior to DBL. All the identified IPDs will be collected via the Clinical Trial Management System (CTMS) log. Any protocol deviation which are not defined as important will not be reported or discussed in the CSR. Subjects excluded from the PK set will be listed.

# 3 PRIMARY AND SECONDARY VARIABLES

## 3.1 General Principles

### 3.1.1 Baseline definitions

In general, the last non-missing measurement prior to the first dose of study treatment will serve as the baseline measurement. If there is no value prior to first dose of study treatment,

then the baseline value will not be imputed, and will be set to missing.

The screening clinical chemistry and haematology samples collected at Visit 1 (Day -28 to Day -14) will be used as baseline. However, if Visit 2 (Day 0) is done > 28 days after Visit 1, then the corresponding clinical chemistry and haematology samples collected at Visit 2 and prior to the first dose of study treatment, will be used as baseline.

The PK sample collected on the same day but at a time prior to the first dose of study treatment (Visit 2) will be included in the baseline definition. If there is no PK sample value prior to the first dose of study treatment, then the baseline value will not be imputed and will be set to missing. If the PK sample prior to the first IP is below the lower limit of quantification (LLOQ) then the baseline will be set to zero.

For physical examination and vital signs, baseline will be defined as the latest non-missing assessment prior to first dose at Visit 2. If no time is recorded for an assessment, and the assessment takes place at Visit 2, this will be assumed to be a pre-dose assessment.

### 3.1.2 Study day

Whenever data are summarised over time, study day will be calculated based on the actual assessment date, and is defined as:

*Study day = Date of assessment – date of first dose of study treatment.*

*Study day 0 is defined as the date of the first dose of study treatment.*

### 3.1.3 Study Periods

The following study periods are defined for analysis purposes:

- Pre-Treatment (Screening period): starting on the date of the first study procedure and ending one day prior to date assigned study treatment (for subjects assigned study treatment) or on the date of the last study procedure (for screening failures). If any subject is re-screened, the latest available screening will be used for this purpose.
- On-treatment period: defined as starting between day of first dose of study treatment and scheduled end of treatment (EOT) visit or early discontinuation (DXD) visit for those patients who prematurely discontinue study treatment, inclusive. If both EOT and DXD visits are missing then the upper limit of the on-treatment period is defined as the day of last dose of study treatment + 56 days. If the upper limit is after the end of on-study period, then the upper limit is end of on-study period
- On-study period: starting on the date of first dose of IP and ending on the study completion or withdrawal date

### 3.1.4 Visit windows

Table 1 of the CSP detailed the time points and visit window for the study assessments. All summaries which are presented by time point will use a visit window to classify the data record, which is derived from the assessment date relative to the reference start date (date if first dose of study treatment). This approach allows appropriate classification of visits which may have occurred significantly earlier or later than the protocol assessment schedule, as well as the use of data captured at visits which have no fixed timing.
Inclusion within the visit window should be based on the actual date and not the intended nominal date of the visit.

Any data collected at unscheduled or repeat visits will be listed, and will be included in baseline definitions (Section 3.1.1), and in any definitions of maximum value, minimum value or last value within the relevant study period.
Data collected at unscheduled or repeat visits will also be included in visit windows, and therefore may be included in summaries by visit. In the case of a missing value at a scheduled visit, which is then followed by a non-missing value at an unscheduled or repeat assessment within the same visit window, the non-missing value at the unscheduled/repeat assessment will replace the missing value at the scheduled visit.
If a subject has more than one non-missing value within the same visit window, the following rules will apply:

- The non-missing value closest to the target day will be selected for analysis at that visit
- If two non-missing values are the same distance from the target day, the earlier of the two values will be selected for analysis at that visit
- If two non-missing values are recorded on the same day and have a different assessment time associated with both of them, the value with the earliest assessment time will be selected for analysis at that visit.
- If two non-missing values are recorded on the same day and have no assessment time associated with at least one of them, or the same assessment time associated with both of them, the average of the two values will be selected for analysis at that visit.
  If a subject has no value within a particular visit window, then the subject will have a missing value at that visit in summaries.

Due to the overlap in the week 1 and 2 visit window schedule of assessments the following rules will apply subject to the above rules described in this section above:

- If Week 1 timepoint has only one record within analysis days 3-10 then this will be assigned to the Week 1 analysis visit, as described above.

- If Week 1 timepoint has multiple records (with evaluable results) within analysis days 3-10 then:

a) if the latest record (using time) has analysis day = 10, then this record will be considered for selection within the Week 2 analysis visit, subject to the existing rules described in this section above, and
b) all earlier records within analysis days 3-10 will be considered for selection within the Week 1 analysis visit, subject to the existing rules described in this section above

For PK measures, if there are 2 samples from the same date, the value from the scheduled visit will be used. If the scheduled visit is missing, then the record from the unscheduled visit will be used. If the sampling times are different, both PK samples will be transferred to database and used in population PK (PopPK) analysis.

Blood samples for determination of PK parameters in serum will be taken at timelines as specified in Table 1 of CSP. Blood samples taken at visits when a dose of benralizumab is administered must be taken pre-dose. Blood samples taken at visits when no benralizumab dose is administered may be taken at any time during the day of the visit. The time and date of blood samples taken for PK analysis must be recorded on the eCRF

For PK serum concentration-time data, any post-dose samples taken outside the window from scheduled time point will be excluded from the summary tables and figures.

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.

Visit windows following baseline will be constructed in such a way that the upper limit of the interval falls halfway between the two visits (the lower limit of the first post-baseline visit will be study day 1). If an even number of days exists between two consecutive visits then the upper limit will be taken as the midpoint value minus 1 day. Visit windows are constructed so that every observation collected can be allocated to a visit (Table 1). No visit windows will be defined for screening visits.

**Table 1: Visit windows for assessments**

| Timepoint Target | Day | Visit Window | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | AE, CM, Asthma Exac and VS | PK sampling | ACQ-IA | Clinical chemistry, Haematology, Serology, Urinalysis, and FEV1 | Brief PE | ADA, | PGIC-IA and CGIC | Height and Weight | ECG |
| Baseline Week 0 day 0 | 0 | See section 3.1.1 for baseline definitions | | | | | | | | |
| Week 0 day 1 | 1 | 1-2 | 1-2 | | | | | | | |
| Week 1 | 7 | 3-10 | 3-10 | 1-10 | | | | | | |
| Week 2 | 14 | 11-20 | 11-20 | 11-20 | | | | | | |
| Week 4 | 28 | 21-41 | 21-41 | 21-41 | 1-41 | 1-41 | | | | |
| Week 8 | 56 | 42-69 | 42-69 | 42-69 | 42-69 | 42-69 | 1-83 | | | |
| Week 12 | 84 | 70-97 | 70-97 | 70-97 | 70-97 | 70-97 | | | | |
| Week 16 | 112 | 98-139 | 98-139 | 98-139 | 98-139 | 98-139 | 84-139 | 1-139 | 1-139 | 1-251 |
| Week 24 | 168 | 140-195 | 140-195 | 140-195 | 140-251 | 140-195 | 140-195 | 140-195 | 140-251 | |
| Week 32 | 224 | 196-251 | | 196-251 | | 196-251 | | 196-279 | | |
| Week 40 | 280 | 252-307 | | 252-307 | | ≥252 | | | | |
| Week 48 | 336 | 308-348 | 308-348 | 308-348 | ≥252 | | 308-348 | ≥280 | ≥252 | ≥252 |
| Follow-up (Week 52) | 362 | ≥ 349 | | ≥349 | | | | | | |

Abbreviations: ACQ-IA interviewer-administered asthma control questionnaire, ADA anti-drug antibody(ies), PGIC-IA interviewer administered patient global impression of change, PK pharmacokinetics, VS vital signs, AE adverse events, CM concomitant medication, ACQ-IA interviewer-administered asthma control questionnaire, Exac Asthma exacerbation, PE Physical examination, ECG electrocardiogram.

### 3.1.5 Handling of missing data

There will be no imputation for safety data.

Missing dates are not anticipated, except for concomitant medication dates. Medications with missing partial start date or end date such that it is not possible to classify as prior or concomitant will be considered as concomitant.

Details on the algorithm for handling medication and adverse event partial missing dates can be found in Appendix I .

Details on the handling of missing PK data can be found in section 4.2.5.1

## 3.2 Primary outcome variables

### 3.2.1 Primary PK variables

The primary PK outcome measure is the evaluation of benralizumab administered SC in children with severe eosinophilic asthma by assessing benralizumab concentrations versus time profile and the PK parameters derived.

The PK parameters to be determined are:

- Clearance
- $AUC_{0-28}$
- $C_{max}$
- $t_{1/2}$
- $T_{max}$

### 3.2.2 Primary PD variable

#### 3.2.2.1 Blood eosinophil levels

Blood samples for determination of eosinophil count levels (haematology) will be taken at the time points detailed in Table 1 of the CSP and will be assessed in a central laboratory. Blood eosinophil counts levels will be evaluated at Screening (Visit 1, Day -28 to -14) and the change from baseline to Weeks 4, 8, 12 and 16 (Part A), and Weeks 24 and 48 (Part B) is the primary PD variable to evaluate the PD of benralizumab administered SC in children with severe eosinophilic asthma.

## 3.3 Secondary outcome variables

### 3.3.1 Body weight-adjusted clearance

Body weight-adjusted clearance parameter is one of the secondary variables that will be used to further assess the PK of benralizumab.

### 3.3.2 Immunogenicity Variable

Serum samples for the determination of ADA in serum will be taken prior to IP administration at the study visits indicated in CSP Table 1. Serum samples for ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titre). 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 antibody (nAb) will be tested in all ADA-positive samples using a ligand-binding assay. The nAb results will be reported as positive or negative. Details of the analytical methods used will be described in a separate validation report.

### 3.3.3 Pre-bronchodilator forced expiratory volume in first second (pre-BD FEV1)

Change from baseline in pre-dose (when applicable), pre-bronchodilator, $FEV_1$ measured at Weeks 4, 8, 12, and 16 (Part A), and Weeks 24 and 48 (Part B) will be used as a secondary variable to evaluate the effect of benralizumab on pulmonary function.

The pre-BD $FEV_1$ will be measured by spirometry at the study centre.

Multiple forced expiratory efforts (at least 3 but no more than 8) will be performed for each centre spirometry session and the 2 best efforts that meet the American Thoracic Society (ATS)/ European Respiratory Society (ERS) acceptability and reproducibility criteria will be recorded in the eCRF. The best efforts will be based on the highest $FEV_1$. The absolute measurement (for $FEV_1$), and the percentage of predicted normal value will be recorded using the local spirometer at the site with predicted values derived from a reference value.

### 3.3.4 Interviewer-administered asthma control questionnaire (ACQ-IA)

The change from baseline in ACQ-IA score, obtained at all post-baseline visits as indicated on Table 1 of the CSP will be used as a secondary variable to assess the effect of benralizumab on asthma symptoms and other asthma control metrics.

The ACQ-IA is a 6-item assessment comprised of 6 patient-reported items: 5 symptoms (night-time waking, symptoms on waking, activity limitation, shortness of breath, and wheezing) and use of short-acting β2 agonist (SABA) over the previous week using a 7-point scale (0 = no impairment; 6 = maximum impairment). The ACQ-IA score is calculated by taking the mean of the 6 equally weighted items.

The ACQ score range is 0 (well controlled) to 6 (extremely poorly controlled).

The estimated threshold indicating poor asthma control is an ACQ-IA score ≥ 1.25 in patients ages 6 to 17 years (Nguyen et al 2014, Juniper et al 2006, Juniper et al 2005). The estimated minimal clinically important difference is 0.5 (Juniper et al 2010)

The questionnaire will be completed at the study centre during every study visit except Visit 3 on Day 1 as indicated in Table 1 of CSP.

Other variables based on ACQ-IA to be reported at each time point include:

1. ACQ-IA responder (Yes=1/No=0):

- Responder: Change from baseline ACQ-IA score ≤ -0.5
- Non-responder: Change from baseline ACQ-IA score > -0.5.

2. ACQ-IA response (Improved/No Change/Deterioration):

- Improvement: Change from baseline ACQ-IA score ≤ -0.5
- No change: -0.5 < Change from baseline ACQ-IA score < 0.5
- Deterioration: Change from baseline ACQ-IA score ≥ 0.5

3. Subject's asthma control as measured by ACQ-IA score:

- Well controlled: ACQ-IA score ≤ 0.75
- Partly controlled: 0.75 < ACQ-IA score < 1.25
- Not well controlled: ACQ-IA score ≥ 1.25.

### 3.3.5 Global Impression of Change

Clinician global impression of change (CGIC) and interviewer-administered patient global impression of change (PGIC-IA) instruments are used for an overall evaluation of response to treatment, conducted separately by the Investigator and by the patient administered by trained individuals, using a 7-point scale: 1=Very Much Improved; 2=Much Improved; 3=Minimally Improved; 4=No Change; 5=Minimally Worse; 6=Much Worse; and 7=Very Much Worse.

The Investigator (clinician) and the patient will be asked to rate the degree of change in the overall asthma status compared to the start of study treatment visit. The questionnaire will be completed by the patients and clinicians at Week 16 (Part A), and Weeks 24, 32, and 48 (Part B).

Patients will also be categorized according to the following responses post-baseline, separately for CGIC and PGIC:

- Very much improved, much improved, minimally improved → 'Improved'
- Very much improved, much improved → 'Much improved'
- Very much improved → 'Very much improved'

Agreement between CGIC and PGIC-IA will be assessed at each visit, where agreement is achieved when both the patient and clinician provide the same response (e.g., if both the patient and clinician indicate a response of 1 (very much improved) at a particular visit, agreement is achieved for that visit). Agreement will also be assessed for categorized responses at each visit.

An interviewer administered PGIC (PGIC-IA) will be used in this study to help the child understand what is being asked. The PGIC-IA will be administered by trained individuals according to standardized instructions to help the child understand the question and response options. Help from caregivers/parents is sought only as a last resort. The PGIC-IA will be completed at the study centre at Visits 9, 10, 11 and 13 (CSP table 1).

### 3.3.6 Safety outcome variables

The following safety data will be collected: reported AEs (including SAEs), haematology, clinical chemistry, urinalysis, 12-lead electrocardiogram (ECG), physical examination and vital signs.

All safety measurements will use all available data for analyses, including data from unscheduled visits and repeated measurements.

Change from baseline to each post-treatment time point where scheduled assessments were made will be calculated for relevant measurements. AEs will be summarised by means of descriptive statistics and qualitative summaries.

No safety data will be imputed. The handling of partial/missing dates for AEs is detailed in Appendix I .

#### 3.3.6.1 Adverse events (AEs)

Adverse events (including SAEs) 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 categorized according to their onset date into the following study periods:

- AEs in the on-study period, defined as:

  *date of first dose of IP ≤ AE onset date ≤ study completion or withdrawal date.*

- *AEs in the pre-treatment period (screening period) are defined as those with onset before the day of first dose of study treatment.* If any subject is re-screened, the latest available screening will be used for this purpose

If the AE has a completely missing (and unresolvable) onset date, then the AE will be assumed to be treatment-emergent, unless the end date indicates unambiguously that the AE resolved before treatment started. If the AE has a partially missing (and unresolvable) onset date, then the AE will also be assumed to be treatment-emergent, unless either the end date

indicates unambiguously that the AE resolved before treatment started, or the partial onset date is in the month/year prior to start of treatment.

#### 3.3.6.2 Laboratory variables

Samples for determination of clinical chemistry, haematology, virology and urinalysis parameters will be taken at the times detailed in the Table 1 of the CSP and assessed in a central laboratory. The parameters outlined in Table 8 of the CSP will be collected.

Changes in haematology and clinical chemistry variables between baseline and each post-baseline assessment will be calculated. The change from baseline is defined as the post-baseline value minus the baseline value. There will be no imputation for missing values. 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.

The investigator will assess the available lab results with regards to clinically relevant abnormalities. 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 that will be used will follow the most recent version of the AZ standard reference ranges and unit conversion external data. All absolute values falling outside the AZ provided reference ranges will be flagged in the listings. These classifications will also be used for shift tables.

Urinalysis data will be categorised as negative (0), positive (+), or strongly positive (++, +++, or >+++) at each timepoint.
For the purpose of shift tables, baseline will be defined as specified in section 3.1.1.
Maximum or minimum value post-baseline will be calculated over the entire post-baseline period.
For the liver function tests: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase 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,

i.e. 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 ≥ 2x ULN

#### 3.3.6.3 Vital signs

Vital signs such as systolic blood pressure, diastolic blood pressure, pulse rate, weight, height, Body mass index (BMI) and body temperature will be assessed. The assessment will be conducted while sitting with a completely automated device with a calibrated manometer using an appropriate pediatric cuff and in accordance with the visit schedule provided in Table 1 of the CSP.

Changes in the vital signs variables between baseline and each subsequent scheduled assessment will be calculated. Absolute values will be compared to the given reference ranges (Table 2 and Table 3) and classified as low (below range), normal (within range or on limits) or high (above range). All values (absolute) falling outside the reference ranges will be flagged in the listings.

**Table 2: Vital signs reference ranges for age 6 -11 years**

| Parameter | Standard Units | Lower Limit | Upper Limit |
|---|---|---|---|
| Diastolic Blood Pressure | mmHg | 57 | 80 |
| Systolic Blood Pressure | mmHg | 97 | 120 |
| Pulse Rate | Beats/min | 70 | 110 |
| Body Temperature | Celsius | 35.5 | 37.5 |
| Weight | kg | 15 | NA |
| Height | cm | NA | NA |

**Table 3: Vital signs reference ranges for age 12 -14 years**

| Parameter | Standard Units | Lower Limit | Upper Limit |
|---|---|---|---|
| Diastolic Blood Pressure | mmHg | 64 | 83 |
| Systolic Blood Pressure | mmHg | 110 | 131 |
| Pulse Rate | Beats/min | 55 | 105 |
| Body Temperature | Celsius | 35.5 | 37.5 |
| Weight | kg | 15 | NA |
| Height | cm | NA | NA |

BMI will be calculated from the height and weight as follows:

BMI ($kg/m^2$) = weight (kg) / (height (m)) $^2$

#### 3.3.6.4 ECG

A 12-lead ECG will be obtained as outlined in Table 1 of the CSP using the site's own ECG machines after the patient has rested in the supine position for at least 10 minutes.

The outcome of the investigator's overall ECG evaluation will be recorded as normal/abnormal in the CRF and with any abnormalities recorded as not clinically significant or clinically significant. Changes from baseline in continuous 12-lead ECG variables will be calculated at relevant visits as specified in Table 1.

#### 3.3.6.5 Physical examination

A complete physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities), and neurological systems.

A brief physical examination will include the following: general appearance, respiratory, cardiovascular, and abdomen systems.

Complete and brief physical examinations will be performed at time points specified in CSP Table 1. Baseline data will be collected prior to first dose and any new finding(s) or aggravated existing finding(s), judged as clinically significant by the investigator or designee, will be reported as an AE.

### 3.3.7 Exploratory outcome variable

#### 3.3.7.1 Annualised asthma exacerbation rate

For this study 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 emergency department (ED) visit requiring use of systemic corticosteroids and/or an in-patient hospitalization due to asthma.

The start of an exacerbation is defined as the start date of systemic corticosteroids or of an increase in oral steroid dose, date of ED requiring systemic corticosteroids, or date of hospital admission due to asthma, whichever occurs earlier. The end date of an exacerbation is defined as the last date of systemic corticosteroids or of an increase in oral steroid dose, date of ED, or date of hospital discharge, whichever occurs later.

If less than 7 days have elapsed since the end date of an asthma exacerbation and the start date of a new asthma exacerbation, the second event will be considered a relapse of the prior asthma exacerbation and will be recorded in the eCRF as the same exacerbation event. Asthma exacerbation information will be collected with a recall period of 'since the last scheduled visit'.

Information collected for asthma exacerbation will include in-patient hospitalizations, number of days in the hospital, and ED visits collected by the investigator/authorized delegate at each visit (as shown in table 1 of the CSP) and recorded in the eCRF. Asthma-related hospitalization and ED visit information will be collected with a recall period of 'since the last scheduled visit'.

Time to first asthma exacerbation is the time from first IP dose to the first asthma exacerbation and is derived as follows:

*Start date of first asthma exacerbation − Date of first IP 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 EOT visit (Week 48) for patients who complete study treatment. Patients who discontinue study treatment or are lost to follow-up before EOT visit will be censored at the last visit date after which an exacerbation could not be assessed.

The annualised asthma exacerbation rate (AAER) is an exploratory variable and will be calculated using the time-based risk approach as:

*AAER = 365.25*Total number of exacerbations /Total duration of at risk on-treatment period (days).*

# 4 ANALYSIS METHODS

## 4.1 General principles

The statistical analyses will be performed by IQVIA under the direction of the Biostatistics Group, AstraZeneca. The data analyses will be conducted using SAS® System (SAS Institute Inc., Cary, NC), Version 9.4 or higher. All analyses will be performed according to AstraZeneca standard operating procedures unless otherwise stated.

No formal statistical hypotheses will be tested in this study.

For PK related data summaries for patients aged 6 to 11 years will be presented in tabular format by treatment/weight groups (benralizumab [CCI] mg in patients < 35 kg at screening and benralizumab [CCI] mg in patients ≥ 35 kg at screening). Up to 3 Japanese patients aged 12 to 14 years will be enrolled and listed for PK related data. Additional summaries for non-PK related data for patients aged 6 to 11 years, and aged 6 to 14 years overall will be provided.

Descriptive statistics on continuous data will be summarised by treatment/weight group including number of patients with available data (n), arithmetic mean (Amean), standard deviation (SD), median, minimum value and maximum value (unless stated otherwise) for non-PK data. Geometric mean (Gmean) and geometric coefficient of variation (gCV%) will also be produced for log-transformed data including PK concentration data. The Amean, median, Gmean and gCV% will be presented with one more decimal place than the raw data. The SD will be presented with two more decimal places than the raw data. In general, minimum and maximum values will have the same number of decimal places as the raw data except specified otherwise (see section 4.2.5.1 for PK parameters).

Gmean is calculated as $\exp[\mu]$, where $\mu$ is the mean of the data on a logarithmic scale.

gCV% is calculated as $100 \sqrt{[\exp(s^2)-1]}$, where s is the SD of the data on a log scale.

Categorical data will be summarised by treatment/weight group using the number and percentage of patients in each category and the percentages will be rounded to 1 decimal place. Percentages will be calculated using the number of patients within each treatment/weight group and overall as the denominator.

When assessing minimum/maximum during the study, all assessments, including unscheduled/repeated assessments will be used. For analysis assessing change from baseline, only patients with both baseline and at least 1 post-baseline measure will be included. Unless otherwise specified, no algorithm for missing data imputation will be employed.

Although the study is conducted in two parts, Part A and Part B for 48 weeks of treatment period, the analysis of the study outcome variables will be analysed altogether not separately

by part and will include all data captured during screening period of up to 28 days and a treatment period of 48 weeks, and a safety follow-up visit at Week 52. A patient who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of discontinuation, as appropriate.

Medical and surgical histories will be recorded using the latest version of medical dictionary for regulatory activities (MedDRA) Preferred Term (PT) within the System Organ Class (SOC) level of MedDRA.

Data listings will be sorted by patient number. Summaries by visit will include baseline.

## 4.2 Analysis methods

No formal analyses will be performed for this study. Demographic and other baseline characteristics, exposure, safety and tolerability data and PK will be summarised and listed.

### 4.2.1 Patient disposition

Patient disposition will be summarised using all enrolled subjects (all patients set) who signed the informed consent form, including screening failures.

The number and percentage of patients will be presented by the following categories: assigned study treatment, not assigned study treatment (including reason), received study treatment, did not receive study treatment (including reason), completed treatment, discontinued from study treatment (including reason), completed study, and prematurely withdrawn from study (including reason). Study discontinuation reasons are detailed in CSP Section 7.1. Also subjects who completed study will be summarized by subjects who completed IP and study, and subjects who discontinued IP but completed study assessments.

Reasons for not having received study treatment, discontinuation of IP and prematurely withdrawing from study will also be listed including the study day of treatment discontinuation.

Important protocol deviations will be summarised by treatment/weight group and listed for the safety analysis set.

The number and percentage of patients included and excluded from each analysis set will be summarised by treatment/weight group, including the reason for exclusion from each analysis set. Patients in the safety analysis set excluded from the PK analysis set, including reason, will also be listed.

### 4.2.2 Demography data and patient characteristics

Demography data such as age (years), gender, race, and ethnicity will be summarized by treatment/weight group and for all patients in the safety analysis set. 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 characteristics will also be summarized by treatment/weight group and for all patients in the safety analysis set. These include patient characteristics (weight, height and BMI), maintenance asthma medications, maintenance inhaled corticosteroids (ICS) medications, maintenance oral corticosteroids (OCS) use, medical and surgical histories, spirometry lung function data at screening such as $FEV_1$, $FEV_1$/FVC, blood eosinophil count at baseline, and respiratory disease characteristics including asthma duration, age at onset of asthma, 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 Preferred Term (PT) within System Organ Class (SOC) level on MedDRA.

### 4.2.3 Prior and concomitant medications

All medications will be classified by the AstraZeneca designee using the anatomical therapeutic chemical (ATC) classification system according to the latest version of the World Health Organisation (WHO) Drug Dictionary will be presented by treatment/weight group using the safety analysis set and will be categorised as:
prior medications and concomitant medications.

#### 4.2.3.1 Prior medications

A medication will be regarded as prior if it was stopped on or before the date of first dose of study treatment (*medication stop date <= date of first dose of study treatment*).

#### 4.2.3.2 Concomitant medications

A medication will be regarded as concomitant if the start date is on or after the first IP dose date, but prior to the end of study period (date of first dose of study treatment <= medication start date <= study completion or withdrawal date), or if it started on or prior to the first IP dose date and was ongoing after the first IP dose date.

The handling of partial/missing dates for prior/concomitant medications is detailed in Appendix I .

The number and percentage of patients taking maintenance asthma medications such as ICS/ long acting beta agonist (LABA) fixed dose combinations, at baseline will be summarised. Those patients taking ICS and/or OCS at baseline, the converted dose units will also be summarised. The number of patients treated with ICS at baseline will be summarised 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 summarize total daily dose of OCS at baseline

Disallowed medications will include medications defined as prohibited according to Section 6.6 of the CSP. They will be defined following a physician review (prior to database lock) of the unique combinations of Anatomical Therapeutic Chemical (ATC) code classifications and generic terms captured.

Separate tables will be presented for all allowed and disallowed medications received during each of the following periods: pre-treatment and on study period respectively.
Prior and concomitant medications will be listed for the safety analysis set, including allowed and disallowed medications.

### 4.2.4 Study treatment

#### 4.2.4.1 Exposure

Investigational product total treatment duration (days) is defined as the date of last dose minus the date of first dose plus 1 day.

Exposure to IP will be calculated in days as:

*Exposure (days) =Last dose date of IP-first dose date of IP+1,*

and will be summarized by treatment/weight group for the safety analysis set.

The date of all IP administrations, and all missed doses will be listed using the safety analysis set. Reason for missed dose will also be listed.

Exposure data will be summarised and listed for the safety analysis set.

#### 4.2.4.2 Compliance

Study treatment compliance will be summarized descriptively by treatment/weight group for the safety analysis set and will be calculated as:

*Treatment compliance (%) = (Total doses administered/total doses expected up to last treatment date) x 100%.*

Patients who received no study treatment will have zero compliance.

### 4.2.5 PK data

The PK analysis of the serum concentration data for benralizumab will be performed by a third-party vendor, PPD.

The PK summaries, figures, and data listings will be produced by IQVIA. Additional population PK analysis will be performed by AZ.

Patients who have missing PK samples will be evaluated on a case-by-case basis. Any PK data available from patients excluded from the NCA population will be listed for each time point but not summarised. Any data to be excluded from the summary tables and figures for the PK analysis set will be clearly indicated. A deviation (gap between nominal and actual time points) column will be added into the listing of concentration data. The exclusion of any patients from the PK analysis set or from the analysis will be agreed by the study physician, statistician and PK Scientist during the data review meeting.

Serum concentrations and PK parameters will be summarized by treatment/weight group using appropriate descriptive statistics. Figures showing individual and mean of PK concentration-time profiles will be produced on both semi-log and linear scales. Serum concentration data associated with positive ADA status will be flagged in the PK concentration listings by safety analysis set and will be excluded from the summary statistics and mean profiles. If an entire concentration-time profile is below the lower limit of quantification (< LLOQ) the subject will be excluded from both NCA and PK analysis sets.

#### 4.2.5.1 Non-compartmental /PopPK parameter analysis

Blood samples for determination of benralizumab PK parameters in serum will be taken at timepoints specified in Table 1 of the CSP. Benralizumab concentrations in serum will be analysed by a central laboratory on behalf of AstraZeneca, using a validated bioanalytical method. Full details of the analytical method used will be described in the bioanalytical report.

For all serum PK concentrations, values <LLOQ are replaced by a value of zero.

The PK parameters listed in section 3.2.1 will be derived using NCA set or PK analysis set. PK analysis, where possible, will be carried out using actual time recorded in the raw data. If actual times are missing, nominal times will be used.

The PK parameters will be derived using noncompartmental methods with Phoenix WinNonlin® (Certara USA, Inc.) Version 6.3 or higher and/or SAS® Version 9.2, or higher (SAS Institute, Inc., Cary, North Carolina), or via population PK (PopPK) method using NONMEM (version 7.3 or higher)

The following PK parameters will be derived:

- $C_{max}$ Maximum benralizumab concentration obtained directly from the observed concentration versus time over 0-28days.
- $t_{max}$ Time to maximum concentration obtained directly from the observed concentration versus time data.

- $AUC_{(0-28)}$ Area under the concentration-time curve from time zero to the time of the last quantifiable concentration at time "Day 28", calculated by linear up/log down trapezoidal summation.
- $t_{1/2}$ Terminal half-life, calculated as ln(2)/ terminal rate constant ($\lambda_z$).
- *CL/F* Apparent clearance (L/h), estimated as dose divided by AUC.
- $C_{trough(W16)}$ Trough concentration week 16, the lowest concentration reached by Benralizumab before the next dose is administered

Additional PK parameters applicable to the actual PK sampling time may be determined if deemed appropriate.
All data received will be presented in data listings. Descriptive statistics for the PK parameters $C_{max}$, $t_{max}$, $AUC_{(0-28)}$, $t_{1/2}$, and CL/F as well as $C_{trough}$ week 16 for benralizumab will be presented using NCA or PK analysis set

Summary of PK parameters

Data from patients eligible for inclusion in the NCA and any samples taken outside of CSP scheduled time windows (as per CSP Table 1) will be included to determine the PK parameters. In the event where PK parameters cannot be estimated accurately using NCA, the PK parameters may be estimated via population PK approach using data from PK analysis set

All reportable PK parameter data for the patients in the NCA set or PK analysis set will be summarised and listed.

All PK parameters, excluding $t_{max}$, will be summarised by treatment/weight group using the following descriptive statistics:

- Number of observations (n)
- Gmean, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale
- gCV%, calculated as 100 √ [exp($s^2$)-1], where s is the SD of the data on a log scale
- Amean
- SD
- Median (min, max)

For PK parameter $t_{max}$, only n, median, min and max will be produced.

Precision and rounding rules for PK parameters

PK parameter listings will be presented according to the following rules:

- $C_{max}$ to be presented to the same number of significant figures as received from the bioanalytical laboratory
- $t_{max}$, $t_{last}$ (time to last quantifiable concentration)
- $AUC_{(0-28)}$, $t_{1/2}$, , CL/F, all ratios of PK parameters and coefficient of determination adjusted (Rsq) which is the goodness of fit statistic for calculation of $\lambda_z$
- N to be presented as an integer (no decimals)

The descriptive statistics for PK parameter data will all be presented to at least 2 decimal places apart from the following:

- $t_{max}$: present as received in the data, usually to 2 decimal places
- n: present as integer

#### 4.2.5.2 Summary Statistics of PK serum concentrations

Serum concentrations will be presented by assessment day in tables and listings. The serum concentrations summaries will include:

- n
- n<LLOQ ((n<LLOQ)/n at time point) *100%
- Gmean (gCV%)
- gSD Amean
- arithmetic standard deviation (SD), median (min, max)

For DXD, only the PK samples collected within one dosing cycle after last dose will be included in the summary statistics of schedule visits during treatment period.
The exclusion of concentration data from the PK analysis for an individual time point will be documented by the PK Scientist including the reason(s) for exclusion. These individual concentration data will also be excluded from the summary tables and corresponding figures.

For those patients eligible for inclusion in the PK Analysis set, the concentration-time data will be summarised by the scheduled time point. Any post-dose samples taken outside the window of the scheduled time will be flagged by the PK Scientist and excluded from the summary tables and figures but will be included in the PK analysis to determine the PK parameters.

Serum concentrations that are <LLOQ will be reported as follows:

Individual concentrations below the LLOQ of the bioanalytical assay are non-quantifiable and will be reported as <LLOQ in the listings with the LLOQ defined in the footnotes of the relevant tables, figures and listings. Non-reportable individual concentrations that is a PK parameter (e.g. $C_{max}$) will be listed as not reportable (NR) and concentrations that are missing

will be listed as no sample (NS) in the listings. Serum concentrations that are <LLOQ, NR or NS will be handled as follows for the provision of descriptive statistics:

- Any values reported as NR or NS will be excluded from summary tables and figures.
- All <LLOQ values will be substituted with a value of zero, and will be excluded from summary descriptive statistics.
- If all concentrations are <LLOQ at a time point, no descriptive statistics will be calculated for that time point. The Gmean, Amean, SD, min, median and max will be reported as <LLOQ and the gCV%, gSD, and SD as not calculated (NC).
- The number of <LLOQ values, n will be reported for each time point along with the total number of collected values (n).

The serum PK concentration data for benralizumab will be displayed graphically. For DXD, only the scheduled PK samples collected within one dosing cycle after last dose will be included in the mean serum-concentrations time profiles graphs. Figures for the Gmean (gSD) concentration-time data will be presented on both a linear and semi-logarithmic scale. Individual concentration time will be graphically presented on linear and semi-logarithmic scales. <LLOQ samples will be plotted as LLOQ with footnote in the graphs.
Displays will include:

- Individual patient serum concentration-time profiles on the linear and semi-log scale showing single dose on Day 1, 2 ,7,28 on same plot, stratified by treatment/weight groups and color-coded by ADA status.

- Gmean serum concentration-time profiles (with gSD error bars) on the linear and semi-log scale showing single dose on Day 1, 2, 7 and 28, stratified by treatment/weight groups

- Serum trough concentrations boxplots to include median and n values on the plot

- n will be reported for each time point

Precision and rounding rules for PK concentration data

PK concentration data listings will be presented to the same number of significant figures as the data received from the bioanalytical laboratory. PK concentrations descriptive statistics will all be presented to 2 decimal places with the exception of n and number of <LLOQs which will be presented as integers.

## 4.2.6 Pharmacodynamic variables

### 4.2.6.1 Change in Eosinophils count

Peripheral blood eosinophils values and changes from baseline at each visit will be summarized using descriptive statistics for each treatment/weight group based on safety

analysis set. For DXD, only the PD samples collected within one dosing cycle after last dose will be included in the summary statistics during treatment period.

### 4.2.7 Body weight-adjusted clearance

Body weight-adjusted clearance will be calculated using the PK population model by AZ and will be summarized descriptively by treatment/weight group based on PK analysis set.

### 4.2.8 Immunogenicity Analysis

All listings and summary of ADA results will be based on safety analysis set. Immunogenicity of benralizumab (ADA) results by treatment/weight group will be listed by patient's study status with positive study status first then followed by patients with negative status, and schedule visit including ADA. All ADA positive samples will be tested for neutralizing antibodies (nAb) using a ligand binding assay. The nAb results will be reported as positive or negative.

The number and percentage of subjects who developed detectable ADA to benralizumab will be determined for each of the following categories. However, if the number of ADA positive subjects in the safety analysis set is small then the ADA variables may be listed only in the CSR.

- ADA positive at any time, including baseline and/or post-baseline. The denominator for percentage calculation is the number of subjects with any ADA result at baseline and/or post-baseline. This percentage is known as ADA prevalence.

- Treatment-emergent ADA positive, defined as either treatment-induced ADA positive (ADA negative at baseline and positive at post-baseline) or treatment-boosted ADA positive (baseline ADA titer that was boosted by greater than 4-fold following drug administration). The denominator for percentage calculation is the number of subjects with at least one post-baseline assessment. This percentage is known as ADA incidence.

- ADA positive at both baseline and at least one post-baseline measurement. The denominator for percentage calculation is the number of subjects with an ADA result at baseline and at least one post-baseline assessment.

- ADA positive at baseline only. The denominator for percentage calculation is the number of subjects with an ADA result at baseline.

- Persistently positive ADA, defined as having at least 2 post-baseline ADA positive measurements with at least 16 weeks (112 days) between the first and last positive measurements, or an ADA positive result at the last available assessment. The

denominator for percentage calculation is the number of subjects with at least one post-baseline assessment.

- Transiently positive ADA, defined as having at least one post-baseline ADA positive measurement and not fulfilling the conditions for persistently positive. The denominator for percentage calculation is the number of subjects with at least one post-baseline assessment.

- nAb positive at baseline and/or post-baseline (nAb prevalence). The denominator for percentage calculation is the number of subjects with any ADA result at baseline and/or post-baseline.

- Treatment-induced nAb positive (nAb incidence); defined as nAb negative at baseline (or ADA negative at baseline) and nAb positive at any post-baseline visit. Subjects who are ADA-negative at baseline are included to ensure that all subjects who are nAb positive for the first time post-baseline satisfy this definition, given that all subjects who are ADA negative at baseline do not have a nAb result reported.

For ADA summaries at a single time point (e.g. baseline ADA or by visit) the corresponding titre summary will be based on the titre of the positive sample for that particular visit. For proportions summarising across visits (e.g. any ADA post-baseline) the corresponding titre summaries will be based on the maximum titre of all positive samples for each subject.

The hypersensitivity AEs reported on treatment period will be presented by preferred term for ADA status.

### 4.2.9 Forced expiratory volume in first second (FEV1)

$FEV_1$ measurements and changes from baseline at each visit will be summarized using descriptive statistics for each treatment/weight group based on safety analysis set.

### 4.2.10 Asthma control questionnaire (ACQ-IA)

The mean ACQ-IA score and change from baseline at each visit will be summarized for each time point using descriptive statistics for each treatment/weight group based on safety analysis set.

The number and percentage of ACQ-IA responders (yes, no), ACQ-IA responses (improved, no change, deterioration), subject's asthma control (well controlled, partially controlled, and not well controlled) at each post-baseline visit will be also be presented.

### 4.2.11 Global impression of change

The CGIC and PGIC-IA responses will be summarised by treatment/weight group and visit using the safety analysis set. The number and percentage of patients will be presented for CGIC, PGIC-IA, and for the response agreement between CGIC and PGIC-IA.

The number and percentage of patients defined as responders based on categorized responses for CGIC and PGIC-IA (improved, much improved, very much improved) will also be presented by treatment/weight group and visit.

### 4.2.12 Safety Analysis

All safety and tolerability variables will be summarised by treatment/weight group and overall and evaluated descriptively using the safety analysis set. No formal hypothesis testing of safety data is planned.

Out-of-range values for safety laboratory, vital signs, and ECGs will be flagged in individual listings.

#### 4.2.12.1 Adverse Events

All AEs experienced by the patients will be collected throughout the study, as per CSP Table 1, and will be coded by the AstraZeneca designee using the latest version of MedDRA.

The timings of AEs will be assigned to the period in which they occurred. AEs occurring during the screening period will be listed, but not summarised separately.

AEs or Serious Adverse Events (SAEs) will be categorised as occurring on-study period based on their onset date:

An overall summary table will be produced showing the number and percentage of patients with at least one AE in each of the following categories: any AEs, SAEs, AEs with outcome of death, and AEs leading to discontinuation of IP (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, SAEs, AEs with outcome of death, and DAEs will be summarised by SOC and PT assigned to the event using the MedDRA dictionary by descending frequency order in the overall benralizumab treatment group. For each PT, the number and percentage of patients reporting at least one occurrence of the event will be presented (i.e. subjects with multiple occurrences of the same PT will only be counted once). A summary of the most common (frequency of >5%) AEs in any treatment group will be presented by PT.

AEs and SAEs will be summarized by PT and Investigator's causality assessment (related versus not related) and maximum intensity. If a patient reports multiple occurrences of the same AE within the same reported period, the maximum intensity will be taken as the highest recorded maximum intensity (the order being mild, moderate, and severe).

Separate listings of subjects with AEs, SAEs, AEs with outcome of death, or DAEs will be presented.

### 4.2.13 Laboratory variables

All continuous laboratory parameters will be summarized descriptively by absolute value by each planned visit by treatment/weight group, together with the corresponding changes from baseline using the safety analysis set. These summaries will be produced for the on-study period, as defined in section 3.1.3. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean and SD. Mean changes from baseline over time will also be plotted by treatment group. All variables will be summarized in SI units, with the exception of blood eosinophil counts which will be summarized in both SI and conventional units.

Central laboratory normal reference ranges will be used for the identification of abnormalities. A shift table will be produced for each laboratory variable to display low, normal, high and missing values. The shift tables will present baseline and maximum/minimum/last post-baseline values for each variable.

Shift plots showing each individual patients' laboratory value at baseline and at maximum/minimum/last value 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. The diagonal line of no change, and horizontal and vertical reference lines indicating the limits of the normal reference ranges, will also be displayed on the shift plots.

Maximum post-baseline TBL elevations by maximum post-baseline ALT and AST will be presented, expressed as multiples of ULN. TBL 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 TBL will be presented (<2 and ≥2 x ULN) 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 TBL 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.

For urinalysis data, a shift table will be generated to present changes from baseline to maximum post-baseline value for each variable and will include subjects with both baseline and post-baseline data.
shift table will also be provided for each urinalysis qualitative assessment using the number and percentage of patients with baseline results of negative, trace or positive versus the maximum on treatment result of negative, trace or positive.

The number of patients with treatment-emergent changes will also be summarised.

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

### 4.2.14 Vital signs

All vital signs variables including height, weight and BMI will be summarized by absolute value at each visit by treatment/weight group using the safety analysis set, together with the corresponding changes from baseline. These summaries will be produced for the on-treatment period, as defined in section 3.1.3. The summary statistics presented will be the minimum, 1st quartile, median, 3rd quartile, maximum, mean and SD. The normal reference ranges listed in Table 2 and Table 3 will be used for the identification of individual abnormalities. A shift table will be produced for each vital sign variable to display low, normal, high and missing values. The shift tables will present baseline and maximum/minimum/last post-baseline values for each variable.

Shift plots showing each individual patient's vital signs value at baseline and at maximum/minimum/last value post-baseline will be produced for each continuous vital sign variable.

All recorded vital signs data will be listed.

### 4.2.15 ECG variable

The outcome of the overall investigator ECG evaluation recorded as normal or abnormal with any abnormalities recorded as not clinically significant or clinically significant will be listed for all patients by safety analysis set.

Abnormal values will not be recorded as AEs unless deemed clinically significant.

A summary table will be produced for baseline ECG evaluation to display normal, abnormal – not clinically significant, abnormal – clinically significant and not done. ECG data will also be listed by safety analysis set.

A shift table will be produced for each ECG parameter to display normal (includes borderline), abnormal - not clinically significant, abnormal - clinically significant, and not done. The shift tables will present baseline and last observation post-baseline value.

### 4.2.16 Physical examinations

Physical examination data will not be summarized but will be listed only.

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

### 4.2.17 Exploratory analyses

#### 4.2.17.1 Annualised asthma exacerbation rate

Exacerbations experienced during the treatment period will be summarized descriptively for each treatment/weight group, including the number of exacerbations associated with an ED visit or hospitalization.

For the production of summary statistics, the AAER will be calculated using the time-based risk approach:

*AAER = 365.25*Total number of exacerbations /Total duration of at risk on-treatment period (days)*

Summaries will also include the number of patients experiencing at least one exacerbation. Kaplan-Meier plots will be used to describe the time to first exacerbation

### 4.2.18 Subgroup Analysis

For the following data, descriptive summaries in Japan subgroup by treatment/weight group and overall will be presented:

- Disposition
- Demography and patient characteristics
- Study treatment
- PK
- PD
- FEV1
- ACQ-IA
- Global impression of change
- AEs
- Asthma exacerbation

## 5 INTERIM ANALYSES

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# 6 CHANGES OF ANALYSIS FROM PROTOCOL

No change to the analysis stated in the CSP

# 7 REFERENCES

The following AZ internal documents are referenced:

D3250C00025-CSP-v3.0 (Study Protocol)

Nguyen et al 2014
Nguyen JM, Holbrook JT, Wei CY, Gerald LB, Teague WG, Wise RA. Validation and psychometric properties of the Asthma Control Questionnaire among children. J Allergy Clin Immunol. 2014;133:91-7.

Juniper et al 2005
Juniper EF, Svensson K, Mork, A, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med. 2005;99:553-8.

Juniper et al 2006
Juniper EJ, Bousquet J, Abetz L, Batemain ED. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med. 2006;100:616-21.

Juniper et al 2010
Juniper EF, Gruffydd-Joes K, Ward S, Svensson K. Asthma Control Questionnaire in children: validation, measurement properties, interpretation. Eur Respir J. 2010;36:1410-16.

# 8 APPENDIX

## Appendix I Partial dates for AEs and prior/concomitant medication

- **Adverse Events**
  - The missing day of onset of an AE will be set to:
    - First day of the month that the event occurred, if the onset YYYY-MM is after the YYYY-MM of first study treatment
    - The day of the first study treatment, if the onset YYYY-MM is the same as YYYY-MM of the first study treatment
    - The date of informed consent, if the onset YYYY-MM is before the YYYY-MM of the first treatment.
  - The missing day of resolution of an AE will be set to:
    - The last day of the month of the occurrence. If the patient died in the same month, then set the imputed date as the death date.
  - If the onset date of an AE is missing both the day and month, the onset date will be set to:
    - January 1 of the year of onset, if the onset year is after the year of the first study treatment.
    - The date of the first treatment, if the onset year is the same as the year of the first study treatment.
    - The date of informed consent, if the onset year is before the year of the first treatment.
  - If the resolution date of an AE or end date of a IP is missing both the day and month, the date will be set to:
    - December 31 of the year of occurrence. If the patient died in the same year, then set the imputed date as the death date.

- **Prior/concomitant medication**

Dates missing the day or both the day and month of the year will adhere to the following conventions in order to classify prior/concomitant medications:

- The missing day of start date of a therapy will be set to the first day of the month that the event occurred.
- The missing day of end date of a therapy will be set to the last day of the month of the occurrence.
- If the start date of a therapy is missing both the day and month, the onset date will be set to January 1 of the year of onset.
- If the end date of a therapy is missing both the day and month, the date will be set to December 31 of the year of occurrence.

- If the start date of a therapy is null and the end date is not a complete date then the start date will be set to the date of the first study visit.
- If the start date of a therapy is null and the end date is a complete date:
  - and the end date is after the date of the first study visit then the start date will be set to the date of the first study visit.
  - otherwise the start date will be set to the end date of the therapy.
- If the end date of a therapy is null and the start date is not a complete date then the end date will be set to the date of the last study visit.
- If the end date of a therapy is null and the start date is a complete date:
  - and the start date is prior to the date of the last study visit then the end date will be set to the date of the last study visit.
  - otherwise, the end date will be set to the start date of the therapy.

# SIGNATURE PAGE

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