AstraZeneca

Statistical Analysis Plan	
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A Multicenter, Open-label, Functionality, Reliability and Performance Study of a Single-use Auto-injector with Home-administered Subcutaneous Benralizumab in Adult Patients with Severe Asthma (GRECO)

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Global Product Statistician	Redacted	Redacted
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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
AI	Auto-Injector
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AZDD	AstraZeneca drug dictionary
BMI	Body mass index
CSP	Clinical study protocol
CSR	Clinical Study report
DAE	AEs causing discontinuation of investigational product
ECG	Electrocardiogram
eCRF	Electronic case report form
EOT	End-of-treatment
FAS	Full analysis set
FEV1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
GGT	Gamma-glutamyl transpeptidase
HIV	Human immunodeficiency virus
ICS	Inhaled corticosteroids
IFU	Instructions for Use
IP	Investigational product
IPD	Premature IP Discontinuation
MedDRA	Medical Dictionary for Regulatory Activities
nAb	Neutralizing antibody
N/A	Not applicable
OCS	Oral corticosteroids

Abbreviation or special term	Explanation
PI	Principal investigator
PK	Pharmacokinetic(s)
Post-BD	Post-bronchodilator
PT	Preferred term
SAE	Serious adverse event
SAS	SAS Institute Inc., Cary, NC
SC	Subcutaneous
SD	Standard deviation
SI	International System of Units
SOC	System organ class
TBL	Total bilirubin
TIA	Transient ischemic attack
ULN	Upper limit of normal
Unsch	Unscheduled
WBDC	Web Based Data Capture
WOCBP	Women of childbearing potential

AMENDMENT HISTORY

Date	Brief description of change
9/25/2017	1. The study is reported using the AstraZeneca drug dictionary (AZDD) instead of pre-specified WHO drug dictionary (WHODD) because the timeline for transition to the WHODD was delayed. 2. Visit Window adjusted to protocol schedule at assessment item level (See Section 2.2.2) 3. Added Section 6 Change of analysis from protocol for the analysis of physical examination data

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary Objective

Objective	Outcome measure
To assess patient- or caregiver-reported functionality and reliability of the benralizumab single-use auto-injector (AI) in an at-home setting and performance of the AI device after use.	• Proportion of patients/caregivers who successfully administered benralizumab 30 mg subcutaneously (SC) by injection with an AI device at home • Proportion of returned AI devices used to administer benralizumab at home that have been evaluated as functional • Proportion of AI devices used to administer benralizumab at home or in the clinic and have been reported as malfunctioning (Product Complaints)

1.1.2 Secondary Objectives

Objective	Outcome measure
To monitor metrics of asthma control	• Change from baseline in mean Asthma Control Questionnaire-6 (ACQ-6) score
To evaluate the pharmacokinetics, pharmacodynamics, and immunogenicity of benralizumab	• Pharmacokinetic parameters • Peripheral blood eosinophil levels • Anti-drug antibodies (ADA)

1.1.3 Safety Objective

Safety objectives	Outcome measure
To assess the safety and tolerability of benralizumab	• Adverse events (AEs) and serious adverse events (SAEs) • Laboratory variables • Physical examination

This statistical analysis plan (SAP) outlines the analyses to be generated for the global clinical study report (CSR). Additional analyses required for regional submissions (if applicable) will be pre-specified in a separate analysis plan and will be submitted to the appropriate authorities.

1.2 Study design

This is an open-label study designed to assess patient- or caregiver-reported functionality, performance, and reliability of an AI with a fixed 30 mg dose of benralizumab administered SC in an at-home setting.

Approximately 120 patients, 18 to 75 years of age, globally with severe asthma will enter the treatment period to receive 5 SC doses (Week 0, Week 4, Week 8, Week 12, and Week 16) of benralizumab.

Following a 2-week screening period, eligible patients will receive 3 SC doses of 30 mg of benralizumab at the study site (Week 0, Week 4, and Week 8). At Week 0, the Principal Investigator (PI) or his/her designee will administer the study drug. At Week 4, the patient or caregiver will have the option of administering the study drug under site supervision to ensure they understand the procedure and are capable of doing so. At Week 8, the patient or caregiver will have to perform the injection, again under site staff supervision. Patients or caregivers unable or unwilling to administer investigational product (IP) at this visit will be discontinued from the study.

The patient or caregiver will be given the Instructions for Use (IFU) to refer to for home administrations. The final 2 doses of benralizumab (Week 12 and Week 16) will be self-administered by the patient or administered by the caregiver at home. After each of these administrations, the patient will return for a scheduled on-site visit within 48 hours.

For the at-home administrations, whether the patient is self-administering or the caregiver is administering to a patient, that person administering the dose will fill out a questionnaire designed to indicate whether the device functioned correctly and the dose was successfully administered. Both the completed questionnaire and the used device are to be returned to the site during each of the clinic visits (Visit 5 [Week 12] and Visit 6 [Week 16]). The site is to subsequently return the used devices and questionnaires to the Sponsor for evaluation.

An end-of-treatment (EOT) visit will be performed at Week 20 and a follow-up visit at Week 28 (12 weeks after last IP administration).

1.3 Number of subjects

Approximately 120 patients will receive treatment to allow approximately 100 patients to complete the study. It is based upon a targeted recruitment with an adjustment to account for a 17% patient drop-out rate.

2. ANALYSIS SETS

2.1 Definition of analysis sets

Three patient populations are defined below: All patients analysis set, Full analysis set (FAS), and Pharmacokinetics analysis set.

Patients must have provided their informed consent. If no signed informed consent is collected (major protocol deviation [PD]), then the patient will be excluded from all analysis sets defined below.

2.1.1 All patients analysis set

The all patients analysis set will comprise all patients screened for the study, ie, signed informed consent form, and will be used for reporting of disposition and screening failures.

2.1.2 Full analysis set

All patients receiving any IP will be included in the full analysis set (FAS), irrespective of their protocol adherence and continued participation in the study. Patients who withdraw consent to participate in the study will be included up to the date of their study termination.

All analyses, except for PK analysis, will be presented using the FAS.

2.1.3 Pharmacokinetic analysis set

All patients who received benralizumab and from whom PK blood samples were obtained are assumed not to be affected by factors such as protocol violations will be included in the PK analysis dataset. Those patients who had at least 1 quantifiable serum PK observation post 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 still enrolled will be analyzed according to the analysis sets described in Section 2.1. There is no intention to perform a per-protocol analysis in this study.

2.2.1 Important protocol deviations

Important deviations will be those which are considered to potentially impact upon the interpretation of the primary endpoint in the study. Only important protocol deviations will be listed and tabulated in the CSR.

The following categories of protocol deviations will be reviewed by medical advisors and statisticians prior to database lock to determine those which are considered important deviations as outlined above.

- Patients who do not meet the inclusion criteria
- Patients who meet any of the exclusion criteria
- Concomitant use of disallowed medications (to be identified through programming)
- Patients who developed withdrawal criteria during the study but were not withdrawn

Patients for whom a significant protocol deviation was recorded that impacts the interpretation of the study safety outcomes will have a footnote added to applicable output to describe the deviation and its potential impact. Such patients will be identified as part of the protocol deviation review process, prior to database lock.

2.2.2 Visit window definitions

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.

No windows will be applied for the screening visit. For endpoints that present visit-based data, the variables will be summarized based on the scheduled days with adjusted analysis-defined visit windows. The adjusted analysis-defined windows will be based on the collection schedule listed in the protocol and variables will be windowed to the closest scheduled visit for that variable. Visit windows have been constructed so that every observation collected can be allocated to a particular visit. The adjusted analysis-defined windows are summarized in **Error! Reference source not found.**a-1c.

Table 1a Visit windows for assessments [ACQ-6]

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

Table 2b Visit windows for assessments [Laboratory tests - Chemistry, Haematology, Urinalysis]

Defined Windows Visit	Scheduled Study Day	Maximum Windows
Week 0 Day 1	1	Study Day=1
Week 20	141	2≤Study Days≤154
Week 28	197	155≤Study Days

Table 3c Visit windows for assessments [PK and ADA]

Defined Windows Visit	Scheduled Study Day	Maximum Windows
Week 0 Day 1*	1	Study Day=1
Week 8*	57	2 ≤Study Days≤98
Week 20	141	99≤Study Days≤154
Week 28	197	155≤Study Days

* Only take pre-dose. For PK assessments, visit window is only applicable to unscheduled visits.

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

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

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

- If there are 2 or more valid, non-missing observations within the same visit window, then the non-missing one closest to the scheduled visit will be used in the analysis.
- If 2 valid observations are equidistant from the scheduled visit, then the non-missing observation with the earlier collection date will be used in the analysis.
- If 2 or more valid observations are collected on the same day, then the non-missing observation with the earlier collection time will be included in the analysis.

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

All data will be organized and analyzed according to the scheduled visits outlined in the protocol. However, actual observation visit times may differ from the scheduled visit times and where this occurs the results should be allocated to the most appropriate visit. Time

intervals (eg, adjusted visit windows) have been constructed so that every observation collected can be allocated to a particular visit.

Any repeat or additional assessments performed will be included in the individual patient data listings.

For all vital signs, the visit recorded in Web Based Data Capture (WBDC) will be used.

For the central laboratory results and other endpoints that present visit-based data (ADA/nAb, ACQ-6), the variables will be summarized based on the scheduled days with adjusted analysis-defined visit windows.

2.3 Baseline and change from baseline

In general, the last non-missing observation prior to the first dose of study treatment will serve as the baseline measurement. If there is no value prior to the first dose of study treatment, then the baseline value will not be imputed and will be set to missing.

Unless indicated otherwise, Visit 2 (Week 0) is the planned baseline visit, for all assessments carried out at the center.

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.

2.4 Handling of dropouts and missing data

Unless otherwise specified, missing data will not be imputed. All missing data will be reported to data management to be queried.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Primary outcome variables

Three primary endpoints will be evaluated in this study as follows.

- Proportion of patients/caregivers who successfully administered benralizumab 30 mg SC by injection with an AI at home.

The proportion will be calculated among all patients/caregivers who have been deemed by the Principal Investigator to be suitable for at-home administration and are still in the study at the time of benralizumab injection at Week 12 or Week 16. Patients who are still in the study is defined as patients who had been treated for the specified time point. A successful administration is defined as an injection completed, an answer of "Yes" to all 5 questions in the Questionnaire, and adequately passed the visual inspection and function tests. Patients/caregivers who are unwilling to self-administer at Week 8 will not be considered as

failures, but will be counted as unsuitable for at-home administration and follow the premature IP Discontinuation (IPD) procedure.

- Proportion of returned AI used to administer benralizumab at home that have been evaluated as functional among all returned AI used to administer benralizumab at home.

A functional AI is defined as an answer of "Yes" to all the questions in the visual inspection and function tests. Devices that are not returned for evaluation will be excluded from analysis.

- Proportion of AI used to administer benralizumab at home or in the clinic and have been reported as malfunctioning (Product Complaints).

The first 2 endpoints above will be calculated at Weeks 12 and 16, while the third endpoint will be calculated at Week 0, 4, 8, 12 and 16 as well as for the overall study period (from Week 0 to Week 16), the in-clinic administration period (from Week 0 to Week 8) and the at-home administration period (from Week 12 to Week 16).

In addition, the following variables will be calculated among all patients/caregivers who have been deemed by the Investigator to be suitable for at-home administration at Week 8 and are still in the study at Week 16:

- Proportion of patients/caregivers who successfully administered benralizumab with an AI at both Weeks 12 and 16

- Proportion of patients/caregivers who returned an AI used to administer benralizumab at home and evaluated as functional at both Weeks 12 and 16.

3.2 Secondary outcome variable

3.2.1 Asthma Control Questionnaire-6

The Asthma Control Questionnaire-6 (ACQ-6) is a shortened version of the ACQ that assesses asthma symptoms (nighttime waking, symptoms on waking, activity limitation, shortness of breath, wheezing, and short-acting β_2 agonist use) omitting the forced expiratory volume in 1 second (FEV_1) measurement from the original ACQ-7 score.

Patients are asked to recall how their asthma has been during the previous week by responding to 1 bronchodilator use question and 5 symptom questions. Questions are weighted equally and scored from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score is the mean of the responses. The mean score will be missing if any symptom score is missing.

The questionnaire will be completed at the study center at Weeks -2, 0, 4, 8, 12, 16, 20 and IPD.

The outcome variable for ACQ-6 will be the change in mean score from baseline (Week 0) to each of the post-treatment periods. There will be no imputation for missing values.

Asthma control responder status will be evaluated as a supportive analysis. Patients will be categorized according to the following limits (Juniper et al 2005), at the end of treatment, where end of treatment is defined as week 20 (EOT visit):

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

An ACQ-6 responder will be defined as a patient who had improvement on ACQ-6, ie, an ACQ-6 responder variable takes value 1 if change from baseline to end of treatment in ACQ-6$\leq$-0.5 and 0 otherwise. Patients with missing or non-evaluable ACQ-6 data at end of treatment visit will be considered non-responders.

Additionally, patients will be categorized according to their ACQ-6 defined asthma control status at the end of treatment using the following score thresholds (Juniper et al 2006):

- ACQ-6 (EOT) $\leq$0.75 $\rightarrow$ Well controlled
- 0.75<ACQ-6(EOT) <1.5 $\rightarrow$ Partly controlled
- ACQ-6 (EOT) $\geq$1.5 $\rightarrow$ not well controlled

3.2.2 Blood eosinophil levels

Blood eosinophil counts levels will be evaluated at Screening (Week -2), Week 0 (baseline), EOT/IPD visit and Follow-up visit.

Blood samples for determination of eosinophil counts levels (hematology) will be taken at the time points detailed in the clinical study protocol (CSP), and will be assessed in a central laboratory. Eosinophils will be presented in both International System of Units (ie, SI) and conventional units (cells/µL) in summaries.

3.3 Safety variables

Safety variables include AEs, hematology, clinical chemistry, urinalysis, vital signs, and electrocardiograms (ECGs).

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. Adverse events will be summarized by means of descriptive statistics and qualitative summaries.

No safety data will be imputed. The handling of partial/missing dates is detailed in the programming specs.

3.3.1 Adverse events

Adverse events (AEs) experienced by the patients will be collected throughout the entire study and will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) per the Data Management Plan.

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

- AEs in the on-study period are defined as those with onset between day of the first dose of study treatment and scheduled follow-up visit, inclusive.

- AEs in the on-treatment period are defined as those with onset between day of 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. In the event that the EOT or IPD visit is beyond the protocol defined visit window, AEs with onset after the last dose of study treatment date+28 days+3 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, but not including, the EOT visit (or the IPD visit) up to and including follow-up visit.

For instances where a patient attends the safety follow-up visit only, but does not attend an earlier IPD visit or EOT visit, AEs 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.

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

3.3.2 Laboratory variables

Blood and urine samples for determination of clinical chemistry, hematology and urinalysis parameters will be taken at the times detailed in the CSP, and will be assessed in a central laboratory. The parameters outlined in Section 5.2.4, Table 3 of the CSP will be collected. Laboratory data is to be reported in SI units.

Changes in hematology 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 analyzed as 0.01 and listed as <0.01.

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

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

For the purposes of hematology, 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 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.

$$\text{Multiple} = \text{Value}/\text{ULN}$$

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 ≥3xULN
- ALT ≥3xULN
- TBL ≥2xULN

3.3.3 Vital signs

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

Changes in vital signs variables between baseline and each subsequent scheduled assessment will be calculated. Absolute values will be compared to the relevant reference ranges and classified as low (below range), normal (within range or on limits) or high (above range). All values (absolute and change) falling outside the reference ranges (see Table 4) will be flagged.

Table 4 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:

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

3.3.4 Electrocardiograms

The outcome of the overall evaluation is to be recorded as normal/abnormal in the electronic case report form (eCRF) by the investigator/authorized delegate, with any abnormalities being recorded as not clinically significant or clinically significant.

3.4 Pharmacokinetic variables

Blood samples (processed to serum) for pharmacokinetic assessments will be collected from all patients at baseline prior to benralizumab administration at Day 1 and Week 8, at EOT visit (Week 20) or IPD visit and at the Week 28 follow-up visit.

3.5 Immunogenicity variables

Immunogenicity assessments will be collected in a similar schedule as the pharmacokinetic assessments.

These will be handled using the visit windowing described in Section 2.2.2. The proportions of patients with ADA results will be presented together with descriptive statistics of the ADA titers.

The presence of neutralizing ADA (nAb) will be tested in ADA-positive samples and the proportions of patients with nAb results will be summarized.

4. ANALYSIS METHODS

4.1 General principles

The data analyses will be conducted using the SAS® System version 9.2 or above (SAS Institute Inc., Cary, NC). All SAS® programs used to generate analytical results will be developed and validated according to AstraZeneca SAS® programming standards.

Summary data will be presented in tabular format. Categorical data will be summarized by the number and percentage of patients in each category. Continuous data will be summarized by descriptive statistics including N, mean, standard deviation (SD), median, and range. For PK data, in addition, geometric mean and coefficient of variation (CV%) based on log-transformation will be presented. All data will be listed. Data listings will be sorted by patient number.

There are no formal statistical hypotheses to be tested in this study.

4.2 Analysis methods

4.2.1 Patient disposition

Patient disposition will be summarized using the all patients analysis set. The total number of patients will be summarized for the following groups: those who enrolled, those who entered run-in, and those who did not receive treatment after they have been enrolled. The number and percentage of patients within each treatment group will be presented by the following categories; enrolled, received treatment with study drug, did not receive treatment with study drug (and reason), completed treatment with study drug, and withdrawn from study (and reason).

The number of patients enrolled by country and center will be summarized for the FAS.

4.2.2 Demographics and patient characteristics

Demography data such as age, sex, race, and ethnicity will be summarized for the all patients in the FAS. 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.

Descriptive statistics will be presented for the following demographic data:

- Age
- Age group (≥18-<50 years, ≥50-<65 years or ≥65 years)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, native Hawaiian or other Pacific islander, American Indian or Alaska native, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

Descriptive statistics will be presented for the following baseline characteristics:

- Height (cm)
- Weight (kg)

- BMI (kg/m^2)
- BMI group (Normal: ≤25, Overweight: >25 – 30, Obese: >30-35, Morbidly obese: >35)

Various disease related baseline characteristics will also be summarized for the FAS. These include respiratory disease characteristics such as asthma duration, the number of exacerbations in the previous 12 months, and the number of exacerbations requiring hospitalizations in the previous 12 months.

4.2.3 Prior and concomitant medications

A medication will be regarded as prior if it was stopped on or before the first IP dose date (ie, medication stop date ≤first IP dose date).

A medication will be regarded as concomitant if the start date is after the first IP dose date, but prior to the end of treatment period, or if it started prior to the first IP dose date and was ongoing after the first IP dose date.

The number and percentage of patients who take prior medications, those who take allowed concomitant medications, and those who take disallowed concomitant medications during the study, will be presented for the FAS. Prior and concomitant medications will be classified according to the AZDD. The summary tables will present data by anatomical therapeutic chemical (ATC) classification category and generic term.

All prior and concomitant medications will be listed.

4.2.4 Maintenance asthma/inhaled corticosteroids/oral corticosteroids medications

Maintenance asthma medications, maintenance inhaled corticosteroid (ICS) medications and maintenance oral corticosteroid (OCS) medications will be summarized for the FAS by ATC and preferred term (PT).

4.2.5 Medical history, past and current,-not respiratory

Medical history will be coded using the latest MedDRA version.

Relevant medical conditions will be summarized by system organ class (SOC) and PT for the FAS.

A separate summary will be presented for past and current conditions.

Medical history data will be fully listed.

4.2.6 Surgical history

Surgical history will be coded using the latest MedDRA version.

Relevant surgical procedures will be summarized by SOC and PT for the FAS.

Surgical history data will be fully listed including a Yes/No for any current medication taken for the surgical procedures.

4.2.7 Lung function data at baseline

Descriptive statistics will be presented for the FAS for the following lung function data: Pre-bronchodilator (Pre-BD) lung function data (FEV_1 [L], FEV_1 [% PN], FVC [L], FVC [% PN] and FEV_1/FVC) and post-bronchodilator data (FEV_1 reversibility [%]).

All lung function data will be fully listed.

4.2.8 Primary outcome variables

4.2.8.1 Primary analyses

For each of the primary endpoints in Section 3.1, the data will be summarized along with their corresponding exact 95% confidence interval estimates (Clopper-Pearson method).

In addition, the proportion of AI used to administer benralizumab at home or in the clinic will also be summarized by the malfunction reasons (Product Complaints).

All data from the administration related questionnaire will be listed by patient and visit.

4.2.8.2 Subgroup analysis

To explore the uniformity of the estimates, the primary endpoints will also be summarized separately for patients self-administering and caregivers who are administering to the patient.

The same output will be presented for each subgroup as for the primary analysis.

4.2.9 Secondary outcome variables

4.2.9.1 Change from baseline in ACQ-6 score

Summary statistics (n, mean, median, minimum and maximum) of the change from baseline in ACQ-6 score for all weeks will be produced.

The asthma control status will be presented showing the number and percentage of patients achieving mean ACQ-6 $\leq$0.75 (well controlled), 0.75< mean ACQ-6 <1.5 (partly controlled) and mean ACQ-6 of $\geq$1.5 (not well controlled) at both baseline and Week 20 will be summarized.

Additionally, the number and percentage of patients achieving an improvement, no change, or deterioration, as per Section 3.2.1, will be summarized.

4.2.9.2 Blood eosinophil levels

Blood eosinophil counts and change from baseline will be summarized using standard summary statistics and plots at each visit.

4.2.10 Safety outcome variables

All safety variables will be summarized using the FAS. Safety data will be summarized and listed.

4.2.10.1 Study treatments

Exposure to investigational product will be calculated in days as:

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

and will be summarized for the FAS.

4.2.10.2 Adverse events

Adverse events will be summarized for the on-study, on-treatment, and post-treatment periods, as defined in Section 3.3.1. All AEs will be listed regardless of treatment period.

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, deaths due to AE, serious AEs (SAEs), and AEs causing discontinuation of IP (DAEs). 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).

Adverse events, DAEs and SAEs will be summarized by SOC and PT assigned to the event by MedDRA. For each PT, the number and percentage of patients reporting at least 1 occurrence will be presented, ie, for a patient multiple occurrences of an AE will only be counted once. Serious AEs causing discontinuation of the study treatment and SAEs causing discontinuation from the study will also be summarized.

Adverse events and SAEs (by PT) will be summarized by Investigator's causality 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). Deaths will also be summarized in separate tables.

A summary of the most common (ie, frequency of >5%) AEs will also be presented.

Adverse events of injection site reactions (high level term of administration and injection site) will be summarized by PT for the on-treatment period. In addition, if there are sufficient amount of hypersensitivity events (standardized MedDRA query of hypersensitivity), it will also be summarized by PT for the on-treatment period as well as the on-study period.

Separate listings of patients with AEs, SAEs, death due to AE, or discontinuations due to AEs will be presented.

4.2.10.3 Laboratory data

All continuous laboratory parameters will be summarized descriptively by absolute value at each visit, together with the corresponding changes from baseline. All parameters will be summarized in SI units, with the exception of blood eosinophil counts which will be summarized 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 changes outside central laboratory reference ranges will be presented. This data presentation will include all visits for this subset of patients.

Maximum post-baseline TBL 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 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. A line plot of liver biochemistry test results (including ALP, ALT, AST, TBL and GGT) over time will also be presented 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 parameter and will include patients with both baseline and post-baseline data.

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

4.2.10.4 Vital signs

Descriptive statistics and change from baseline for vital signs data will be presented 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.

4.2.10.5 Electrocardiograms

The Investigator's assessment of the 12-lead ECG (normal, abnormal, or borderline) at baseline will be listed for all patients. For abnormal assessments, further details will be shown for the reason for abnormality and whether abnormalities were clinically significant or not.

The overall Investigator's assessment will be summarized for baseline.

4.2.11 Pharmacokinetic variables

The pharmacokinetic analyses will be performed at or under the guidance of AstraZeneca Research and Development.

Benralizumab serum concentrations will be summarized using descriptive statistics at each visit. Observed serum concentrations of benralizumab for each individual will be listed by visit to confirm benralizumab administration.

4.2.12 Immunogenicity variables

The analysis of ADA to benralizumab is documented in the benralizumab ADA statistical analysis plan but the scope of the study ADA analysis will be modified as follows.

The ADA responses and nAb responses at any time point and at each specific time point will be summarized. ADA cumulative response will also be summarized by each time point. Summary of ADA titer will be presented by descriptive statistics.

Association between ADA and safety will be explored through summary statistics if there is sufficient number of ADA positive.

Due to limited efficacy data collection per study design and expected small number of ADA positive, the subgroup analyses for patients who are persistently or transiently ADA positive will not be evaluated. The association between ADA and efficacy will not be evaluated either for the same reason. In addition, summaries will not be produced by baseline blood eosinophils count cut off ($\geq$300 or <300 cells/μL) due to the limited sample size in the subgroup.

5. INTERIM ANALYSES (NOT APPLICABLE)

6. CHANGES OF ANALYSIS FROM PROTOCOL

Protocol Section 8.5.2 specifies to produce a shift table of physical examination from normal to abnormal between baseline and follow-up. However, the data collection standard was revised to not collect physical examination results into the database. Instead, any abnormal result is reported in the AE dataset. Therefore the shift table will not be produced for the study report.

7. REFERENCES

Juniper et al 2005
Juniper EF, Svensson K, Mörk AK, 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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Juniper E.F, Bousquet J., Abetz L., Bateman E.D.,The GOAL Committee. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med. 2006 100:616–21.

8. APPENDIX

8.1 Appendix A: Schedule of Events

Table 3 Study Plan – Enrolment, screening period

Assessment/ activity	Refer to protocol section	Screening	
		V1 (W –2)	V1A[d] (V1 + max. 3 days)
Informed consent	10.4	X	
Inclusion/exclusion criteria	3.1/3.2	X	
Medical and asthma history	4.1.1	X	
Complete physical examination	5.2.1.1	X	
Weight, Height, BMI	5.3.1	X	
Vital Signs	5.2.2	X	
Local ECG	5.2.3	X	
Serum chemistry	5.2.4	X	
Hematology	5.2.4	X	
Urinalysis	5.2.4	X	
Blood concentration (digoxin, theophylline) [a]	3.5.2.2	X	
Serology (hepatitis B,C; HIV-1; HIV-2)	5.3.3.1	X	
Serum pregnancy test	5.2.4.1	X	
FSH [b]	5.2.4.1	X	
Adverse events	7.1	X	
Concomitant medication	3.5	X	
ACQ-6 at Study Center	5.3.2.1	X	
Pre- and post-bronchodilator spirometry[c]	5.1.1	X	X[d]
Review of the AI IFU and the Administration Questionnaire	6.6	X	
Training on epinephrine-containing device	3.5.1.2	X	

[a] If and when appropriate prior to treatment period; for patients who are on theophylline or digoxin, (see Section 3.5.2.2)

[b] FSH test done only for female patients to confirm postmenopausal status in women <50 years who have been amenorrheic for >12 month

[c] Pre- and post-bronchodilator spirometry can be done at Visit 1 (or optional Visit 1A[d]) OR Visit 2

[d] Visit 1A is optional for spirometry measurement only

Table 4 Study Plan – Treatment period, and follow-up

Assessment/ activity	Refer to protocol section	Treatment					EOT	IPD	FU	Unsch
		V2	V3	V4	V5	V6	V7		V8	
		W0	W4	W8	W12	W16	W20		W28	
		Visit window (days) [a]								
		±3	±3	±3	±3[h]	±3[h]	±3	±3	±3	N/A
Inclusion/exclusion criteria	3.1/3.2	X								
Review of the AI IFU and Questionnaire	6.6	X	X	X	X[b]	X[b]				X[b]
Training on epinephrine-containing device	3.5.1.2	X	X	X	X					X[b]
Complete physical examination	5.2.1.1	X					X	X	X	
Brief physical examination	5.2.1.2		X	X	X	X				X
Vital Signs	5.2.2	X	X	X	X	X	X	X	X	X
Serum chemistry	5.2.4	X					X	X	X	
Hematology	5.2.4	X					X	X	X	
Urinalysis	5.2.4	X					X	X	X	
Urine pregnancy test (dipstick) [c]	5.2.4.1	X	X	X	X	X	X	X	X	
At-home urine pregnancy test before IP administration[c]	5.2.4.1				X	X				
PK	5.3.4	X*		X*			X	X	X	
ADA/nAb[j]	5.3.6	X*		X*			X	X	X	
ACQ-6 at Study Center	5.3.2.1	X	X	X	X	X	X	X		

Table 4 Study Plan – Treatment period, and follow-up

Assessment/ activity	Refer to protocol section	Treatment					EOT	IPD	FU	Unsch
		V2	V3	V4	V5	V6	V7		V8	
		W0	W4	W8	W12	W16	W20		W28	
		Visit window (days) [a]								
		±3	±3	±3	±3[h]	±3[h]	±3	±3	±3	N/A
Pre- and post-bronchodilator spirometry[i]	5.1.1	X								
Adverse events	7.1	X	X	X	X	X	X	X	X	X
Concomitant medication	3.5	X	X	X	X	X	X	X	X	X
IP Administration at site [g]	6.6	X[d]	X[e]	X[e]						
IP Administration at home [g]	6.6				X[e]	X[e]				
Visit Reminder Call [f]	6.6				X	X				
Return of AI and admin. questionnaire	6.5				X	X				

[a] All visits are to be scheduled from the date of Visit 2 but not from the date of previous visit except in the case of early discontinuation from IP (see Section 3.6 for details).

[b] At those Visits training/review with the patient is optional.

[c] For WOCBP only, a urine HCG test must be done prior to IP administration at Visits 2 (Week 0), 3 (Week 4), and 4 (Week 8) at the study center. At-home urine pregnancy tests are to be done by WOCBP prior to IP administration at Weeks 12 and 16 and repeated by the center staff at Visits 5 and 6. In the case of a positive test, the patient is NOT to administer IP and is to call the study center. Urine pregnancy tests will be done at the study center at the EOT visit (Visit 7, Week 20) and the Follow-up visit (Visit 8, Week 28).

[d] Study drug will be administered on site by HCP in either the arm, thigh, or abdomen

[e] At Visit 3, the patient/caregiver has the option to administer the study drug. At Visits 4, 5, and 6, the patient/caregiver must administer the study drug. If self-administered by the patient, the study drug can be given in the thigh or abdomen. If administered by the caregiver, the sites of injection are in the upper arm, thigh, or abdomen

[f] Study center to perform visit reminder call to the patient within 48 prior scheduled home administration date for V5 & V6

[g] In case of anaphylaxis, additional samples to be taken (see Section 6.7 and Appendix D)

[h] The ±3 day window is related to the IP administration at home and not the clinic visit, which should occur no later than 48h after IP administration

[i] Pre- and post-bronchodilator spirometry can be done at Visit 1 (optional Visit 1A) OR Visit 2.

[j] Neutralizing antibody (nAb) testing will occur for all samples that are ADA positive. Samples that are ADA negative will not be tested for nAb.

*** pre-dose sample**

EOT End-of-treatment; FU Follow-up; HCG Human chorionic gonadotropin; HCP Healthcare provider; IFU Instructions for Use; V Visit; W Week.