AstraZeneca

Statistical Analysis Plan

Study Code	D3250C00033
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A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3b Study to Evaluate the Potential Effect of Benralizumab on the Humoral Immune Response to the Seasonal Influenza Vaccination in Adolescent and Young Adult Patients with Severe Asthma (ALIZE)

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Study Statistician

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Global Product Statistician

[redacted]

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACQ-6	Asthma Control Questionnaire 6
ADA	Anti-drug antibodies
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
ARE	Antibody Response Evaluation
AST	Aspartate transaminase
ATS/ERS	American Thoracic Society/European Respiratory Society
Beta-HCG	Beta-human chorionic gonadotropin
BMI	Body mass index
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence interval
CO_2	Carbon dioxide
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of variation
ECG	Electrocardiogram
EOT	End of treatment
FAS	Full analysis set
FEV_1	Forced expiratory volume in 1 second
FU	Follow-up
FVC	Forced vital capacity
Gamma-GT	Gamma-glutamyl transpeptidase
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
GSD	Geometric standard deviation
HAI	Hemagglutination-inhibition
HCG	Human chorionic gonadotropin

Abbreviation or special term	Explanation
HIV	Human immunodeficiency virus
HPF	High power field
ICF	Informed consent form
ICS	Inhaled corticosteroids
IM	Inter-muscular
IP	Investigational product
IPD	Premature IP Discontinuation
ITT	Intent-to-Treat
LABA	Long-acting β_2 agonists
LSmeans	Least-square means
MedDRA	Medical Dictionary for Regulatory Activities
MN	Microneutralization antibodies to influenza vaccine
MVC	Mean corpuscular volume
PK	Pharmacokinetic
PT	MedDRA Preferred term
Post-BD	Post-bronchodilator
Pre-BD	Pre-bronchodilator
PRO	Patient-Reported Outcome
PT	Preferred term
RBC	Red blood cell
SABA	Short-acting β_2 agonists
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SI	Standard international
SOC	System organ class
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of childbearing potential

AMENDMENT HISTORY

Date	Brief description of change
	N/A
23Jan2017	Updated safety and tolerability analysis text based on updates to the table, listing, and figure mock shells. Updated the definition of the efficacy analysis set.

1. STUDY DETAILS

The study is a randomized, double-blind, parallel group, placebo-controlled study designed to investigate the potential effect of a fixed dose of benralizumab (30 mg) administered subcutaneously (SC) on humoral immune response following seasonal influenza virus vaccination.

This statistical analysis plan (SAP) is based on version 1.0 of the clinical study protocol (CSP – 14 December 2015) for the study D3250C00033.

1.1 Study objectives

1.1.1 Primary objectives

Objective	Endpoint
To evaluate the potential effect of benralizumab on the humoral immune response following seasonal influenza virus vaccination in adolescent and young adult patients with severe asthma	• Post-dose strain-specific hemagglutination-inhibition (HAI) antibody geometric mean fold rises (GMFRs) from Week 8 • Post-dose strain-specific serum HAI antibody geometric meant titers (GMTs) obtained at Week 12 • Proportion of patients who experience a strain-specific post-dose antibody response at Week 12 with antibody response defined as a ≥4-fold rise in HAI antibody titer from Week 8 • Proportion of patients who achieve a strain-specific post-dose HAI antibody titer ≥40 at Week 12

1.1.2 Secondary objectives

Objective	Endpoint
To further evaluate the potential effect of benralizumab on the humoral immune response following seasonal influenza virus vaccination in adolescent and young adult patients with severe asthma	• Proportion of patients who achieve a strain-specific post-dose HAI antibody titer ≥320 at Week 12 • Post-dose strain-specific microneutralization (MN) antibody GMFRs from Week 8 • Post-dose strain-specific serum MN antibody GMTs obtained at Week 12 • Proportion of patients who experience a strain-specific post-dose antibody response at Week 12 with antibody response defined as a ≥4-fold rise in MN antibody titer from Week 8
To assess the potential effect of benralizumab on asthma control	• Change from baseline in mean Asthma Control Questionnaire-6 (ACQ-6) score at Week 12

1.1.3 Safety objectives

Objective	Endpoint
To assess the safety and tolerability of benralizumab	• Adverse events (AEs) and serious adverse events (SAEs) • Laboratory variables • Physical Examination

1.2 Study design

This is a randomized, double-blind, parallel group, placebo-controlled study designed to investigate the potential effect of a fixed dose of benralizumab (30 mg) administered SC on the humoral immune response following seasonal influenza virus vaccination.

Approximately 100 male and female adolescent and young adult patients between 12 to 21 years of age with severe asthma will be randomized to receive SC benralizumab 30 mg or placebo administered at Weeks 0, 4, and 8. Randomization to the treatment groups will be assigned in each stratum (adolescents [12 to 17 years of age] and young adults [18 to 21 years of age]) as patients become eligible for randomization. Fifty percent or more of the patients will be in the adolescent age group (12 to 17 years of age). Patients will receive 1 dose of seasonal influenza virus vaccine inter-muscular (IM) at Week 8. Samples for evaluation of antibody response will be drawn at Week 8 and Week 12. An End of Treatment (EOT) visit

will be conducted at Week 12 and a Follow-up (FU) visit will be conducted at Week 20. Patients will be maintained on their currently prescribed inhaled corticosteroids (ICS)-long-acting β_2 agonists (LABA) therapy(ies) without change from enrollment throughout the screening and treatment period.

1.2.1 Duration of the Study

The total planned study duration is a maximum of 23 weeks.

1.2.1.1 Enrollment (Visit 1), Screening (Visit 2), and Re-screening

Each potential patient will provide written informed consent (ICF)/assent as appropriate with local guidance prior to any study specific procedures and undergo assessments applicable for the enrollment visit (Visit 1). After enrollment and confirmation of entry criteria, patients will proceed to screening period of a minimum of 2 weeks to allow adequate time for all of the eligibility criteria to be evaluated. Re-screening is allowed only once for the patient. Re-screened patient/parent or legal guardian should re-sign ICF/assent on the rescreening Visit 1. All procedures from the screening period should be repeated. Patients who experience an asthma exacerbation during screening should be treated according to local medical practice and will be considered a screen failure.

1.2.1.2 Randomization treatment period

Patients confirmed to be eligible will be randomized at Week 0 to receive 3 SC doses (at Weeks 0, 4, and 8) of benralizumab 30 mg or placebo. Patients will receive 1 dose of seasonal influenza virus vaccine IM at Week 8. Samples for evaluation of antibody response will be drawn at Week 8 (prior to administration of the vaccine) and Week 12. The EOT visit will be at Week 12, following the antibody response evaluation (ARE) assessments. All patients who prematurely discontinue investigational product (IP) should return to the study center and complete the procedures described for the premature IP discontinuation (IPD) visit within 4 weeks±3 days.

1.2.1.3 Follow-up Period

Patients who complete the double-blind randomized treatment period will be followed for 12 weeks after the last dose of IP for the Week 20 FU visit.

1.3 Number of subjects

The study will have an estimated sample size of 50 patients in each treatment group. No formal statistical hypotheses will be tested. The sample size justification is based on the precision of the estimate of the geometric mean titers (GMTs) (as $GMT_{vaccine}$ / $GMT_{benralizumab+vaccine}$). With 50 patients per arm, the 90% confidence interval (CI) for the GMT ratio would be 0.67 to 1.48, assuming an observed ratio of 1, and that the log (post-dose hemagglutination-inhibition [HAI] antibody titer or post-dose microneutralization antibodies to influenza vaccine [MN] antibody titer) is normally distributed with a standard deviation (SD) of 1.2 on the natural log scale (Langley et al 2013).

2. ANALYSIS SETS

2.1 Definition of analysis sets

Antibody endpoints to the influenza vaccine, strain-specific HAI and MN antibody geometric mean fold rises (GMFRs) and GMTs, will be analyzed using the vaccine immunogenicity analysis set. All remaining efficacy analyses will be performed using an Intent-to-Treat (ITT) approach based on the full analysis set (FAS). For consistency, demographic and baseline characteristics will be presented using the FAS. Safety objectives and anti-drug antibodies (ADA) will be analyzed based on the safety analysis set.

2.1.1 All patients analysis set

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

2.1.2 Full analysis set (FAS)

All patients randomized and receiving any IP will be included in the FAS, irrespective of their protocol adherence and continued participation in the study. Patients will be analyzed according to their randomized treatment, irrespective of whether or not they have prematurely discontinued, according to the ITT principle. Patients who withdraw consent to participate in the study will be included up to the date of their study termination.

2.1.3 Vaccine immunogenicity analysis set

The vaccine immunogenicity analysis set will include all randomized patients who received at least 1 dose of planned IP (ie, 1 dose of influenza vaccine, plus 1 dose of benralizumab or placebo), had pre- (Visit 5/Week 8) and post-dose (Visit 6/Week 12) for HAI or MN antibody measurements, and had no protocol deviations judged to have the potential to interfere with the generation or interpretation of an antibody response. The analyses conducted using this analysis set will be based on the actual treatment received. Protocol deviations will be reviewed and finalized by the study team before unblinding.

2.1.4 Safety analysis set

All patients who received at least 1 dose of IP will be included in the safety analysis set. Patients will be classified according to the treatment they actually received. A patient who has on one or several occasions received active treatment will be classified as active. All safety and ADA summaries will be based on this analysis set.

2.1.5 Pharmacokinetic analysis set

All patients who received benralizumab and from whom pharmacokinetic (PK) blood samples were obtained are assumed not to be affected by factors such as protocol violations. 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

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. All patients who meet the definition of FAS and safety analysis set will be included in the FAS and safety analysis set, respectively, regardless of these important protocol deviations. Definition of important protocol deviations based on inclusion and exclusion criteria are listed in Appendix A.

Important protocol deviations will be reviewed and finalized by the medical advisors and statisticians prior to database lock to help define the vaccine immunogenicity analysis set and PK analysis set.

2.2.1 Randomization issues

If the wrong treatment is administered to a patient, and the reason for the incorrect treatment is documented, this will be noted in the clinical study report (CSR). All safety data will be analyzed and presented according to the actual treatment received. Patients given the wrong medication to which they are randomized will not be included in the vaccine immunogenicity analysis set and PK analysis set.

2.3 Visit window definitions

Visit windows for assessments (ie, Laboratories, ACQ-6) will be based on the following tables.

Table 1 Visit windows for assessments conducted every 4 weeks

Adjusted Defined Windows Visit	Scheduled Study Day	Maximum Windows
Week 0 Day 1	1	Study Day=1
Week 4	29	2 ≤ Study Days ≤ 56
Week 12	85	57 ≤ Study Days

Table 2 Visit windows for laboratory assessments

Adjusted Defined Windows Visit	Scheduled Study Day	Maximum Windows
Week 0 Day 1	1	Study Day=1
Week 12	85	2 ≤ Study Days ≤ 112
Week 20 (Follow-up)	141	113 ≤ Study Days

3. PRIMARY AND SECONDARY VARIABLES

3.1 Efficacy variables

All efficacy objectives will be evaluated for the double-blind treatment period, defined as the period after administration of randomized IP at Week 0 and the conclusion of Visit 6 (Week 12; ARE/EOT) visit, inclusive.

3.1.1 Humoral immune response following seasonal influenza virus vaccination

Serum HAI and MN antibody testing for antibody responses will be performed at Visit 5 (Week 8) and Visit 6 (Week 12; ARE/EOT). The benralizumab versus placebo humoral immune responses following seasonal influenza virus vaccination will be assessed.

3.1.1.1 Primary outcome variables

- Post-dose strain-specific HAI antibody geometric mean folder rises (GMFRs) from Visit 5 (Week 8)
- Post-dose strain-specific HAI antibody geometric mean titers (GMTs) obtained at Visit 6 (Week 12; ARE/EOT)
- Proportion of patients who experience a strain-specific post-dose antibody response at Visit 6 (Week 12; ARE/EOT) with antibody response defined as a ≥4-fold rise in HAI antibody titer from Visit 5 (Week 8)
- Proportion of patients who achieve a strain-specific post-dose HAI antibody titer ≥40 at Visit 6 (Week 12; ARE/EOT).

3.1.1.2 Secondary outcome variables

- Proportion of patients who achieve a strain-specific post-dose HAI antibody titer ≥320 at Visit 6 (Week 12; ARE/EOT)
- Post-dose strain-specific microneutralization (MN) antibody GMFRs from Visit 5 (Week 8)
- Post-dose strain-specific serum MN antibody GMTs obtained at Visit 6 (Week 12; ARE/EOT)
- Proportion of patients who experience a strain-specific post-dose antibody response at Visit 6 (Week 12; ARE/EOT) with antibody response defined as a ≥4-fold rise in MN antibody titer from Visit 5 (Week 8)

3.1.2 Patient-reported outcome variables (PRO)

3.1.2.1 Secondary variable: Asthma Control Questionnaire (ACQ-6)

The questionnaire will be completed at the study center during the Treatment visits (Visit 3/Week 0, Visit 4/Week 4, and Visit 5/Week 8), Visit 6 (Week 12; ARE/EOT), and IPD visit when applicable.

The Asthma Control Questionnaire (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 β2 agonist use) omitting the forced expiratory volume in 1 second (FEV_1) measurement from the original ACQ 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 to the questions. The outcome variable for ACQ-6 will be the change in mean score from baseline at Visit 3 (Week 0).

Asthma control status will be categorized according to the following limits of the 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 Safety variables

The following safety data will be collected: all reported adverse events (AEs) and serious adverse events (SAEs), concomitant medications, hematology, clinical chemistry, urinalysis, physical examination, vital signs, electrocardiogram (ECG), asthma exacerbation, and ADA to benralizumab.

3.2.1 Spirometry (Baseline and Historical)

Lung function (reversibility, FEV_1, and forced vital capacity [FVC]) at the study center will be measured by spirometry at Visit 1 (Enrollment) or Visit 2 (Screening). Spirometry should be performed by the Investigator or authorized delegate according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller et al 2005). Patients should withhold their Short-acting β_2 agonists (SABA) medication(s) for at least 6 hours prior to Visit 2. If Visits 1 and 2 are combined, bronchodilator therapy(ies) with or without ICS should be withheld for 12-24 hours depending on whether the patient is using twice or once-daily bronchodilator-containing therapy.

Multiple forced expiratory efforts (at least 3 but no more than 8) will be performed for each center spirometry session and the 2 best efforts that meet the ATS/ERS acceptability and reproducibility criteria will be recorded. The best efforts will be based on the highest FEV_1. The absolute measurement (FEV_1 and FVC), the percentage of predicted normal value, and FEV_1/FVC ratio will be recorded using the local spirometer at the site with predicted values derived from the reference value of choice, eg, NHANES III 2010and Quanjer et al 2012. The highest FVC will also be reported regardless of the effort in which it occurred (even if the effort did not result in the highest FEV_1).

Post-bronchodilator spirometry

Post-bronchodilator (BD) spirometry will be performed to satisfy reversibility inclusion criterion 8 as defined in the CSP. The post-BD spirometry procedure should commence within 30±15 minutes according to the regimen for reversibility testing outlined in Section 5.1.2.1 of the CSP. The patient's usual morning asthma controller therapy must not be given until after the initial pre-medication, pre-BD spirogram is completed; usual asthma controller may be given after the post-BD spirogram.

The highest pre- and post-BD FEV1 should be used to determine reversibility.

Reversibility is calculated as follows:

$$\% \text{ Reversibility} = \frac{(\text{post-BD } FEV_1 - \text{pre-BD } FEV_1) \times 100}{\text{pre-BD FEV1}}$$

3.2.2 Adverse Events (AE)

The 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.

Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. The term AE is used to include both serious and non-serious AEs.

Definitions of serious adverse event

A SAE is an AE occurring during any study phase (ie, screening/run-in, treatment, washout, and follow-up), that fulfills one or more of the following criteria:

- Results in death

- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Recording of adverse events

All AEs, including SAEs, will be collected from the time the patient, parent, or legal guardian signs the ICF/assent throughout the treatment period and including the follow-up period (through Visit 7 [Week 20]).

Any AEs that are unresolved at follow-up in the study will be followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

The requirement to follow-up AEs is not intended to delay database lock or production of the CSR. These activities should proceed as planned with ongoing AEs if necessary.

Any follow-up information of ongoing SAEs after database lock will be reported to AstraZeneca.

The AE data will be categorized according to onset date:

- The AEs collected during the on-study are defined as those with onset date between day of first dose of study treatment and the day of the scheduled FU visit. This includes the day of the scheduled EOT visit for patients who complete study treatment or IPD visit for 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 summary analysis, but will still be presented in the data listings.

Any AEs with an onset date prior to the day of first dose of study treatment will only be presented in patient listings.

Rules for imputing AE start/stop dates which are completely or partially missing can be found in Appendix B. Missing start/stop dates will appear as missing in the patient data listings, but will be imputed to permit proper tabulation of AE data.

It is important to distinguish between SAEs and severe AEs. Severity is a measure of intensity (mild, moderate, or severe), whereas seriousness is defined by the criteria stated above. An AE of severe intensity need not necessarily be considered serious. If a patient reports multiple occurrences of the same AE within the same study period, the maximum intensity will be taken as the highest recorded maximum intensity (the order being mild, moderate, and severe).

The Investigator will assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'. A guide to the interpretation of the causality question is found in Appendix B of the CSP.

Potential Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of Aspartate transaminase (AST) or Alanine transaminase (ALT) ≥3xULN together with total bilirubin ≥2xULN may need to be reported as SAEs. Potential Hy's law definition and case confirmation are given in Appendix D of the CSP.

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

- AST
  ≥3 - <5x ULN
  ≥5 - <10x ULN
  ≥10x ULN

- ALT
  ≥3 - <5x ULN
  ≥5 - <10x ULN
  ≥10x ULN

- Total Bilirubin (Bilirubin)
  ≥2x ULN

3.2.3 Prior/concomitant medication

Prior medications are defined as those taken by the patients within 90 days and have stopped on or before the date of first dose of the IP at Visit 3 (Week 0).

Concomitant medications (allowed and disallowed) are defined:

- Medications that started prior to the date of first dose of the IP and continued after the first dose of the IP to study completion/discontinuation or stopped after the first dose of the IP.

- Medications taken on or after the date of first dose of the IP to study completion/discontinuation or stopped after the first dose of the IP.

Concomitant medications collected throughout the entire study and will be coded using the latest version of the WHO Drug Dictionary per the Data Management Plan.

3.2.4 Safety assessments

3.2.4.1 Clinical laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at Visit 1 (Enrollment), Visit 3 (Week 0), Visit 6 (Week 12; ARE/EOT), Visit 7 (Week 20; FU), and IPD visit when applicable.

The following laboratory variables will be measured:

Hematology	Clinical Chemistry	Urinalysis
Hematocrit	Alkaline phosphatase (ALP)	Appearance
Hemoglobin	Alanine transaminase (ALT)	Blood
Mean corpuscular volume (MCV)	Aspartate transaminase (AST)	Color
Platelet count	BUN (blood urea nitrogen)	Glucose
Red blood cell (RBC) count	Calcium	Ketones
White blood cell (WBC) count with differential[a]	Chloride	Microscopy including WBC/high power field (HPF), RBC/HPF
	CO2 (carbon dioxide)	
	Creatinine	
	Gamma-GT (gamma-glutamyl transpeptidase)	pH
		Specific gravity
	Glucose	
	Phosphorus	
	Potassium	
	Sodium	
	Total bilirubin	
	Total cholesterol	
	Uric acid	
	Theophylline[b]	

[a] In order to maintain blinding on treatment assignment, eosinophil, basophil and monocyte counts will be redacted from the central laboratory reports, except for Visit 1.
[b] Samples only collected for patients on theophylline at Visit 1.

Blood and urine samples will be assessed in a central laboratory. Laboratory data is to be reported in standard international (SI) units. Observed 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 range will be used for laboratory parameters. If the laboratory reference range is missing, the missing range will be queried to the central laboratory to confirm the reference range is not required for the laboratory parameter. All observed values falling outside the central lab reference ranges will be flagged. Baseline will be defined as last available non-missing result collected prior to IP dosing on Visit 3 (Week 0).

The following tests are applicable to female patients only:

- Serum beta-human chorionic gonadotropin (HCG): To be done at Visit 1 only, for women of childbearing potential (WOCBP) (analyzed at central laboratory)

- Urine HCG: To be performed at the study center for WOCBP at each treatment visit (before IP administration on Visits 3 to 5) using a dipstick. A positive urine test result must be confirmed with serum beta HCG.

3.2.4.2 Serology

Hepatitis B surface antigen, hepatitis C antibody: To be done only at Visit 1; test to be performed at central laboratory.

HIV-1 and HIV-2 antibodies: To be done only at Visit 1; test to be performed at central laboratory.

3.2.4.3 Vital signs

Pre-dose vital signs (pulse, blood pressure, respiration rate, and body temperature) are to be obtained at Visit 1 (Enrollment), Visit 2 (Screening), Treatment visits (Visit 3/Week 0, Visit 4/Week 4, and Visit 5/Week 8), Visit 6 (Week 12; ARE/EOT), Visit 7 (Week 20; FU), and IPD visit when applicable.

Body temperature is to be recorded in degrees Celsius.

Baseline will be defined as last available non-missing result collected prior to IP dosing on Visit 3 (Week 0).

Absolute values will be compared to the reference ranges in Table 3 and classified as low (below range), normal (within range or on limits), or high (above range). All absolute values falling outside the reference ranges will be flagged.

Table 3 Vital signs reference ranges

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

3.2.4.4 Physical examination

Complete physical examinations will be performed at Visit 1 (Enrollment), Visit 3 (Week 0), Visit 6 (Week 12; ARE/EOT), Visit 7 (Week 20; FU), and IPD visit when applicable. The brief physical examinations will be done at Treatment visits (Visit 4/Week 4 and Visit 5/Week 8).

Baseline data will be collected at Visit 1. Any new finding(s) or aggravated existing finding(s) judged as clinically significant by the Investigator will be reported as an AE.

The complete physical examination includes an assessment of the following: general appearance, skin, head and neck (including eyes, ears, nose, mouth, and throat), lymph nodes, abdomen, musculoskeletal (including spine and extremities), cardiovascular, respiratory, and neurological systems.

The brief physical examination includes an assessment of the general appearance, abdomen, cardiovascular, and respiratory system. For the brief physical examination only information on whether the assessment was performed or not is to be recorded.

3.2.4.5 Local electrocardiogram

The ECGs are to be performed at Visit 1 (Enrollment).

A 12-lead ECG will be taken in supine position, after the patient has been resting for at least 5 minutes. The assessment should be performed before interventions with the patient (eg, spirometry).

3.2.5 Other safety assessments

3.2.5.1 Weight and height

Weight and height will be measured, and body mass index (BMI) calculated at Visit 1 (Enrollment).

The patient’s weight will be recorded in kilograms; height will be recorded in centimeters.

3.2.5.2 Assessment of asthma exacerbation

An asthma exacerbation is defined by a worsening of asthma requiring the use of systemic corticosteroids (or an increase in oral steroid dose for those already on systemic corticosteroids) and/or an in-patient hospitalization, and/or an emergency department visit. Asthma exacerbation will be assessed at Treatment visits (Visit 3/Week 0, Visit 4/Week 4, and Visit 5/Week 8), Visit 6 (Week 12; ARE/EOT), Visit 7 (Week 20; FU), and IPD visit when applicable.

An asthma exacerbation that occurs ≤7 days following the last dose of systemic steroids (oral, IM, IV), prescribed for a prior exacerbation, will be recorded as the same exacerbation event.

Asthma exacerbation information will be collected with a recall period of 'since the last scheduled visit'.

3.2.5.3 Benralizumab immunogenicity variables

Serum samples for ADA assessments will be collected pre-dose at Treatment visits (Visit 3/Week 0 and Visit 5/Week 8), Visit 6 (Week 12; ARE/EOT), Visit 7 (Week 20; FU), and IPD visit when applicable to measure presence of ADA to benralizumab.

A 3-tiered testing plan, which consisted of validated screening, confirmatory, and titering assays, was used to analyze clinical samples. The samples will be retained for repeat analysis of ADA at AstraZeneca or a designee for a maximum of 1 year following completion of the CSR.

ADA result from each sample will be reported as either positive or negative. A subject with a positive result will also be further defined as persistent or transient positive. Persistent positive is defined as positive result at ≥2 post-baseline assessments (with ≥16 weeks between first and last positive) or positive at last post-baseline assessment. Transient positive is defined as having at least one post baseline ADA positive assessment and not fulfilling the conditions of persistent positive. If the sample is positive, the ADA titer will be reported as well.

3.3 Pharmacokinetic variables

Benralizumab serum concentrations will be collected pre-dose at Treatment visits (Visit 3/Week 0 and Visit 5/Week 8), Visit 6 (Week 12; ARE/EOT), Visit 7 (Week 20; FU), and IPD visit when applicable. For the PK analysis it is important that the date and time of each SC injection is recorded for each patient.

Due to the limited sampling schedule, the PK assessment will be primarily based on the observed steady-state serum trough (pre-dose) concentrations, C_{trough}. Empirical evaluation of potential impact of demographic covariates and ADA on C_{trough} will be conducted.

3.4 Pharmacodynamics

Samples for the analysis of peripheral blood eosinophils will be performed in a central laboratory as part of the routine hematology assessment (complete blood count [CBC]). The data will be available after database lock.

4. ANALYSIS METHODS

4.1 General principles

4.1.1 General methodology

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

Individual data will be presented in patient listings. All patient data listings will be sorted by treatment group and patient number.

All efficacy, safety, and PK concentration variables will be summarized using descriptive statistics by treatment group. Graphs will be produced as appropriate. Continuous variables will be summarized by descriptive statistics (sample size [n], arithmetic mean, SD, minimum, median and maximum). Categorical variables will be summarized in frequency tables (frequencies and percentages).

Means and medians will be displayed with one more decimal place than the collected data, and SDs will have one more decimal place than the means and medians. Minimums and maximums will be displayed with the same number of decimal places as the collected data. For discrete variables, population size (N for analysis set size and n for available data) and percentage will be presented. Percentages will be displayed with one decimal place.

Patient characteristics (eg, demographic and other baseline characteristics) and study medication information will be summarized by treatment group and overall. Efficacy, safety, and PK concentration data will be summarized by treatment group and assessment visit, when applicable.

4.1.2 Vaccine immunogenicity data

All observed vaccine immunogenicity values will be included in the primary and secondary analyses. Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics, but will be included in data listings.

4.1.3 Patient-reported outcome data

All PRO values will be included in the secondary analysis. Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics, but will be included in data listings.

4.1.4 Handling of safety data

All patients in the safety analysis set will be included in the safety analyses. All safety measurements will use all available data for analyses, including data from unscheduled visits and repeated measurements. No safety data results will be imputed.

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

For laboratory 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.

4.1.5 Handling of PK concentration data

Samples for determination of benralizumab concentration in serum will be analyzed by a central laboratory on behalf of AstraZeneca, using a validated bioanalytical method. Details of the analytical method used will be described in a bioanalytical report.

4.1.6 Handling of missing data

For the datasets used for summary of demographic and baseline characteristics, efficacy, safety, and PK concentration; each variable will be analyzed and/or summarized using the available data. Patients with missing data will be excluded only from analyses for which data are not available.

Unscheduled visit or retest measurements at a scheduled time point will be provided in subject listings. If the retest measurement occurs prior to the first IP dosing, the retest measurement will be used in the summary statistics if it is the last non-missing measurement taken prior to the first dose. The retest measurements will not be used in summary statistics for post-dose measurements. If all scheduled measurements for a specific variable are missing for a patient, the unscheduled measurements will be included in the analysis and footnoted in the table. The decision to use the unscheduled measurements will be determined prior to database lock.

The PK analysis set will not include a PK measurement with important protocol deviations/violations or events thought to significantly affect the PK analysis as defined in Section 2.1.5. Data from patients excluded from the PK analysis set will be included in the data listings, but not in the descriptive or inferential statistics.

Descriptive presentations will be based on observed cases. No adjustment or imputation will be utilized for missing values or for patients who withdraw prior to completing the study after the enrollment visit, nor will analyses be restricted to patients with complete data.

AE and concomitant medication missing start/stop dates will appear as missing in the patient data listings, but will be imputed to permit the proper tabulation of AE and medication data. The imputation of missing AE and concomitant medication onset/start and end/stop dates will

be used to determine the status of each AE and the previous/concomitant status of each medication. Please refer to Appendix B for the method of imputation of missing AE onset/start and end/stop dates and Appendix C for the method of imputation of missing concomitant medication onset/start and end/stop dates.

4.2 Analysis methods

4.2.1 Analysis of patient characteristics

Descriptive statistics on patient disposition will be summarized using the all patients analysis set defined in Section 2.1.1. All descriptive statistics for demographic and other baseline characteristics, medical history, and prior and concomitant medications will be presented based on the FAS.

4.2.1.1 Patient disposition

The total number of patients will be summarized for the following groups: those who enrolled, and those who were not randomized (and reason). The number and percentage of patients within each treatment group and overall will be presented by the following categories; randomized, received treatment, did not receive treatment (and reason), completed treatment, discontinued treatment (and reason), discontinued treatment but completed study follow-up, completed study, and withdrawn from study (and reason).

Screen failure information will be listed for the all patients analysis set.

The number and percentage of patients included in each of the analysis sets; vaccine immunogenicity, PK, and safety, will be tabulated. Reasons for exclusion from analysis datasets will also be provided.

A listing will be presented to describe: study treatment, date treatment/study completed or terminated, and the reason for post-randomization discontinuation for each patient.

4.2.1.2 Important protocol deviations

The number and percentages of patients with at least one important protocol deviation will be summarized for treatment group and overall.

A listing of all patients with any important protocol deviations will be provided.

4.2.1.3 Demographic and other baseline characteristics

Demographic characteristics and other baseline characteristics such as age, sex, race, ethnicity, weight, height, BMI, and BMI groups will be summarized by treatment group and overall using descriptive statistics. Age will be derived from the date of informed consent-date of birth, rounded down to the nearest integer. The BMI groups are Underweight (<18.5), Normal (≥18.5 to <25), Overweight (25 to 30), and Obese (>30).

Listings of all patients demographic and baseline characteristics will be provided.

4.2.1.4 Concomitant treatments

All prior and concomitant medications will be classified according to the terminology of the latest of the WHO Drug Dictionary per the Data Management Plan. The number and percentage of patients with disallowed and allowed concomitant medications will be tabulated by ATC Term and Drug Preferred Name by treatment group and overall.

Patients taking the same medication multiple times will only be counted once for that ATC Term or drug preferred name.

Medications with start/stop dates that are partially/completely missing will be analyzed as described in Appendix C.

Listing of all prior and concomitant medications for each patient will be provided.

4.2.1.5 Past and current medical conditions/diseases

All medical/surgical/respiratory disease history will be classified according to the terminology of the latest version of the MedDRA.

Past medical conditions/diseases are those medical conditions/diseases that stopped prior to the study entry (Visit 1) while current medical conditions/diseases are those medical conditions/diseases that are still present at the study entry (Visit 1).

The number of patients with any relevant past and current medical conditions/diseases will be tabulated by MedDRA system organ class (SOC) and preferred term (PT) by treatment group. A patient will only be counted once within a particular SOC (or PT) even if he/she has multiple conditions/diseases in the same SOC (or PT).

Past and current medical history and surgical history will be presented as part of the patient data listings.

4.2.2 Spirometry (baseline and historical)

Lung function data for pre-BD, post-BD, and reversibility (Section 3.2.1) results will be summarized by treatment group and overall using descriptive statistics.

All lung function data will be provided in patient data listings.

4.2.3 Efficacy analysis (primary and secondary variables)

4.2.3.1 Primary and secondary variables: Humoral immune response following seasonal influenza virus vaccination

The analysis of the antibody endpoints will be summarized by descriptive statistics (strain-specific GMFRs and GMTs, geometric standard deviation [GSD] and geometric coefficient of variation [CV]).

GMFRs for the HAI and MN antibody measurements are defined as:

$$GMFR = antilog_z (mean [log_z x])$$

Where x is the post-dose HAI or MN antibody titer fold rise from Visit 5 (Week 8) and z is the natural logarithm. The GMFR value for each subject will be calculated as the GMT ratio between Visit 6 (Week 12)/Visit 5 (Week 8), where GMT is calculated for each subject at each visit based on the definition below.

GMTs for the HAI and MN antibody measurements are defined as:

$$GMT = antilog_z (mean [log_z y])$$

Where y is the HAI or MN antibody titer and z is the natural logarithm.

The analysis of the HAI or MN antibody endpoints (Section 3.1.1.1), strain-specific GMFRs and GMTs, will be performed on the vaccine immunogenicity analysis set.

Number and percentage of patients with HAI or MN antibodies will be summarized by titer, visit, and treatment group. Incidence of negative and positive antibodies will also be summarized descriptively by visit and treatment group.

The strain-specific HAI or MN antibody endpoints (GMFRs and GMTs) will be summarized by treatment group for each assessment visit.

For GMFR and GMT, the geometric least square mean (LSmean) ratio between treatment (placebo/benralizumab) along with the corresponding 90% CI will be calculated via an Analysis of covariance (ANCOVA) model on the log transformed variable (antibody titer fold rise from Week 8 or antibody titer at Week 12). The linear model effects are treatment group as a fixed effect and age group (adolescents and young adults) as fixed categorical covariate. The model based natural log estimates of the LSmeans for each treatment and the differences of the LSmeans (placebo - benralizumab) along with the corresponding 90% CI will be exponentiated. The geometric LSmeans for each treatment and geometric LSmean ratio with 90% CI will be presented.

Antibody response is defined as a ≥4-fold rise in HAI or MN antibody from Week 8 to Week 12. The proportion of patients who experience a post-dose antibody response at Week 12 and corresponding 90% Clopper-Pearson exact CI will be summarized by treatment.

The proportion of patients who achieve a post-dose HAI antibody titer ≥40 at Week 12 and corresponding 90% Clopper-Pearson exact CI will be summarized by treatment.

The proportion of patients who achieve a post-dose HAI antibody titer ≥320 at Week 12 and corresponding 90% Clopper-Pearson exact CI will be summarized by treatment.

4.2.4 Patient-reported outcome (PRO) variables

4.2.4.1 Secondary variable: Asthma Control Questionnaire (ACQ-6)

The analysis of the ACQ-6 score data (Section 3.1.2.1) will be performed on the FAS. The ACQ-6 score data actual and change from baseline results will be summarized by visit and treatment group using descriptive statistics. The frequency (number and percentage) of ACQ-6 asthma control responder status will be summarized at Baseline and Week 12 (EOT) by treatment group according to the following limits:

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

4.2.5 Safety and tolerability analysis

All safety and tolerability variables will be summarized descriptively by treatment group using the safety analysis set.

4.2.5.1 Adverse events

All AEs will be coded using the MedDRA.

- The number and percentages of patients who experienced at least 1 AE will be summarized by SOC and PT.
- SAEs and AEs leading to study discontinuation will be tabulated.
- AEs will be summarized by maximum intensity and causally-related to study medication.
- AEs, SAEs, and AEs leading to study discontinuation will be listed with time to onset of event from the recent IP dose and total dose of IP received prior to the event.

Unless otherwise specified, all percentages (%) will be calculated out of the number of patients per treatment group in the safety analysis set.

All summary tables will be sorted by decreasing order of frequency of MedDRA SOC (if applicable) and within each SOC by decreasing order of frequency of PT by overall number.

An overview of AEs will be given describing the total number patients with AEs during the enrollment and during the randomized treatment period in each of the following categories:

- Any AE

- Any AE with outcome = death
- Any SAE (including outcome = death)
- Any AE leading to discontinuation of investigational product
- Any AE of maximum intensity
- Any causally related AE as judged by the Investigator

All AEs and SAEs will be provided in patient data listings.

The frequency of maximum post-baseline ALT/AST values with respect to maximum post-baseline bilirubin values for assessing potential Hy's law criteria will be tabulated by treatment group. Patients that meet potential Hy's Law criteria will be provided in patient data listings.

4.2.5.2 Clinical laboratory

Laboratory data for hematology and clinical chemistry (Section 3.2.4.1) actual and change from baseline results will be summarized by visit and treatment group using descriptive statistics. The frequency of changes (shift from baseline) with respect to normal ranges (high/low/normal findings) between baseline and minimum/maximum post-baseline values will be tabulated by treatment group. Shifts from normal to out of range values between baseline and maximum post-baseline values will be evaluated for categorical urinalysis tests by treatment group.

All laboratory data will be provided in patient data listings.

4.2.5.3 Vital signs

Vital signs (Section 3.2.4.2) actual and change from baseline results will be summarized by visit and treatment group using descriptive statistics. The frequency of changes (shift from baseline) with respect to normal ranges (high/low/normal findings) between baseline and minimum/maximum post-baseline values will be tabulated by treatment group.

4.2.5.4 Assessment of asthma exacerbation

The frequency (number and percentage) of number of asthma exacerbations (Section 3.2.5.2) will be summarized by treatment group. The total follow-up time since the last exacerbation will be summarized (median, minimum, and maximum) by treatment group.

4.2.5.5 Benralizumab immunogenicity variables analysis

The incidence of negative or positive ADA response to benralizumab (Section 3.2.5.3) will be summarized descriptively by visit. A table will present a listings of patients with persistent and transient positive ADA result at any time point, along with the corresponding PK concentration.

4.2.6 Pharmacokinetic variables analysis

The analysis of the benralizumab serum concentrations data (Section 3.3) will performed on the PK analysis set. Benralizumab serum concentrations will be summarized using descriptive statistics at each visit by treatment group. Graphical assessments of steady-state for benralizumab will be performed using C_{trough} concentration samples collected following multiple-dose administration. Arithmetic mean predose concentrations (±SD) will be plotted against visit to visually evaluate attainment of steady-state for benralizumab.

All benralizumab serum concentrations will be provided in patient data listings.

5. INTERIM ANALYSES

There are no interim analyses planned for this study.

6. CHANGES OF ANALYSIS FROM PROTOCOL

The definition of the vaccine immunogenicity analysis set was updated to include subjects in the analysis if the subjects have pre- and post-dose of HAI or MN antibody measurements. The CSP stated that subjects should have antibody measurements from both HAI and MN antibodies.

The CSP stated that AEs will be summarized by study period (on-study, on-treatment, and follow-up period). Since the study duration time is short, the summary of the AEs was updated to summarize on-study AEs.

7. REFERENCES

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8. APPENDIX

8.1 Appendix A: Important Protocol Deviations

Table 8.1.1 Definition of important protocol deviations

Visit	Number	Important deviation
Treatment	V1	Time from influenza vaccine (Visit 5) to antibody response assessment (Visit 6) is less than 14 days.
Enrollment and Randomization	V2	ICS dose <500 µg fluticasone propionate dry powder formulation or equivalent daily using separate inhaler for ICS.

ICS = Inhaled corticosteroids

Reference V1: https://www.cdc.gov/flu/protect/keyfacts.htm.

Reference V2: This is a subsection of inclusion criterion question 6 in the CSP.

8.2 Appendix B: Partial Date Conventions for Adverse Events

Missing type	Action
If only the **day part** of the AE **onset date** is missing and occurs in the same month and year as the first dose of study medication, the missing day of onset of 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.
If the **day and month parts** of the AE **onset date** are missing and occur in the same year as the first dose of study medication, the date of onset of AE 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 only the **day part** of the AE **resolution date** is missing and occurs before or in the same month and year as the first dose of study medication, the missing day of resolution of 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 **day and month parts** of the AE **resolution date** are missing, the date of resolution of AE 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.

8.3 Appendix C: Algorithm for Prior/Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date ≥ study med start date and start date ≤ study med last date +30 days, assign as concomitant If stop date ≥ study med start date and start date > study med last date +30 days, assign as post study
	Partial	Impute stop date as latest possible date (ie, last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date ≥ study med start date and start date ≤ study med last date + 30 days, assign as concomitant If stop date ≥ study med start date and start date > study med last date + 30 days, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date ≤ study med last date + 30 days, assign as concomitant If start date > study med last date + 30 days, assign as post treatment
Partial	Known	Impute start date as earliest possible date (ie, first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date ≥ study med start date and start date ≤ study med last date +30 days, assign as concomitant If stop date ≥ study med start date and start date > study med last date +30 days, assign as post treatment
	Partial	Impute start date as earliest possible date (ie, first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (ie, last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date ≥ study med start date and start date ≤ study med last date +30 days, assign as concomitant If stop date ≥ study med start date and start date > study med last date +30 days, assign as post treatment
	Missing	Impute start date as earliest possible date (ie, first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date ≤ study med last date +30 days, assign as concomitant If start date > study med last date +30 days, assign as post treatment

START DATE	STOP DATE	ACTION
Missing	Known	If stop date < study med start date, assign as prior If stop date ≥ study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (ie, last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date ≥ study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant