Clinical Study Protocol	
Study Intervention	Benralizumab
Study Code	D3256C00001
Version	3
Date	04 May 2021

A Phase 2 Multinational, Randomized, Double-blind, Parallel-group, 16-week Placebo-controlled Study with a 36–week Extension to Investigate the Use of Benralizumab for Patients with Moderate to Severe Atopic Dermatitis Despite Treatment with Topical Medications (The HILLIER Study)

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Regulatory Agency Identifying Number(s):

EudraCT number 2020-000285-42; IND CCI

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D3256C00001

Amendment Number: 2

Study Intervention: Benralizumab

Study Phase: 2

Short Title:

A phase 2 study to investigate the use of benralizumab in patients with moderate to severe atopic dermatitis

The HILLIER Study

Study Physician Name and Contact Information will be provided separately

International Co-ordinating Investigator:

PPD

NY 10029
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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	04 May 2021
Amendment 1	18 June 2020
Original Protocol	19 March 2020

Amendment 2 (04 May 2021)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The primary rationale for this amendment is to align the contents of the clinical study protocol with the updated project specific safety requirements for benralizumab studies. Other changes were made as points of clarification, alignment with the updated protocol template, and correction of minor errors or omissions.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Throughout	The term “medical monitor” was replaced by “study physician”.	To ensure consistency with the latest protocol template.	Non-substantial
Throughout	The term “congenital abnormalities” was amended to “congenital anomalies”.	To ensure consistency with the latest protocol template.	Non-substantial
Throughout	The term “women” was amended to “females”.	To ensure consistency throughout the protocol and to reflect the adolescent population.	Non-substantial
Throughout	Minor editorial changes.	To ensure consistency with the latest protocol template.	Non-substantial
Title Page	The IND number was updated and the amendment number changed to amendment 2.	The IND number was updated on request from the FDA.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Title Page	The Coordinating Investigator address was updated.	To update to the current Coordinating Investigator address.	Non-substantial
1.2 Schema	The study schematic was replaced with an updated version.	The updated version of the schematic is provided for additional clarity.	Non-substantial
1.3 Schedule of Activities	The healthcare resource utilization assessment at run-in was removed.	This was previously included at run-in in error.	Non-substantial
	The electrocardiogram assessment was moved from Visit 2 to Visit 1.	To ensure that electrocardiogram results are available no later than randomization.	Non-substantial
	A hematology assessment to include eosinophils only was added to Visit 3.	Previously omitted from the table in error.	Non-substantial
	The following samples were removed from the follow-up visit: • Pharmacokinetic sample prior to IP administration • Immunogenicity sample.	These assessments are not needed for the follow-up visit and thus were removed.	Non-substantial
2.3.2 Risk Assessment, 6.1.1 Investigational Products, 8.3.12 Management of Investigational Product-related Drug Reactions	Removal of 'one hour' in relation to the duration of observation following IP administration, and addition of the more general statement of 'in line with clinical practice'.	Updated based on benralizumab safety data	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
4.1.1 Study Conduct Mitigation During Disruptions	New wording was added to clarify that if participant testing is performed due to the public health crisis, the results may be documented for this study.	Updated in consistency with other studies of the same program and to better clarify mitigation procedures during disruptions.	Non-substantial
5.1 Inclusion Criterion	Criterion 3 "body weight ≥ 35 kg" was removed.	Benralizumab exposure is not affected by weight and therefore this criterion is not required.	Non-substantial
	Criterion 9 was amended to correct the reference to exclusion criterion 23 to state exclusion criterion 11.	To correct previous error.	Non-substantial
5.2 Exclusion Criterion	Criterion 6 "history of Guillain-Barré syndrome" was removed.	Guillain-Barré syndrome is not a required exclusion criterion for benralizumab and was previously included in error.	Non-substantial
	Criterion 13 was replaced with the following "Use of immunosuppressive medication, including, but not limited to: methotrexate, cyclosporine, azathioprine, systemic corticosteroids within 4 weeks or 5 half-lives prior to the date informed consent/assent is obtained, whichever is longer."	Text amended to align with the updated project specific safety requirements for the benralizumab development program.	Non-substantial
	Criterion 21 was updated to clarify that elective major surgical procedures during the conduct of the study lead to participant exclusion.	Updated for improved clarity.	Non-substantial
5.3 Lifestyle considerations	The inclusion criterion number referring to the definition of females of childbearing potential was updated from 13 to 11.	Updated to reflect the correct number in this protocol version.	Non-substantial
6.3.2 Blinding	It was clarified that CCI assessments will be made in a central laboratory.	Updated for improved clarity.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
6.5 Concomitant Medications	Clarified in the text that any prior biologic medication(s) are to be collected in the electronic case report form.	Updated to clarify that prior biologic medication(s) are to be collected.	Non-substantial
6.5.4 Restrictions	Topical anti-inflammatory medications were removed from the list of restricted medications.	This bullet has been included in duplicate.	Non-substantial
	The following bullet was added to the restrictions: • Receipt of inactive/killed vaccinations (eg, inactive influenza) is allowed provided they are not administered within 1 week before/after any IP administration; additionally, it is recommended to rotate the next IP site injection to a site distant from the vaccine site injection.	Exclusion of inactive vaccines was inadvertently not included in the previous versions and has been added so as to align with the current benralizumab safety information.	Non-substantial
8 Study assessments and procedures	A note was added, stating that if not all laboratory kits are available at a given visit, the Investigator should contact the Study Physician to confirm whether the assessment is critical or may be postponed until supplies are available.	To allow for improved feasibility and to conduct study visits, in case specific laboratory kits are not available at a given time point.	Non-substantial
8.2.1.1 Pregnancy tests	The inclusion criterion number referring to the definition of females not of childbearing potential was updated from 11 to 12.	Updated to reflect the correct number in this protocol version.	Non-substantial
8.2.3 Vital signs	Wording was updated to clarify that pulse rate and blood pressure will be (instead of "should be") measured after the participant has been resting for at least 5 minutes, and that the pulse rate should be (instead of "will be") obtained before blood pressure.	Updated for improved clarity.	Non-substantial
8.3.2 Follow-up of AEs and SAEs	"Description of AE" was included as one of the variables to be collected for SAEs.	Omitted previously from the protocol by error.	Non-substantial
8.3.9 Device	Section was added to provide details of actions required in the case of a deficiency in the drug	Section was updated to meet	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Constituent Deficiencies	device constituents. In consequence, the previous Section 8.3.9 "malfunction of CCI [redacted]" was removed.	new regulatory requirements.	
8.3.10 Serious Adverse Device Effect Reporting	This section was added to provide details of reporting requirements in case of SADE.	Section was updated to meet new regulatory requirements.	Non-substantial
Appendix A 1 Regulatory and Ethical Considerations	The following text has been included: "The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations."	To align with the updated protocol template.	Non-substantial
Appendix A 3 Informed Consent/Assent Process	The following sentence was removed "If a participant's partner becomes pregnant during or within 12 weeks after the last dose of study drug, the partner will be asked to sign the "Adult Study Informed Consent/Assent Form for Pregnant Partners of Study Participants" and provide information about the pregnancy accordingly."	Text amended to align with the updated project specific safety requirements for the benralizumab development program.	Non-substantial
Appendix A 6 Dissemination of Clinical Study Data	The link http://astrazenecaclinicaltrials.com was replaced with http://astrazenecagrouptrials.pharmacm.com.	To align with the updated protocol template.	Non-substantial
Appendix A 7 Data Quality Assurance	Text updated to clarify that the Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the electronic case report form.	To align with the updated protocol template and procedures.	Non-substantial

CFR, Code of Federal Regulations; FDA, Food and Drug Administration; IEC, Independent Ethics Committee; ICH, International Council for Harmonisation; IND, Investigational New Drug; IP, investigational product; IRB, Institutional Review Board SADE, serious adverse device effects.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A Phase 2 Multinational, Randomized, Double-blind, Parallel-group, 16-week Placebo-controlled Study with a 36–week Extension to Investigate the Use of Benralizumab for Patients with Moderate to Severe Atopic Dermatitis Despite Treatment with Topical Medications (The HILLIER Study)

Short Title:

A Phase 2 study to investigate the use of benralizumab in patients with moderate to severe atopic dermatitis despite treatment with topical medications (The HILLIER Study)

Rationale: The aim of this study is to investigate the use of benralizumab as treatment for patients with moderate to severe atopic dermatitis (AD) who remain symptomatic despite treatment with topical medications. It is proposed that benralizumab will deplete eosinophils from affected skin, improve symptoms of AD, and improve AD-related quality of life. This Phase 2 study is designed to compare the efficacy of 16 weeks of treatment with benralizumab 30 mg versus placebo and compare benralizumab maintenance dosing regimens (every 8 weeks [Q8W] versus every 4 weeks [Q4W]) in the 36-week extension period.

Objectives and Endpoints:

The primary and secondary objectives and associated endpoints are detailed below. For tertiary/exploratory objectives and endpoints, see Section 3 of this protocol.

Table 1 Primary and Secondary Objectives

Primary objective:	**Estimand description/endpoints**
To compare the clinical efficacy of benralizumab 30 mg with placebo in patients with AD despite treatment with topical medications [a].	• Population: Full analysis set • Endpoint: A binary response giving the proportion of patients with an IGA 0/1 and a decrease in IGA of ≥ 2 points at Week 16 relative to baseline • Intercurrent events: Participants who withdraw from the study or require rescue therapy [b] will be considered as non-responders from the time these events occur up to Week 16. • Summary measure: Difference in proportions between benralizumab and placebo at Week 16
Secondary objectives:	**Endpoint/variable:**
To compare the effect of benralizumab with placebo on supportive measures of clinical efficacy in patients with AD despite treatment with topical medications [a].	• Key secondary endpoint [c]: proportion of patients with skin clearance (EASI-75) at Week 16 • Key secondary endpoint [c]: proportion of patients with an improvement of ≥ 4 or more points in peak pruritus weekly score at Week 16 • Key secondary endpoint [c]: proportion of patients with skin clearance (EASI-90) at Week 16 • Proportion of patients with skin clearance (EASI-50) at Week 16 • Proportion of patients with skin clearance (EASI-100) at Week 16 • Change from baseline in EASI score at Week 16 • Change from baseline in peak pruritus score at Week 2 • Change from baseline in POEM score at Week 16 • Change from baseline in SCORAD score at Week 16
To compare benralizumab with placebo on patient-reported health-related quality of life measures in patients with AD despite treatment with topical medications [a].	• Change from baseline in DLQI and CDLQI at Week 16
To estimate the PK and immunogenicity of benralizumab 30 mg in patients with AD despite treatment with topical medications [a].	• Serum benralizumab concentration • ADA
To compare long-term treatment with benralizumab 30 mg Q8W versus benralizumab 30 mg Q4W up to Week 52 in patients with AD despite treatment with topical medications [a].	• Change from baseline in EASI total score at Week 52. • Proportion of patients with an IGA 0/1 and a decrease in IGA of ≥ 2 points at Week 52 relative to baseline • Proportion of patients with EASI-75 at Week 52 • Other supportive efficacy assessments at Week 52 as appropriate.

Table 1 Primary and Secondary Objectives

Safety	
To compare the safety and tolerability of benralizumab with placebo in patients with AD despite treatment with topical medications [a].	Safety and tolerability will be evaluated in terms of AEs, Vital signs, and Clinical laboratory values. Assessments related to AEs cover: • Occurrence/frequency • Relationship to IP as assessed by Investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP Vital signs parameters include systolic and diastolic blood pressure, and pulse, as well as respiration rate, body temperature, body weight, and height. Assessments related to vital signs cover: • Observed value • Absolute and percent change from baseline values over time

[a] The locally-approved regimen of topical medication.

[b] Rescue therapy is defined in Section 6.5.3.

[c] The key secondary endpoints will use the same estimand as outlined for the primary endpoint. For all other endpoints, the estimands will be detailed in the SAP.

AD, atopic dermatitis; ADA, anti-drug antibodies; AE, adverse event; CDLQI, The Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; IP, investigational product; PK, pharmacokinetics; POEM, Patient Oriented Eczema Measure; Q4W, every 4 weeks; Q8W, every 8 weeks; SAP, Statistical Analysis Plan; SCORAD, SCORing Atopic Dermatitis.

Overall Design

This is a Phase 2 multinational, randomized, double-blind, placebo-controlled, parallel-group study to compare the efficacy and safety of benralizumab 30 mg monotherapy with placebo in patients ≥ 12 years of age with moderate to severe AD who remain symptomatic despite treatment with standard of care treatment with topical medications. The purpose of the study is to compare the efficacy and safety of benralizumab 30 mg subcutaneously (SC) Q4W versus placebo SC Q4W for 16 weeks and to compare benralizumab 30 mg Q4W and Q8W maintenance dosing regimens during a 36-week extension period.

The study comprises the following consecutive periods:

- A 1- to 4-week run-in period, which includes a 7-day washout period of topical medications prior to randomization
- A 16-week placebo-controlled, double-blind treatment period
- A 36-week blinded-to-dosing regimen extension period for maintenance treatment.

Following informed consent/assent, all eligible participants will enter a run-in period of 1 to 4 weeks during which inclusion/exclusion criteria will be assessed, medical history taken, and a complete physical exam will be conducted. Potentially eligible participants will enter a 7-day washout period (prior to randomization) during which all topical medications for AD except the stable emollient moisturizer regimen must be discontinued. Randomization will be stratified by baseline blood eosinophil and age subgroups.

An independent Data and Safety Monitoring Board (DSMB) will be utilized.

Disclosure Statement:

This is a Phase 2 parallel-group, placebo-controlled study with 3 treatment sequences that are participant- and investigator-blinded.

Number of Participants:

Approximately 270 participants are expected to be enrolled/screened in order to achieve at least 160, and a maximum of 200, eligible study participants randomly assigned to study intervention to ensure that a broad distribution of participants is recruited across the range of ages and blood eosinophil levels to allow potential identification of responding subpopulations and appropriate cut-offs for future studies, if necessary.

Note: "Enrolled" is defined as a participant's agreement to participate in a clinical study following completion of the informed consent/assent process. Potential participants who are screened for the purpose of determining eligibility for the study but are not randomized to the study will be considered “screen failures”, unless otherwise specified by the protocol.

Intervention Groups and Duration:

Following a 1- to 4-week run-in period, a minimum of approximately 160 participants will be randomized in a ratio of 1:1:2, respectively, to 1 of the following 3 treatment sequences (refer also to Figure 1 and Figure 2):

- **Benralizumab 30 mg Q4W** until Week 16, followed by an extension period with **benralizumab 30 mg Q4W** administered until Week 52 (n = 40)
- **Benralizumab 30 mg Q4W** until Week 16, followed by an extension period with **benralizumab 30 mg Q8W** administered until Week 52 (n = 40)

- **Placebo Q4W** until Week 16, followed by an extension period with **benralizumab 30 mg Q4W** administered until Week 28, and then **benralizumab 30 mg Q8W** administered until Week 52 (n = 80).

Up to Week 16 (ie, prior to the start of the 36-week extension period evaluating the benralizumab 30 mg Q4W and Q8W maintenance regimens), participants who receive benralizumab 30 mg Q4W initially will be grouped together and considered as a single treatment group. Randomization will be stratified by blood eosinophils at baseline (< 300 cells/µL, ≥ 300 cells/µL) and age (≥ 12 to < 18 years and ≥ 18 years). Participants will be randomized in minimum cohort sizes across the baseline blood eosinophil and age subgroups; the intended distribution of participants in total across the treatment groups for each combination of these factors is summarized in Table 2. If the minimum recruitment target in any cohort is achieved, that cohort may remain open in order to fulfill minimum recruitment targets for the remaining cohorts. Thus, minimum recruitment targets may be exceeded in cohorts that remain open while fulfilling recruitment targets for other cohorts. Recruitment will stop when a maximum of 200 participants in total is achieved.

Table 2 Number of Patients Randomized by Stratification Factors

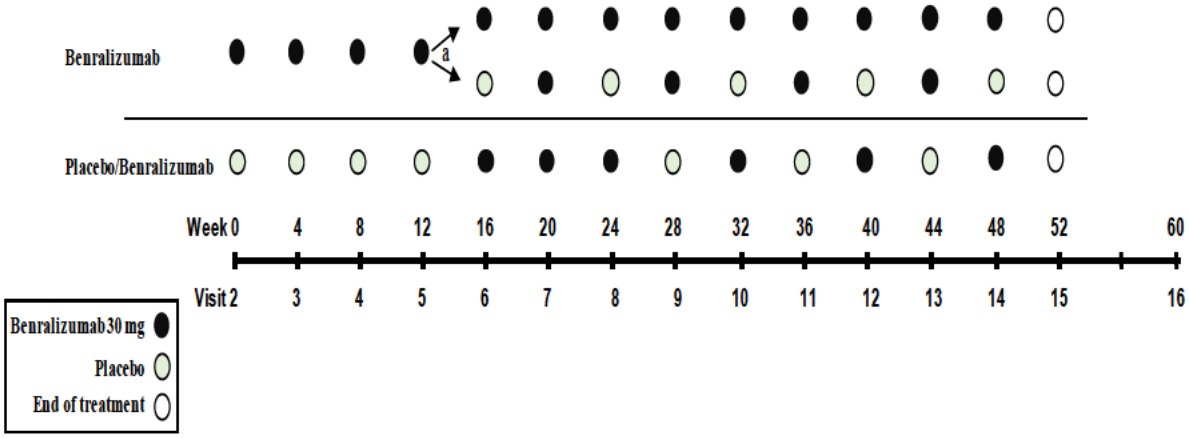
	Baseline blood eosinophils	
	<300 cells/µL	**≥300 cells/µL**
Adolescents (≥ 12 to < 18 years), n	30	50
Adults (≥ 18 years), n	30	50

Blinded investigational product (benralizumab or placebo) will be administered by SC injection at the investigational site Q4W for up to 48 Weeks.

In order to maintain blinding to the benralizumab Q4W treatment regimen in the extension period, participants randomized to receive benralizumab Q8W will also receive Q8W placebo injections at intervening visits where they are not scheduled to receive benralizumab (Figure 1).

The final dose of benralizumab/placebo will be administered at Week 48.

Figure 1 **Investigational Product Administered Q4W by Randomized Treatment Sequence**



[a] In the extension phase, participants will receive benralizumab on a Q8W or Q4W dosing regimen, as predetermined at randomization (Visit 2). Participants randomized to receive benralizumab Q8W in the extension phase will also receive placebo at intervening study visits when they are not receiving benralizumab.

Q4W, every 4 weeks; Q8W, every 8 weeks.

Data Monitoring Committee: Yes

An independent DSMB will be employed.

Statistical Methods

Sample Size Calculations

For the initial 16-week treatment period, the aim is to recruit a minimum of 80 participants into the placebo group, and a minimum of 80 participants into the benralizumab 30 mg Q4W group. (Note that participants who receive benralizumab 30 mg Q4W during the first 16 weeks will be grouped together and considered as a single treatment group.)

The sample size calculations are based on the primary endpoint, ie, the proportion of patients with an Investigator Global Assessment (IGA) 0/1 and a decrease in IGA of ≥ 2 points relative to baseline. The calculations are associated with differences between benralizumab 30 mg Q4W and placebo at Week 16 during the initial double-blind, placebo-controlled phase of the study (Figure 2). For the primary analysis, the sample size calculation will power the study to detect a difference between benralizumab 30 mg Q4W and placebo in the overall population. Additional calculations are provided to ensure that the study is adequately powered to detect treatment differences and consistency of effect in potential subgroups, should efficacy be limited to a subset of the population.

Primary analysis: In the overall population, a minimum of 80 participants per treatment group will provide a high level of power (> 95%) to detect a 30% difference between benralizumab 30 mg Q4W and placebo for the primary endpoint. This calculation is based on a 2-sided test

and a 5% significance level and assumes a response rate of 40% for benralizumab 30 mg Q4W and 10% for placebo.

Subgroup analyses: As a benchmark, a minimum of 35 participants per treatment will provide at least 80% power to detect a 30% difference between benralizumab 30 mg Q4W and placebo. (As for the primary analysis, these calculations are based on a 2-sided test and a 5% significance level and assumes the same response rates for benralizumab 30 mg Q4W and placebo.) Thus, there is a high probability of detecting differences between treatments in the baseline blood eosinophils ≥ 300 cells/μL subgroup (with 50 participants per treatment), in the adult subgroup (with 40 participants per treatment), and in the adolescent subgroup (with 40 participants per treatment). Note that in the baseline blood eosinophils < 300 cells/μL subgroup, 30 participants per treatment group will provide an adequate amount of data to explore treatment differences, and will allow different cut-offs between 'low' and 'high' eosinophils at baseline to be assessed.

Assessing consistency of effect: Consistency of effect will be assessed between adults and adolescents in the overall population and in any identified subgroup for baseline blood eosinophils. By aiming for 25 adults and 25 adolescents per treatment in the baseline blood eosinophils ≥ 300 cells/μL subgroup, the probability of detecting consistent effects between adults and adolescents is high. That is, assuming the true increase in response rate between benralizumab 30 mg Q4W and placebo is 30%, there is > 85% chance of observing a treatment difference for adolescents of at least half of the treatment difference observed for adults.

Assessment of the First 16 Weeks of Treatment Intervention

The primary efficacy analysis will be based on the initial 16-week, double-blind, placebo-controlled phase of the study, and will compare benralizumab 30 mg Q4W versus placebo. The primary estimand will be based on the full analysis set (refer to Table 12). Intercurrent events will consist of participants who withdraw from the study or require rescue therapy (defined in Section 6.5.3). The primary estimand will regard these participants as non-responders from the time such events occur up to Week 16. A participant with missing data at a specific time point will also be considered as a non-responder at that time point.

The primary endpoint is a binary response, identifying responders with IGA 0/1 (ie, clear or almost clear) and a decrease in IGA of 2 or more points at Week 16, relative to baseline. For the primary analysis, a logistic regression model will be fitted to the primary endpoint using a logit link function. The model will include treatment group and baseline covariates for age (adolescents; adults) and blood eosinophils (< 300 cells/μL; ≥ 300 cells/μL). The model will be used to estimate the proportion of responders for benralizumab 30 mg Q4W and placebo, the difference between these proportions (benralizumab 30 mg Q4W – placebo), and an odds

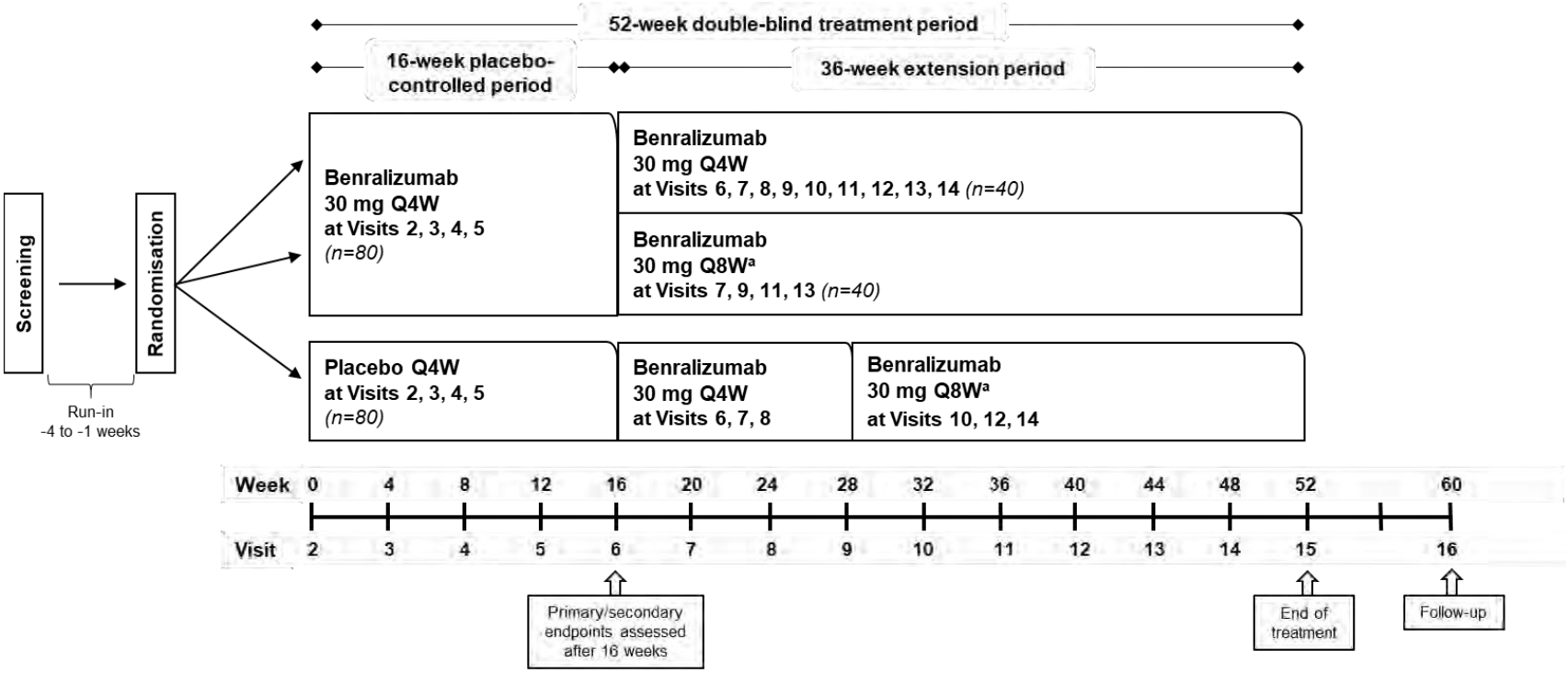
ratio, with corresponding 95% confidence limits. A p-value, corresponding to a 2-sided test, will be presented to compare the benralizumab 30 mg Q4W and placebo treatment groups.

The first and third key secondary endpoints will be derived from the Eczema Area and Severity Index (EASI) and will include the proportion of patients with EASI-75 at Week 16 and the proportion of patients with EASI-90 at Week 16, respectively. The second key secondary endpoint will be the proportion of patients with an improvement of 4 or more points in peak pruritus weekly score at Week 16 relative to baseline.

1.2 Schema

The general study design is summarized in Figure 2.

Figure 2 Study Design



[a] To maintain blinding, patients will receive investigational product every Q4W during the extension period. Placebo will be administered Q8W, occurring 4 weeks after each benralizumab administration.

n, number; Q4W, every 4 weeks; Q8W, every 8 weeks.

1.3 Schedule of Activities

The Schedule of Activities (SoA) at each site visit for this study is provided in Table 3. Details of the schedule for home and site visit patient-reported outcome (PRO) assessments are provided in Table 4.

Table 3 Schedule of Site Visit Activities

Procedure	Run-in	Double-blind placebo-controlled treatment period					Double-blind extension period (to EoT)									Follow-up			
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**Unsch Visit [c]**	**IP Disc. [d]**	**CSP section or appendix with details**
Week [a]	**-4 to -1 [b]**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**60**			
General procedures																			
Informed consent/assent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Appendix A 3
Demography/medical history	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Sections 5.1 and 5.2
Inclusion/exclusion criteria	X	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Sections 5.1 and 5.2
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.5
Randomization	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Section 6.3.1
Efficacy assessments																			
Handheld device distribution for PRO collection	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Section 8.1.4
Review compliance of at-home PRO assessments	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.1 and Table 4
At-site PRO assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.1 and Table 4
IGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.1.1
EASI, BSA, SCORAD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.1.2 and Section 8.1.3

Table 3 Schedule of Site Visit Activities

Procedure	Run-in	Double-blind placebo-controlled treatment period					Double-blind extension period (to EoT)									Follow-up			
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**Unsch Visit [c]**	**IP Disc. [d]**	**CSP section or appendix with details**
Week [a]	**-4 to -1 [b]**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**60**			
Other assessments in-office																			
Patient reported experience (free text entry)	X	-	X	X	X	X	-	-	X	-	-	X	-	-	X	-	-	-	Section 8.1.7
Healthcare resource utilization	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X	Section 8.8
Photographic skin assessment	-	X	-	X	-	X	-	-	-	-	-	-	-	-	-	-	-	-	Section 8.1.5
Safety assessments																			
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3
Complete (Brief) physical exam	X	(X)	(X)	(X)	(X)	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X	-	X	-	Section 8.2.2
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.3
Weight and height	X	-	-	-	-	X	-	-	-	-	-	-	-	-	X	-	-	-	Section 8.2.2
ECG	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Section 8.2.4
Laboratory assessments																			
Hematology, clinical chemistry, and urinalysis	X	X [e]	X [e]	-	-	X	-	-	X	-	-	X	-	-	X	-	-	X	Section 8.2.1
Serum pregnancy test	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Section 8.2.1.1
Urine dipstick pregnancy test	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	X	Section 8.2.1.1

Table 3 Schedule of Site Visit Activities

Procedure	Run-in	Double-blind placebo-controlled treatment period					Double-blind extension period (to EoT)									Follow-up			
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unsch Visit [c]	IP Disc. [d]	CSP section or appendix with details
Week [a]	-4 to -1 [b]	0	4	8	12	16	20	24	28	32	36	40	44	48	52	60			
Post-menopause confirmation (FSH)	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Section 8.2.1.1
Hepatitis/HIV screening	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Section 8.2.1.2
Pharmacokinetics sample prior to IP administration [f]	-	X	-	X	-	X	-	-	X	-	-	X	-	-	X	-	-	X	Section 8.5.1
Immunogenicity sample (ADA)	-	X	-	X	-	X	-	-	X	-	-	X	-	-	X	-	-	X	Section 8.5.2
CCI																			

Table 3 Schedule of Site Visit Activities

Procedure	Run-in	Double-blind placebo-controlled treatment period					Double-blind extension period (to EoT)									Follow-up			
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Unsch Visit [c]	IP Disc. [d]	CSP section or appendix with details
Week [a]	-4 to -1 [b]	0	4	8	12	16	20	24	28	32	36	40	44	48	52	60			
Investigational product administration																			
IP administration [g]	-	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-	-	-	Section 4.1.1 Section 6.1

[a] The window for Visits 3 through 16 will be ± 3 days.

[b] The run-in period is a maximum of 4 weeks and a minimum of 1 week. The washout period is 7 days prior to randomization during which participants must discontinue use of topical medications for AD.

[c] Unscheduled Visit: may be initiated as needed; procedures should be performed as clinically indicated at the discretion of the Investigator.

[d] Investigational Product Discontinuation: In case of early discontinuation from investigational product, visit procedures should be performed 4 weeks ± 7 days after the last dose of IP or as soon as feasible if this interval is missed (eg, if decision on discontinuation was made later). Note: The IPD visit replaces the nearest regular visit.

[e] Only absolute eosinophil counts will be measured at this visit.

[f] No IP will be administered at Week 52.

[g] Review of self-administration of IP procedures may be offered at Visits 2 and 3.

AD, Atopic dermatitis; ADA, Anti-drug antibodies; AE, Adverse Event; BSA, body surface area; CSP, Clinical Study Protocol; EASI, Eczema Area and Severity Index; ECG, Electrocardiogram; CCI [redacted]; EoT, End of treatment; FSH, Follicle-stimulating hormone; HIV, Human immunodeficiency virus; IGA, Investigator Global Assessment; IP, Investigational product; IPD, Investigational product discontinuation; PRO, Patient-reported outcomes; CCI [redacted]; SCORAD, SCORing Atopic Dermatitis; Unsch, unscheduled.

If an at-home PRO is available according to the assessment schedule in Table 4 but has not been completed prior to the site visit, then site staff will direct the participant to complete the assessment at the site before any other study procedures are conducted.

Table 4 Schedule of PRO Assessments

Instruments	Schedule
Daily PRO at home: Peak Pruritus NRS	Every evening [a]. First assessment at home the day of V1.
Periodic PROs: CCI [redacted], EQ-5D-5L, SF-36v2	At site at V1 and V2. At home every 28±3 days after V2 until V6 is confirmed. At site at V6, V7, V12, and V16. Required at IPD visit. Optional at unscheduled visit.
Periodic PROs: POEM, DLQI/CDLQI, HADS, PGI-S, Patient-reported experience (free text entry)	At site at V1, V2, V3, V4, V5, V6, V9, V12, V15, and V16. Required at IPD visit. Optional at unscheduled visit. CDLQI will be assessed in participants ≤ 16 years of age at V1; DLQI will be assessed in all other patients > 16 years of age.
PRO at site: CCI [redacted]	At site at V6 and V15. Required at IPD visit.

[a] Evening is defined as 17:00 to 23:59.

CCI [redacted]

CCI [redacted] CDLQI, The Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EQ-5D-5L, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; IPD, Investigational product discontinuation; NRS, Numerical Rating Scale; CCI [redacted]; PGI-S, Patient Global Impression of Severity; POEM, Patient Oriented Eczema Measure; PRO, Patient-reported outcome; SF-36v2, Short Form 36-item Health Survey Version 2; CCI [redacted]; V, Visit.

2 INTRODUCTION

2.1 Study Rationale

Atopic dermatitis (AD), also referred to as eczema, is characterized by intense itch and eczematous skin lesions. It is the most common chronic inflammatory skin disease, affecting between 2.1% and 4.9% of adults (Barbarot et al 2018), and up to 20% of children in some countries (Nutten 2015). The disease often precedes the development of food allergy, asthma, and allergic rhinitis (referred to as the 'atopic march'), and poses a significant burden on health-care resources and patients' quality of life (Leung and Guttman-Yassky 2014, Nutten 2015); however, treatment options for patients with moderate to severe AD are limited (Leung and Guttman-Yassky 2014).

Patients with AD are commonly colonized with Staphylococcus aureus and have been shown to have more severe disease, allergen sensitization, barrier disruption, lactate dehydrogenase level elevation and higher levels of type 2 biomarkers (eosinophil count, total IgE , CCL17, and periostin) than noncolonized patients with AD (Simpson et al 2018). While blood eosinophilia is variable in the general population of patients with AD, it increases with disease severity, thereby supporting the eosinophilic nature of the disease (Jenerowicz et al 2007). Skin biopsies often do not demonstrate marked eosinophil presence; eosinophils are more likely to be present in acutely diseased skin samples than in chronically diseased samples. However, the markers of eosinophil activation and degradation (eg, eosinophil peroxidase, major basic protein [MBP], eosinophil cationic protein and [redacted],]), as revealed by immunofluorescence and eosinophil membrane disruption by electron microscopy, are prominent within AD skin samples providing further evidence of eosinophil involvement in the pathophysiology of AD (Ott et al 1994 and Rasheed et al 2018). This evidence for a role of eosinophils in the pathophysiology of AD suggests that a direct eosinophil-depleting approach, as provided by benralizumab, may prove beneficial in the treatment of AD. Additionally, results from a pilot study of patients with hypereosinophilic syndrome (HES) showed improvements in skin-related symptoms, with an absence of eosinophils in skin biopsies after 12 weeks of treatment with benralizumab (Kuang et al 2019). Based on these results, further investigation of the efficacy and safety of benralizumab in treating moderate to severe AD is warranted.

2.2 Background

AD is characterized by itchy lesions with an increased number of inflammatory cells in the skin. The pathophysiology of AD is complex and the drivers of the disease process are unknown. It has been suggested that the interaction of a dysfunctional epidermal barrier in genetically predisposed individuals with harmful effects of environmental agents leads to the development of the disease (Nutten 2015). A combination of genetic, environmental, and immunologic factors likely account for the heterogeneity of AD onset and the severity and

natural history of the disease. Thus, effective control of local and systemic immune activation is necessary for optimal management of AD (Leung and Guttman-Yassky 2014). There are few effective medications available for long-term use and current treatments target symptom control rather than a cure. These treatments attempt to manage skin barrier integrity or impairment and include topical corticosteroids (TCS), emollients, antibiotics and, in refractory disease, short course systemic corticosteroids, phototherapy, and immunosuppressants (Leung and Guttman-Yassky 2014). Cyclosporine A is approved in some countries for treatment of severe AD but generally only as a short-term rescue therapy (≤ 1 year) due to cumulative nephrotoxicity (Megna et al 2017). Dupilumab is approved for treatment of moderate to severe AD; however, ≤ 40% of patients achieved clear or almost clear skin (as defined by ≥ 90% improvement in Eczema Area and Severity Index [EASI-90] or Investigator Global Assessment of 0 or 1 [IGA 0/1]) (Blauvelt et al 2017, Simpson et al 2016, and Thaci et al 2016). The lack of approved treatments has led to recommendations for use of other agents not approved for AD (eg, methotrexate and azathioprine) (Boguniewicz et al 2018). Thus, there remains an unmet medical need for more effective, long-term treatments for AD that target both local and systemic immune activation.

The role of eosinophils in the pathophysiology of AD suggests that a direct eosinophil-depleting approach may prove beneficial in the treatment of AD. Eosinophilic diseases are in large part driven by T2 cytokines, including IL-4, interleukin-5 (IL-5,), and IL-13, which are produced by type-2 T helper cells, innate lymphocyte type 2 cells, and mast cells (Valent et al 2012); serum IL-13 and blood eosinophil levels have been shown to be significantly increased in children with early-onset AD (Lee et al 2016). Benralizumab is a humanized, recombinant IgG1k monoclonal antibody that binds to the alpha subunit of human alpha chain of the IL-5 receptor (IL-5Rα.). This receptor is selectively expressed by mature eosinophils, eosinophil progenitor cells, and basophils. The antibody has been engineered to be afucosylated, or without a fucose sugar residue in the Fc domain, which also facilitates binding to FcγRIII receptors on immune effectors cells, such as natural killer cells, leading to apoptosis of eosinophils and basophils through enhanced antibody-dependent cell-mediated cytotoxicity (ADCC). In asthmatic patients, the enhanced ADCC activity of benralizumab results in the rapid and nearly complete depletion of eosinophils in the blood as well as depletion of eosinophils in the lung tissue, sputum and bone marrow (Busse et al 2013, Kolbeck et al 2010, Laviolette et al 2013). Thus, benralizumab may potentially be effective in AD and eosinophilic-driven skin diseases (Simon and Simon 2019; Eberle et al 2019).

This Phase 2 study is designed to investigate the efficacy and safety of benralizumab 30 mg subcutaneously (SC) in treating patients with moderate to severe AD who remain symptomatic despite treatment with at least approved doses of topical medications.

A detailed description of the chemistry, pharmacology, efficacy, and safety of benralizumab is provided in the Investigator's Brochure.

2.3 Benefit/risk Assessment

2.3.1 Benefit Assessment

AD is a chronic inflammatory disease that most commonly affects children and has a marked impact on quality of life measures (Section 2.1). The development of AD in infancy is also a major risk factor for later development of other chronic allergic diseases such as allergic rhinitis and asthma, which is referred to as atopic march (Bantz et al 2014). Infections are frequent complications of AD and can result in severe restrictions and further psychological stresses (Werfel et al 2016). Studies have shown that 10% to 20% of children with AD continue to suffer with the disease in adolescence (Ricci et al 2012). AD persistence during adolescence is correlated with psychological disorders such as anxiety and depression, feelings of isolation, sleep disturbance and general feelings of physical and emotional illness (Ricci et al 2012). Stress and the psychological problems represent a serious burden on both the adolescents living with the disease and the family members who care for them. Furthermore, due to the associated risks with its chronic recurrent course, there remains an unmet medical need for efficacious and safe treatments in this subpopulation of patients with AD (Section 2.2). Expected benefits of benralizumab over placebo include clinically significant improvement in symptoms and quality of life measures related to AD in both adult and adolescent participants in this study.

The direct eosinophil-depleting ability of benralizumab has been shown to be effective in the treatment of eosinophilic asthma in patients 12 to 75 years of age (SIROCCO [Bleecker et al 2016] and CALIMA [FitzGerald et al 2016]) and steroid-dependent asthma (Nair et al 2017). In Phase 3 studies in patients with severe asthma, the pharmacodynamic (PD) profile of benralizumab was similar in adolescent (≥ 12 to < 18 years) and adult patients, with both populations demonstrating near complete depletion of blood eosinophils that was maintained throughout the treatment period. Refer to the Investigator Brochure for details of results of these studies.

Results from 2 clinical studies provide additional evidence of benralizumab's eosinophil-depleting mechanism of action specifically in skin and tissue. A Phase 2 double-blind, placebo-controlled study was conducted in 20 adult patients with HES. HES is a group of diseases with persistent blood eosinophilia and eosinophil-related end-organ involvement, which commonly involves the skin, heart, lungs, central nervous system, or gastrointestinal tract (Andreae et al 2016 and Kuang et al 2019). The study enrolled patients with high baseline eosinophil counts (≥ 1000 cells/μL) and included 4 patients with dermatological involvement (Kuang et al 2019 and Legrand et al 2017). Two of these patients had previous evidence of eosinophilia in skin-biopsy samples and had repeated biopsies during the course of the study to evaluate new or worsening rash. Eosinophils were absent in biopsy samples following treatment with benralizumab, and the rash resolved in these 2 patients. The overall study results showed eosinophil reduction (at least 50% reduction in the absolute eosinophil

count at Week 12) occurred in more patients in the benralizumab group than in the placebo group (between-group difference of 60 percentage points); furthermore, clinical and hematologic responses were sustained for 48 weeks in benralizumab-treated patients and were associated with clinical improvement and the ability to taper background therapy in these patients. In the second study, a small single-blinded, placebo run-in study in 12 patients with chronic idiopathic urticaria, benralizumab treatment resulted in significant reductions in weekly Urticaria Activity Scores (assessing hives and itch) and improvements in Chronic Urticaria Quality of Life Questionnaire Scores (Bernstein and Singh 2019). Improvements in skin conditions following benralizumab treatment have also been reported in a patient with chronic symptomatic dermographism (Bergmann et al 2019). These results support the benefit of benralizumab's significant eosinophil-depleting capabilities in the skin and suggest that benralizumab will also be effective for the treatment of AD.

2.3.2 Risk Assessment

The efficacy and safety of benralizumab have been established in patients 12 to 75 years of age with asthma (Bleecker et al 2016 and FitzGerald et al 2016); in the United States, it is indicated as an add-on therapy for patients 12 years of age and older with severe eosinophilic asthma (approved 14 November 2017).

Phase 3 studies confirmed the efficacy and safety of benralizumab 30 mg every 8 weeks (Q8W) and every 4 weeks (Q4W) in both adult and adolescent patients with severe asthma (SIROCCO [Bleecker et al 2016] and CALIMA [FitzGerald et al 2016]). The results of these Phase 3 studies demonstrated that benralizumab 30 mg Q4W was well-tolerated during the treatment period of up to 112 weeks with no unexpected safety findings and the safety profile was maintained through Extension Week 56. In adolescents, benralizumab 30 mg Q4W was well-tolerated with no unexpected safety findings over the 108-week on-treatment period and the 12-week post-treatment period. The most commonly reported adverse events (AEs) with benralizumab treatment included nasopharyngitis, asthma, and upper respiratory tract infections. Most AEs were mild to moderate in nature. Fewer patients in the benralizumab group reported serious adverse events (SAEs) compared with placebo. Long-term safety and tolerability of benralizumab 30 mg Q4W and Q8W were demonstrated in adolescent patients in an extension study (BORA), which included a treatment period of approximately 2 years. In general, the safety results of the long-term extension study (BORA) were commensurate with the previous studies (Busse et al 2013). Refer to the Investigator Brochure for the details of study design and results of these studies.

In a more recent Phase 3 study to evaluate efficacy, safety, pharmacokinetic (PK) and immunogenicity of a fixed dose of benralizumab 30 mg administered following seasonal influenza virus vaccination (ALIZE) in patients 12 to 21 years of age with severe asthma, a total of 72 adolescent patients received 3 doses of benralizumab 30 mg Q4W. In this study, benralizumab 30 mg was well-tolerated with no unexpected safety findings. There was no

observable pattern or notable differences in AEs in adolescent and young adult patients. No discontinuations of investigational product (IP) or from the study due to an AE or SAE and no AEs with fatal outcome were reported in this study. Refer to the Investigator Brochure for the details of study design and results.

Overall, the AE profile in adolescents was generally similar to the overall population in Phase 3 studies conducted with benralizumab; few SAEs were reported for adolescent patients. Additionally, during the benralizumab Phase 3 asthma exacerbation studies, extensive evaluation of immunoglobulins and flow cytometric assessment of cell subtypes demonstrated no differences between adolescent patients receiving benralizumab compared with placebo. Of note, mepolizumab had an acceptable AE profile in children with eosinophilic esophagitis as young as 2 years, and the PK in children was similar to adults (Assa'ad et al 2011).

In summary, there have been no safety signals detected in previous clinical studies with benralizumab or other monoclonal antibodies (mepolizumab) that deplete eosinophils that would preclude administration of benralizumab to adolescent participants ≥ 12 years of age.

Serious hypersensitivity reactions (including anaphylaxis) are an identified risk of biologic therapy, including benralizumab. Anaphylaxis may be life-threatening. Risk minimization includes observation in line with clinical practice following IP administration for the appearance of any acute drug reactions. Refer to Appendix E for further information and guidance.

Serious infections have been reported for benralizumab. A relationship between eosinophil depletion and serious infection has not been established.

Development of anti-drug antibodies (ADA) to benralizumab has been documented. Potential risks of developing ADA include decreased drug efficacy and hypersensitivity reactions (eg, anaphylaxis or immune complex disease). To date, no confirmed cases of immune complex disease have been observed and no appearance of a relationship between ADA and treatment-emergent AEs has been established. There was no impact of ADA on overall benralizumab safety or efficacy in the previous Phase 3 studies in asthma.

Eosinophils are a prominent feature of the inflammatory response to helminthic parasitic infections, and the presence of infiltrating eosinophils has been circumstantially associated with a positive prognosis in certain solid tumors. Helminthic parasitic infections and malignancy will continue to be monitored as part of routine pharmacovigilance practices. (Refer to Section 5.2, exclusion criteria).

2.3.3 Overall Benefit:Risk Conclusion

Given the clinical evidence to date to support the use of benralizumab 30 mg Q4W in eosinophilic diseases and the established PK, PD, and safety profile in adolescent and adult

patients with severe asthma, the benefit-risk assessment of the use of benralizumab for AD in adult and adolescent patients appears favorable. Data from the approved severe asthma indication demonstrate that benralizumab 30 mg Q4W is safe and well tolerated among adolescent patients, and treatment with placebo posed no serious risks in adolescent patients. The favorable benefit/risk assessment of benralizumab supports the inclusion of adolescents in this Phase 2 study.

Based on the extensive safety data already available, the benefit risk profile in patients with AD is expected to be commensurate with that observed in the benralizumab asthma pivotal trials. Risk minimization measures include exclusion of patients with allergy or reaction to any component of the IP formulation, untreated parasitic infection, a history of anaphylaxis to any biologic therapy, active or recent malignancy, and exclusion of pregnant females. Risk minimization measures will be maintained during the conduct of this study, in conjunction with the performance of AstraZeneca's routine pharmacovigilance activities.

An independent Data and Safety Monitoring Board (DSMB) will provide oversight, with particular focus on the adolescent participants, to ensure safe and ethical conduct of the study. The DSMB will have the responsibility of evaluating cumulative safety and other clinical trial data at regular intervals and making appropriate recommendations based on the available data. During the study, the benefit/risk assessment will be continuously monitored by the DSMB to ensure that the balance remains favorable. Refer to Appendix A 5 and the DSMB Charter for information regarding the independent DSMB.

Participants with AD in this Phase 2 study will be monitored for AEs throughout treatment with benralizumab or placebo and for 12 weeks following the last dose. This study will be conducted under applicable International Conference on Harmonisation Good Clinical Practice (GCP) Guidelines.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of benralizumab may be found in the Investigator's Brochure.

3 OBJECTIVES AND ENDPOINTS

Table 5 lists the objectives of this study and the endpoints for each objective.

Table 5 Objectives and Endpoints

Objectives	Estimand description / Endpoints
Primary	
To compare the clinical efficacy of benralizumab 30 mg with placebo in patients with AD despite treatment with topical medications [a].	• Population: Full analysis set • Endpoint: A binary response giving the proportion of patients with an IGA 0/1 and a decrease in IGA of ≥ 2 points at Week 16 relative to baseline • Intercurrent events: Participants who withdraw from the study or require rescue therapy [b] will be considered as non-responders from the time these events occur up to Week 16 • Summary measure: Difference in proportions between benralizumab and placebo at Week 16
Secondary	
To compare the effect of benralizumab with placebo on supportive measures of clinical efficacy in patients with AD despite treatment with topical medications [a].	• Key secondary endpoint [c]: proportion of patients with skin clearance (EASI-75) at Week 16 • Key secondary endpoint [c]: proportion of patients with an improvement of ≥ 4 or more points in peak pruritus weekly score at Week 16 • Key secondary endpoint [c]: proportion of patients with skin clearance (EASI-90) at Week 16 • Proportion of patients with skin clearance (EASI-50) at Week 16 • Proportion of patients with skin clearance (EASI-100) at Week 16 • Change from baseline in EASI score at Week 16 • Change from baseline in peak pruritus score at Week 2 • Change from baseline in POEM score at Week 16 • Change from baseline in SCORAD at Week 16
To compare benralizumab with placebo on patient-reported health-related quality of life measures in patients with AD despite treatment with topical medications [a].	• Change from baseline in DLQI and CDLQI at Week 16
To estimate the PK and immunogenicity of benralizumab 30 mg in in patients with AD despite treatment with topical medications [a].	• Serum benralizumab concentration • ADA

Table 5 Objectives and Endpoints

To compare long-term treatment with benralizumab 30 mg Q8W versus benralizumab 30 mg Q4W up to Week 52 in patients with AD despite treatment with topical medications [a].	• Change from baseline in EASI total score at Week 52. • Proportion of patients with an IGA 0/1 and a decrease in IGA of ≥ 2 points at Week 52 relative to baseline • Proportion of patients with EASI-75 at Week 52 • Other supportive efficacy assessments at Week 52 as appropriate.
Safety	
To compare the safety and tolerability of benralizumab with placebo in patients with AD despite treatment with topical medications [a].	Safety and tolerability will be evaluated in terms of AEs, Vital signs, and Clinical laboratory values. Assessments related to AEs cover: • Occurrence/frequency • Relationship to IP as assessed by Investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of IP Vital signs parameters include systolic and diastolic blood pressure, and pulse, as well as respiration rate, body temperature, body weight, and height. Assessments related to vital signs cover: • Observed value • Absolute and percent change from baseline values over time
Tertiary/exploratory	
To explore the effect of benralizumab compared to placebo on healthcare resource utilization due to AD.	Rate of AD-related healthcare resource utilization during the study
To explore the effect of benralizumab compared to placebo on patient-reported health-related quality of life measures in patients with AD despite treatment with topical medications [a].	Change from baseline in scores for: • HADS • PGI-S • SF-36v2 Health Survey • EQ-5D-5L • CCI [redacted] • Patient-reported experience (free text entry)
CCI [redacted]	

Table 5 Objectives and Endpoints

CCI

To explore the use of skin photography to inform clinical efficacy assessments	• Concordance with in-person assessments of clinical efficacy.

[a] The locally-approved regimen of topical medication.

[b] Rescue therapy is defined in Section 6.5.3.

[c] The key secondary endpoints will use the same estimand as outlined for the primary endpoint. For all other endpoints, the estimands will be detailed in the SAP.

CCI; AD, Atopic dermatitis; ADA, anti-drug antibodies; AE, adverse event; CDLQI, The Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EQ-5D-5L, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator Global Assessment; IP, investigational product; CCI; PGI-S, Patient Global Impression of Severity; PK, pharmacokinetics; POEM, Patient Oriented Eczema Measure; Q4W, every 4 weeks; Q8W, every 8 weeks; CCI; SAP, Statistical Analysis Plan; SCORAD, SCORing Atopic Dermatitis; SF-36v2, Short Form 36-item Health Survey Version 2; CCI

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2 multinational, randomized, double-blind, parallel-group, 16-week placebo-controlled study with a 36–week extension. The study will evaluate the efficacy and safety of benralizumab 30 mg in male and female participants ≥ 12 years of age with moderate to severe AD who remain symptomatic despite treatment with standard of care treatment with topical medications. The study is designed to compare the safety and efficacy of benralizumab 30 mg with placebo and identify the appropriate maintenance administration frequency (Q4W versus Q8W).

This study consists of the following consecutive periods:

- A 1- to 4-week run-in period, including a 7-day washout period of topical medications prior to randomization

- A 16-week placebo-controlled, double-blind treatment period
- A 36-week blinded-to-dosing regimen extension period for maintenance treatment.

Following informed consent/assent, all eligible participants will enter a run-in period of 1 to 4 weeks during which inclusion/exclusion criteria will be assessed, medical history taken, and complete physical exam will be conducted (Visit 1,Table 3). Potentially eligible participants will enter a 7-day washout period during which all topical medications for AD except the stable emollient moisturizer regimen must be discontinued. Participants will be provided with a handheld device to respond to PRO questionnaires during the study.

Following the 1- to 4-week run-in period, including the 7-day washout period, a minimum of approximately 160 participants will be randomized at Visit 2, in a ratio of 1:1:2, respectively, to 1 of the following 3 treatment sequences (refer also to Figure 1 and Figure 2):

- **Benralizumab 30 mg Q4W** until Week 16, followed by an extension period with **benralizumab 30 mg Q4W** administered until Week 52 (n = 40)
- **Benralizumab 30 mg Q4W** until Week 16, followed by an extension period with **benralizumab 30 mg Q8W** administered until Week 52 (n = 40)
- **Placebo Q4W** until Week 16, followed by an extension period with **benralizumab 30 mg Q4W** administered until Week 28, and then **benralizumab 30 mg Q8W** administered until Week 52 (n = 80).

Randomization will be stratified by blood eosinophils (< 300 cells/μL; ≥ 300 cells/μL), and age (≥ 12 to < 18 years; ≥ 18 years). Participants will be randomized in minimum cohort sizes across the baseline blood eosinophil and age subgroups. If the minimum recruitment target in any cohort is achieved, the cohort may remain open to further recruitment in order to fulfill minimum recruitment targets for the remaining cohorts for a maximum total study size of 200 participants.

Up to Week 16, participants receiving benralizumab 30 mg Q4W will be considered as a single treatment group (total n = 80).

Blinded IP (benralizumab or placebo) will be administered by SC injection at the investigational site Q4W for up to 48 weeks.

Throughout the study, participants will be required to maintain a stable regimen of their topical emollient (moisturizer) for AD. If medically necessary (ie, to control intolerable AD symptoms), rescue treatment for AD may be provided to study participants at the discretion of the investigator (refer to Section 6.5.3).

The primary database lock (DBL) is targeted to occur when all participants have completed the 16-week double-blind treatment period (Figure 2). The final DBL will occur when all participants have completed the 52-week treatment period and the Week 60 follow-up visit and/or the IP discontinuation/ (IPD)/end-of treatment visit (Table 3). An additional lock, between the primary and final DBL, may be performed to report data accumulated during the extension part of the study to support end of Phase 2 decision making. Participants and investigators will remain blinded to treatments and dosing regimens (refer to Section 4.1.2) until the final DBL.

For an overview of the study design, see Figure 2. For details of the treatments administered and dosing regimens used during the study, see Section 4.1.2 and Figure 3. For details of the efficacy and safety endpoints, see Section 3.

4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this clinical study protocol (CSP) and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The investigator or designee should contact the study Sponsor representative to discuss whether the mitigation plans below should be implemented. The study participants will be required to complete the screening and randomization visits on site prior to having the option to participate in the mitigation plans.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with Good Clinical Practice, and minimize risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/assent for the mitigation procedures (note, in the case of verbal consent/assent, the Informed Consent Form (ICF) should be signed at the participant's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated study physician.
- Home or Remote visit: Performed by a site qualified Health Care Professional (HCP) or HCP provided by a third-party vendor (TPV).

- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home IP administration: Performed by a site qualified HCP or HCP provided by a TPV, or by the participant or the participant's caregiver, if possible. Additional information related to the visit can be obtained via telemedicine.
- If participant testing is performed due to the public health crisis, the results may be documented for this study.

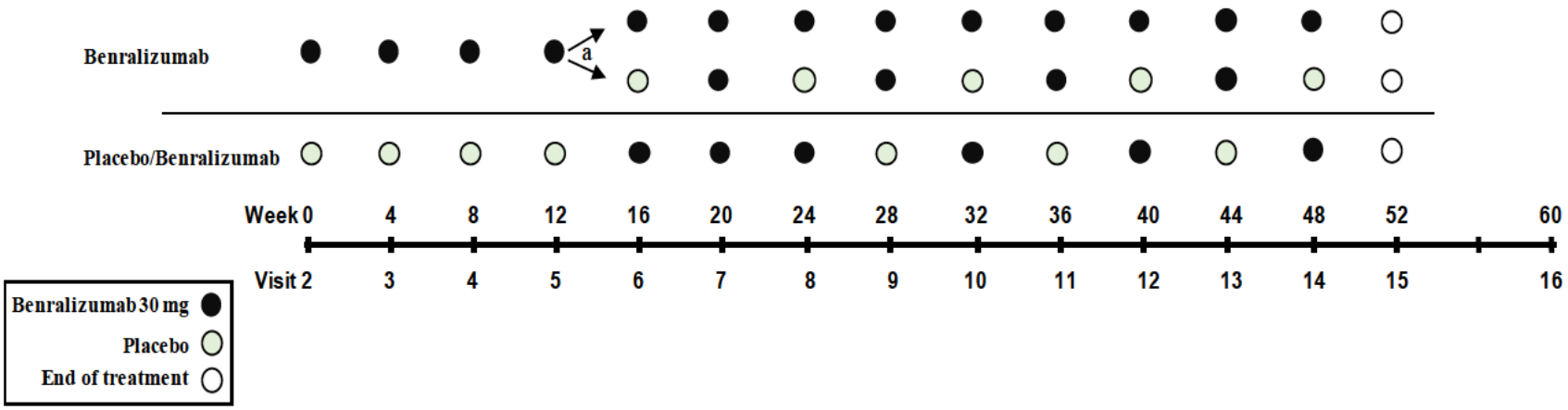
For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix F.

4.1.2 Investigational Product Dosing Regimen

Participants who meet entry criteria will be randomized 1:1:2 by the interactive voice/web response system (IxRS) to 1 of the 3 treatment sequences described in Section 4.1.

Figure 3 presents an overview of the IP that will be administered for each randomized treatment sequence.

Figure 3 Investigational Product Administered Q4W by Randomized Treatment Sequence



[a] In the extension phase, participants will receive benralizumab on a Q8W or Q4W dosing regimen, as predetermined at randomization (Visit 2). Participants randomized to receive benralizumab Q8W in the extension phase will also receive placebo at intervening study visits when they are not receiving benralizumab.

Q4W, every 4 weeks; Q8W, every 8 weeks.

Dosing Regimen at Visits 2, 3, 4, and 5 (Initial 16-Week Double-blind Treatment Period)

All participants will receive randomized double-blind IP Q4W at Weeks 0, 4, 8, and 12 (Figure 3).

Dosing Regimen at Visits 6 Through EOT, Benralizumab 30 mg

At Week 16, participants initially randomized to benralizumab 30 mg will receive benralizumab 30 mg Q4W or Q8W according to their original randomization at Visit 2 (Week 0). Participants randomized to the Q8W regimen will receive placebo at the Week 16 visit and benralizumab 30 mg at the Week 20 visit, and will continue to alternate between these treatments Q4W until Week 48 (Figure 3).

Dosing Regimen at Visits 6 Through EOT, Placebo

At Weeks 16, 20, and 24, participants initially randomized to placebo will receive benralizumab 30 mg Q4W. At Week 28, these participants will transition to receive benralizumab 30 mg Q8W; they will receive placebo at the Week 28 visit and benralizumab 30 mg at the Week 32 visit, and will continue to alternate between these treatments Q4W until Week 48 (Figure 3).

The final dose of benralizumab or placebo will be administered at Week 48.

4.2 Scientific Rationale for Study Design

This is a Phase 2 study designed to evaluate the efficacy and safety of benralizumab in the treatment of patients with moderate to severe AD.

This study's inclusion/exclusion criteria and run-in period (including a 7-day washout of topical medications for AD) are designed to capture a population appropriate for treatment with benralizumab, which is patients with AD who remain symptomatic despite treatment with topical medications. Both patient-reported symptoms and histological findings (ie, eosinophil counts in biopsies) will be captured to ensure the patient population is appropriate for the study and to establish baseline measurements for determining clinical and PD treatment effect.

Loss of skin barrier function and increased severity of AD predisposes patients' skin to microbial colonization and chronic skin inflammation (Leung and Guttman-Yassky 2014). Potential subpopulations with more evident eosinophil-driven AD have been noted in the literature and include Staphylococcus aureus-colonized adult patients with more severe disease and a distinct phenotype (ie, elevated blood eosinophils, major basic protein, CCI in skin, eosinophil cell lysis by Staphylococcus aureus α-hemolysin increasing tissue injury) and children and adolescents, whose disease process is more inflammatory in nature and driven more so by the innate immune system (Simpson et al 2018). Therefore, this study will include minimum cohort sizes for both adults (≥ 18 years of age) and adolescents (≥ 12 to < 18 years

of age) and baseline blood eosinophil cohorts (< 300 versus ≥ 300) to ensure a broad distribution of patients across these characteristics to enable exploration of potential responder populations.

The study's 16–week randomized, double-blind, placebo-controlled, parallel-group treatment period is designed to compare the efficacy and safety of benralizumab 30 mg with placebo. This design is considered appropriate for demonstrating efficacy and safety without bias in a clinical trial (Leshem et al 2019). The study treatment duration is considered appropriate for this disease and was based on the treatment duration for previous studies in patients with AD (Blauvelt et al 2017, Guttman-Yassky et al 2019, Simpson et al 2016, and Thaci et al 2016).

The primary endpoint chosen is the proportion of patients with a binary response of IGA 0/1 and a decrease of ≥ 2 points from baseline in IGA at Week 16. The IGA assesses the overall inflammatory signs of AD (erythema, induration/papulation, lichenification, oozing/crusting) and is recommended by international guidelines to be used in clinical practice to determine disease activity and response to treatment. It has also been used in clinical trials for the registration of other products for the treatment of AD. Additional secondary endpoints are included to provide a complete picture of the efficacy achieved with benralizumab treatment.

The 36-week extension period will provide an opportunity to evaluate long-term benralizumab treatment in patients with AD. The effect of benralizumab 30 mg Q8W as a maintenance dosing regimen will be compared with benralizumab 30 mg Q4W. Participants who received placebo during the initial 16 weeks of the study will switch to benralizumab 30 mg; these participants will receive 3 doses of benralizumab 30 mg Q4W followed by benralizumab 30 mg Q8W for the remainder of the extension period. This regimen has been included in the extension period to provide a preliminary evaluation of the efficacy and safety of the approved dosing regimen for patients with severe asthma, when administered to patients with AD.

4.3 Justification for Dose

The PK of benralizumab are well-characterized (Wang et al 2017), and benralizumab is expected to demonstrate consistent PK across different disease populations. The safety and tolerability of a range of doses of benralizumab have been demonstrated. In Phase 3 asthma studies, over 3500 patients have received benralizumab 30 mg. In Phase 2 and 3 studies in patients with chronic obstructive pulmonary disease, over 1100 patients have received benralizumab 30 mg, and over 1100 patients have received benralizumab 100 mg. No dose-limiting safety issues have been identified with dosing in clinical studies up to 100 mg Q8W for 52 weeks (refer to the Investigator Brochure for details).

The approved dosing regimen of benralizumab in severe asthma is 30 mg Q4W for the first 3 doses, followed by 30 mg Q8W thereafter. In adult and adolescent patients with severe asthma (SIROCCO [Bleecker et al 2016] and CALIMA [FitzGerald et al 2016]), treatment with

benralizumab 30 mg Q8W and Q4W resulted in near complete blood eosinophil depletion for both the Q8W and Q4W dosing regimens. Since the PK/PD relationship of adolescents with asthma has been shown to be consistent with those of adults (SIROCCO and CALIMA) and given PK/PD relationships are consistent across disease populations, the same benralizumab treatment regimen will be administered to adults and adolescents in this study. Treatment with benralizumab 30 mg Q4W has also been shown to reduce blood and tissue eosinophilia in GI tissue of patients with varied clinical subtypes of HES where patients have higher blood eosinophils and significant organ manifestations of eosinophilic inflammation (Kuang et al 2019).

Based on results for the asthma studies, participants will receive benralizumab 30 mg or placebo Q4W during the initial 16-week treatment period. A 16-week treatment period was chosen based on previous studies in patients with AD (Simpson et al 2016) in order to maximize the chances of demonstrating efficacy. Participants will subsequently either transition to a 30 mg Q8W dosing regimen or remain on a 30 mg Q4W regimen during the blinded extension period to evaluate the effect of a Q8W maintenance dosing regimen relative to Q4W over the longer-term treatment period.

4.4 End of Study Definition

The end of study is defined as the last expected visit/contact of the last participant participating in the study.

A participant is considered to have completed the study when he/she has completed his/her last scheduled visit/telephone contact.

See Appendix A 6 for guidelines for the dissemination of study results.

5 STUDY POPULATION

Prospective approval of protocol deviations to inclusion or exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Each participant should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be randomized to IP. Under no circumstances can there be exceptions to this rule. Participants who do not meet the entry requirements are screen failures (Section 5.4).

In this protocol, “enrolled” is defined as a participant’s agreement to participate in a clinical study following completion of the informed consent/assent process. “Randomized” participants are defined as those who undergo randomization and receive a randomization number.

For procedures for withdrawal of incorrectly enrolled participants, refer to Section 7.1.2.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Informed Consent/Assent/age/gender/weight

1 Provision of the signed and dated written informed consent/assent of the participant prior to any mandatory study-specific procedures, sampling, and analyses. The informed consent/assent process is described in Appendix A 3.

2 Male and female participants ≥ 12 years of age at the time of signing the ICF.

Type of Patients and Disease

3 Physician-confirmed diagnosis of AD (according to American Academy of Dermatology Consensus Criteria) that is not adequately controlled with topical medications.

4 EASI score of ≥ 12 at screening and ≥ 16 at randomization.

5 IGA score of ≥ 3 (on a scale of 0 to 4, in which 3 is moderate and 4 is severe) at screening and at randomization.

6 AD involvement of ≥ 8% body-surface area at screening and ≥ 10% body-surface area at randomization.

7 A pruritus numerical rating scale average score for maximum itch intensity of ≥ 4, based on the average of daily pruritus numerical rating scale scores for maximum itch intensity reported during the 7 days prior to randomization.

8 Documented recent history (within 6 months prior to screening) of inadequate response to treatment with topical medications, or patients for whom topical treatments are otherwise medically inadvisable (eg, because of important side effects or safety risks).

9 Participants that have applied a stable dose of topical emollient (moisturizer) twice daily for ≥ 7 consecutive days immediately before the randomization visit. (NOTE: See exclusion criterion 11 for limitations regarding emollients).

10 Participants must be willing and able to complete daily PRO assessments:

(a) Complete at least 70% of daily PRO assessments between Visit 1 and Visit 2 and

(b) Complete at least 5 of 7 daily PRO assessments in the 7 days prior to Visit 2.

Reproduction

11 Females of childbearing potential (FOCBP) must agree to use a highly effective method of birth control (confirmed by the Investigator) from randomization, throughout the study duration, and within 12 weeks after last dose of IP and have a negative serum pregnancy test result on Visit 1.

Highly effective methods of birth control (defined as those that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:

(a) Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, or transdermal.

(b) Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, or implantable.

(c) Intrauterine device.

(d) Intrauterine hormone-releasing system.

(e) Bilateral tubal occlusion or ligation.

(f) Sexual abstinence, ie, refraining from heterosexual intercourse (the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant).

(g) Vasectomized sexual partner (provided that partner is the sole sexual partner of the FOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success).

12 Females not of childbearing potential are defined as females who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or who are postmenopausal. Females will be considered postmenopausal if they have been amenorrheic for ≥ 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:

(a) Females < 50 years old will be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and with follicle-stimulating hormone (FSH) levels in the postmenopausal range. Until FSH is documented to be within menopausal range, the participant should be treated as a FOCBP.

(b) Females ≥ 50 years old will be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 Participants with active dermatological conditions (eg, psoriasis, seborrheic dermatitis, cutaneous lymphoma) other than AD that, in the investigator's opinion, may interfere with the study assessments.

2 Known active allergic or irritant contact dermatitis that, in the investigator's opinion, may interfere with the study assessments.

3 Current malignancy, or history of malignancy, with the exception of:

(a) Participants who have had basal cell carcinoma, localized squamous cell carcinoma of the skin, or in situ carcinoma of the cervix are eligible provided that the participant is in remission and curative therapy was completed at least 12 months prior to the date informed consent/assent, was obtained.

(b) Participants who have had other malignancies are eligible provided that the participant is in remission and curative therapy was completed at least 5 years prior to the date informed consent/assent, was obtained.

4 Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and could:

(a) Affect the safety of the participant throughout the study.

(b) Influence the findings of the studies or their interpretations.

(c) Impede the participant's ability to complete the entire duration of study.

5 History of anaphylaxis to any biologic therapy or vaccine.

6 A helminth parasitic infection diagnosed within 24 weeks prior to the date informed consent/assent is obtained that has not been treated with, or has failed to respond to standard of care therapy.

7 Any clinically significant abnormal findings in physical examination, vital signs, haematology, clinical chemistry, or urinalysis during screening/run-in period which, in the opinion of the Investigator, may put the participant at risk because of his/her participation in the study, or may influence the results of the study, or the participant's ability to complete entire duration of the study.

8 Current active liver disease:

(a) Chronic stable hepatitis B and C (including positive testing for hepatitis B surface antigen or hepatitis C antibody), or other stable chronic liver disease are acceptable if participant otherwise meets eligibility criteria. Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice, or cirrhosis.

(b) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥ 3 times the upper limit of normal, confirmed by repeated testing during the run-in period. Transient increase of AST/ALT level that resolves by the time of randomization is acceptable if in the Investigator's opinion the participant does not have an active liver disease and meets other eligibility criteria.

9 A history of known immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test.

Prior/concomitant Therapy

10 Participants who have received treatment for AD with TCS, topical calcineurin inhibitors (TCI), or topical phosphodiesterase-4 (PDE4) inhibitors within the 7 days prior to the randomization visit.

11 Initiation of treatment of AD with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products during the screening period (patients may continue using stable doses of such moisturizers if initiated before the screening visit).

12 Regular use (2 visits per week) of a tanning booth/parlor or phototherapy for AD within 4 weeks prior to the randomization visit.

13 Use of immunosuppressive medication, including, but not limited to: methotrexate, cyclosporine, azathioprine, systemic corticosteroids within 4 weeks or 5 half-lives prior to the date informed consent/assent is obtained, whichever is longer.

14 Known history of allergy or reaction to any component of the IP formulation.

Other

15 Receipt of immunoglobulin or blood products within 30 days prior to the date informed consent/assent is obtained.

16 Receipt of any marketed or investigational biologic within 4 months or 5 half-lives prior to the date informed consent/assent is obtained, whichever is longer.

17 Receipt of live attenuated vaccines 30 days prior to first dose of IP.

18 Receipt of any investigational nonbiologic within 30 days or 5 half-lives prior to the date informed consent/assent is obtained, whichever is longer.

19 Previously received benralizumab (MEDI-563, FASENRA).

20 Change to allergen immunotherapy or new allergen immunotherapy within 30 days prior to the date of informed consent/assent and anticipated changes in immunotherapy throughout the study.

21 Planned elective major surgical procedures during the conduct of the study.

22 Previous randomization in the present study.

23 Concurrent enrollment in another clinical trial.

24 AstraZeneca staff involved in the planning and/or conduct of the study.

25 For females only: Currently pregnant, breastfeeding, or lactating females.

(a) A serum pregnancy test will be done for FOCBP at Visit 1 and a urine pregnancy test must be performed for FOCBP at each subsequent treatment visit prior to IP administration. A positive urine test result must be confirmed with a serum pregnancy test. If serum test is positive, the participant should be excluded.

5.3 Lifestyle Considerations

Female participants of childbearing potential must use highly effective contraceptive methods throughout the study and at least for 12 weeks after last administration of the IP, as stated in inclusion criterion 11, Section 5.1.

Participants must abstain from donating blood, plasma, or platelets from the time of informed consent/assent and for 12 weeks after last dose of IP.

5.4 Screen Failures

Screen failures are defined as patients who consent/assent to participate in the clinical study but are not subsequently randomly assigned to study intervention/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria not fulfilled, and any SAE. A pregnancy test is not required for FOCBP who are screen failures.

These participants should have the reason for study withdrawal recorded as ‘Screen Failure’ (ie, patient does not meet the required inclusion/exclusion criteria) in the electronic case report form (eCRF.). This reason for study withdrawal is only valid for screen failures and not randomized participants.

5.4.1 Re-screening

If the reason for screen failure was transient (including but not limited to study-supplied equipment failure, unforeseen personal events that mandate missed screening visits, transient events during the screening period that contraindicate IP dosing, etc), participants may potentially be re-screened. These cases must be discussed with the study physician prior to randomization and documented in the Investigator Study File.

Re-screening of a participant for any reason will also be allowed only upon approval of the study physician and allowed only once per participant. A documented approval for re-screening should be filed in the Investigator Study File.

Re-screened participants should be assigned the same participant number as for the initial screening, meaning that the participant should keep the same E-code as was originally assigned.

Re-screened participants should sign a new ICF. All procedures from the screening period should be repeated (eg, a serum pregnancy test must be completed for FOCBP).

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol. Study intervention in this study refers to benralizumab and placebo, CCI .

6.1 Study Interventions Administered

6.1.1 Investigational Products

Descriptions of the IPs are provided in Table 6.

Table 6 Investigational Products

	Study intervention	
	Benralizumab	**Placebo**
Dosage formulation	CCI	
Route of Administration	Subcutaneous injection	Subcutaneous injection
Dosing Instructions	Benralizumab active solution will be administered subcutaneously to participants by health care professionals CCI	Placebo solution will be administered subcutaneously to participants by health care professionals CCI
Use	Experimental	Placebo-comparator
IMP and NIMP	IMP	IMP
Sourcing	AstraZeneca	AstraZeneca
Packaging and Labeling	Study intervention will be provided CCI . Each CCI will be labeled in accordance with GMP Annex 13 and per country regulatory requirement.	Study intervention will be provided CCI Each CCI will be labeled in accordance with GMP Annex 13 and per country regulatory requirement.

CCI GMP, Good Manufacturing Practice; IMP Investigational Medicinal Product; NIMP Non-Investigational Medicinal Product; w/v, weight by volume.

Before IP Administration

All applicable visit procedures, including collection of biomarker, PK, and ADA samples and on-site PRO assessments, should be completed prior to IP administration.

Prior to each IP administration:

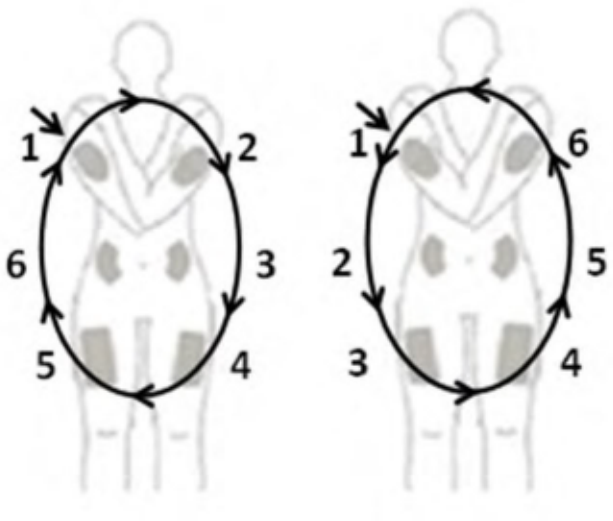
- For FOCBP, the urine pregnancy test must be performed; IP will be administered only when the result of the test is negative (refer to Section 8.2.1.1).
- Investigator, or designee, will evaluate the participant's condition for potential contraindications for dosing (refer to Section 6.5.4).
- Investigator, or designee, will assess the injection site as per standards of medical care.

IP Administration

The IP will be administered SC as a single injection via the [redacted] by the Investigator, or designee (Section 4.1.2).

It is advised that the site of IP injection be rotated such that the participant receives IP at a different anatomical site at each treatment visit. Suggested injection site rotation sequence is presented below (Figure 4). The injection site must be documented in the source at each treatment visit and recorded in the eCRF. The date and time of all IP administrations, as well as any missed doses (IP interruptions), should be recorded in the appropriate section of the eCRF.

Figure 4 Injection Sites and Examples of Rotation Scheme



If rotation of the injection site is not possible, the reason for this must be documented in the source.

At Visits 2 and 3, appropriate participants and/or their caregiver may be trained in IP administration by the investigator or designee. If not possible at Visits 2 and 3 this may occur at later visits. This training will be provided to have participants prepared in case telemedicine

visits may be required secondary to study disruptions as described in Section 4.1.1. Participants may still participate in the study if they do not consent/assent to this training.

The specific details for IP administration are provided in the IP Handling Instruction. The IP administration must be carried out in line with these instructions.

After IP Administration

It is strongly recommended that the participant is observed after IP administration for the appearance of any acute drug reactions in line with clinical practice.

6.1.2 Investigational Product Administration Re-scheduling

Every effort should be taken to keep IP administration within the scheduled window.

If a participant presents with a condition that contraindicates dosing, IP will be withheld and administered as soon as possible after the contraindicating condition resolves.

The IP should not be administered, and the dosing is to be re-scheduled in the presence of the following conditions:

- The participant has an intercurrent illness that, in the opinion of the Investigator, may compromise the safety of the participant in the study.
- The participant has signs of a clinically significant infection. Benralizumab should not be administered to a participant with a clinically significant active infection treated with oral or intravenous (IV) antimicrobials, antivirals, or antifungals until it is confirmed by the Investigator that the infection has resolved.
- The participant is febrile (≥ 38°C; ≥ 100.4°F) within 72 hours prior to IP administration.
- Any event or laboratory abnormality that, in the opinion of the Investigator or AstraZeneca, contraindicates dosing or could result in complications.

It is recommended that the study physician, or designee, be contacted in case of any questions.

When IP dosing needs to be postponed, it is recommended that all scheduled treatment visit procedures (except for pregnancy test and IP administration) are still performed within the visit window.

Re-scheduled IP dose can then be administered at an unscheduled visit along with the pregnancy test. The vital signs assessments are the minimum procedures to be performed at this visit. It may also include remaining visit procedures (not performed at the scheduled visit) and additional assessments as deemed necessary by the Investigator.

If the visit procedures cannot be conducted within the window (eg, the participant is unable to attend the study site), then the entire visit will be re-scheduled along with IP dose.

If a dose is significantly delayed, it is recommended to keep at least a 2-week interval before the next dose. If a postponed dose overlaps with the next treatment visit window, the postponed dose will be skipped, and the next dose of IP given at the regularly scheduled visit. The visit schedule will always be calculated from the randomization visit date.

If 2 or more doses (consecutive or non-consecutive) of IP are missed, a conversation between the Investigator and the study physician should take place to review treatment compliance and decide on the participant's further disposition. All participants, regardless of whether they remain on IP or not, will be encouraged to remain in the study through the end of the treatment period (Visit 16). Discontinuation procedures are described in Section 7.1.1).

6.2 Preparation/handling/storage/accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.2.1 Preparation and Handling of Investigational Product

The IP will be administered at the study site, on treatment visits, and within visit windows as specified in the SoA (Table 3). The IP will be supplied to the site in kits with CCI of either benralizumab or placebo. Each kit will have a unique identifier (ID) that is printed on all labels within the kit (ie, the outer carton label and the label of each container within the carton).

Only participants randomized to the study may receive IP and only authorized site staff may dispense and administer IP.

6.2.2 Shipping and Storage

All shipments of IP include a data logger which will allow the Investigator, or designee, to confirm that appropriate temperature conditions have been maintained during transit for all IP received. Any discrepancies must be reported and resolved before use of the IP.

In the following cases, the site staff should not use affected IP and should immediately contact the AstraZeneca representative for further guidance:

- Temperature excursion upon receipt or during storage at the study site
- Damaged kit upon receipt
- CCI /cartridge

Damaged IP should be documented using an IxRS (refer to IxRS manual and the Pharmacy Manual for further details).

CCI

6.2.3 Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for IP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

An AstraZeneca representative site monitor will account for all IP received at the site, for unused IP, and for appropriate destruction of unused study treatments. Any unused kits will be destroyed locally (for further details, refer to the Pharmacy Manual). Documentation of IP delivery and destruction should be maintained according to applicable AstraZeneca and institution procedures.

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual (provided to the sites). In the case of a malfunctioning IP CCI , the site should contact the AstraZeneca representative study monitor to initiate a product complaint process according to applicable guidelines.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

All participants will be centrally assigned to randomized IP using an IxRS. Randomization codes will be assigned strictly sequentially in each stratum as participants become eligible for randomization. Randomization will be stratified by age (≥ 12 years to < 18 years; ≥ 18 years) and baseline blood eosinophils (< 300 cells/ μL; ≥ 300 cells/ μL) collected at screening into the following strata:

- ≥ 12 years to < 18 years and < 300 cells/μL
- ≥ 12 years to < 18 years and ≥ 300 cells/μL
- ≥ 18 years and < 300 cells/μL
- ≥ 18 years and ≥ 300 cells/μL

Participants who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be randomized or receive IP. There can be no exceptions to this rule. Participants may be rescreened under certain conditions (Section 5.4.1).

If a participant withdraws from the study, then his/her randomization code cannot be reused. Withdrawn participants will not be replaced.

6.3.2 Blinding

Benralizumab and placebo will not be visually distinct from each other. All packaging and labeling of the IP will be done in such a way as to ensure blinding for all AstraZeneca and investigational site staff. Neither the participant nor any of the Investigators or AstraZeneca staff who are involved in the treatment, clinical evaluation, and monitoring of the participants will be aware of the treatment received. Since benralizumab and placebo are not visually distinct, IP will be handled by an appropriately qualified member of the study team (eg, pharmacist, Investigator, or designee) at the site.

All participants will receive one SC injection through Visit 16 (EOT). During the extension period, participants receiving benralizumab 30 mg Q8W will receive a placebo injection at every other site visit; thus, the investigational staff, participants, and AstraZeneca will remain blinded to the participant's dosing regimen (refer to Section 4.1.2 for details on dosing regimens).

A site monitor will perform IP accountability. If the treatment allocation for a participant becomes known to the Investigator or other study staff involved in the management of study participants or needs to be known to treat an individual participant for an AE, AstraZeneca must be notified promptly by the Investigator and before unblinding (if possible).

The following personnel will have access to the randomization list during the study, prior to the primary DBL:

- Those generating the randomization list
- Personnel at the Interactive Voice Response System (IVRS)/ Interactive Web Response System (IWRS) (hereafter referred to as IxRS) company
- The AstraZeneca supply chain department
- Participant safety department at AstraZeneca
- Bioanalytical laboratory performing the PK and ADA sample analysis

The information in the randomization list will be kept from other personnel involved in the conduct of the study in a secure location until after the primary DBL; restricted members of the study team will become unblinded after the primary DBL. No other member of the extended study team, including AstraZeneca, or any Contract Research Organization handling data, will have access to the randomization scheme during the conduct of the study.

Maintaining the Blind to the Participant's Blood Eosinophil and Basophil Counts and [redacted]

Participants on active benralizumab treatment are expected to have lower eosinophil and basophil blood counts and lower levels of [redacted] than participants on placebo based on its established mechanism of action. Procedures to prevent unblinding based on eosinophil and basophil counts and [redacted] will be in place during the induction, maintenance, and extension treatment periods (from Week 0 through Week 52):

- Hematology assessments will be conducted by a central laboratory. Post-randomization (beginning at Visit 2, Week 0), AstraZeneca, study site personnel, and participants will be blinded to the eosinophil and basophil counts. The absolute eosinophil, basophil, and monocyte counts, and percentages will be redacted from the hematology reports provided to the investigational sites.
- If the Investigator orders any local safety laboratory assessments, the requested tests should be restricted to the question at hand. For example, if hemoglobin is desired, the Investigator should avoid ordering a complete blood cell count with a differential count.
- In cases where the Investigator requires an eosinophil, basophil, or monocyte count for managing safety issues, he/she may order these tests as per regular site practice. AstraZeneca should be notified of all such cases without being revealed absolute eosinophil counts, absolute basophil counts, or absolute monocyte counts.
- Site staff who are directly involved in the participant's management should remain blinded to any eosinophil, basophil, and monocyte results included as part of an outside laboratory report or electronic medical record. To help ensure this, each investigational

site will designate an individual (eg, administrator or another ancillary person) not directly involved in participant management, to receive and redact any eosinophil, basophil, and monocyte results prior to the report being handed over to the site staff involved in the participant's management and prior to filing the laboratory report as a source document. Similarly, eosinophil, basophil, and monocyte results must be redacted from all communications with AstraZeneca.

- CCI [redacted]

After the primary DBL, restricted members of the study team will become unblinded to all participants' blood and biopsy cell counts obtained during the double-blind treatment period.

6.3.3 Methods for Unblinding

The IxRS will provide the Investigator(s) or pharmacists the kit ID number(s) to be allocated to the participant at the study site visit. Routines for this will be described in the IxRS user manual and the unblinding plan that will be provided to each site.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization. The Investigator will document and report the action to AstraZeneca representative, without revealing the participant's treatment randomization to AstraZeneca representative or AstraZeneca staff.

Emergency unblinding should also be available to a third-party physician/medical professional who is not participating in the study (eg, staff in hospital ER). As soon as possible, the Investigator should first contact the Study Physician to discuss the medical emergency and the reason for revealing the actual treatment received by that participant; however, this may not be mandatory and should not cause any delay in unblinding in case of emergencies. The treatment assignment will be unblinded by the Investigator through IxRS.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to IP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

6.4 Study Intervention Compliance

Participants are dosed at the site, receiving study intervention directly from the Investigator or designee, under medical supervision. The administration of all IP should be recorded in the

appropriate section of the eCRF. The study treatment provided for this study will be used only as directed in this CSP.

The IP will be administered at the study site on treatment visits and within visit windows as specified in the SoA (Table 3). Any change from the dosing schedule, dose interruptions, or dose discontinuations must be recorded in the eCRF; dose modifications are prohibited. Sites should call participants 1 to 2 days before each visit to remind the participant of the visit.

6.5 Concomitant Therapy

Any prior biologic medication(s) and concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF, along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency
- Investigator, or designee, will collect and record information about concomitant medications and treatments as follows:
  - Stable basic skin care (cleansing and bathing, including bleach baths), emollients (required as background treatment), topical anesthetics, antihistamines, and topical and systemic anti-infective medications for any duration
  - All other medications or procedures taken for any reason in the 3 months prior to Visit 1 (except for prior biologic medication[s], which will be collected regardless of the time of administration)
  - Concomitant treatments given during the study (at each study visit).

6.5.1 Background Medication

Throughout the study, participants will be required to maintain stable doses of their topical moisturizer for AD.

6.5.2 Other Concomitant Treatment

Medication other than that described in Section 6.5.1 (AD therapy), which is considered necessary for the participant's safety and well-being, may be given at the discretion of the Investigator and must be recorded in the appropriate sections of the eCRF.

Brief course(s) of topical antibiotics will be permitted for treatment of local skin infections at the discretion of the Investigator and must be recorded in the appropriate sections of the eCRF.

6.5.3 Rescue Medication

If medically necessary (ie, to control intolerable AD symptoms), rescue treatment for AD may be provided to study participants at the discretion of the investigator.

If medically necessary for intolerable AD symptoms that occur during the treatment or follow-up periods, rescue therapy with otherwise prohibited concomitant medications or therapies may be prescribed to participants at the discretion of the investigator. Rescue therapy is not permitted until at least Visit 3 (Week 4). Rescue therapy should only be prescribed after assessment of the participant in the clinic, either at a scheduled or unscheduled visit. A justification for each participant who commences rescue therapy must be documented by the investigator in the clinical notes.

Rescue therapy should initially be restricted to topical therapies (ie, TCSs or TCIs, or any other topical anti-inflammatory treatment [eg, PDE4 inhibitor]). TCSs should be prescribed at the lowest potency appropriate for the situation. TCIs should be reserved for problem areas only (eg, face, neck, or intertriginous and genital areas). Systemic rescue therapy should be reserved for participants who do not adequately respond to topical rescue therapy after ≥ 7 days of treatment. If a participant receives rescue treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.) study treatment will be immediately discontinued. After the treatment with these medications is completed, study treatment may be resumed if deemed appropriate by the Investigator and the Study Physician, but not sooner than 5 half-lives after the last dose of systemic rescue medication. All participants will complete the schedule of study visits and assessments whether or not they complete study treatment and whether or not they receive rescue treatment for AD.

Participants who require any rescue therapy during the study will be classified as non-responders from the time of rescue use up until week 16 in the primary analysis (see section 9.4.1). Sensitivity analyses will explore the impact of potential rescue use on the statistical analyses.

6.5.4 Restrictions

Use of any of the following concomitant treatments or procedures will not be permitted throughout the study duration, unless otherwise specified:

- Topical corticosteroids, TCIs, and topical PDE4 inhibitors (unless required for rescue medication; refer to Section 6.5.3)
- Steroids/nonsteroidal systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine) (other than for treatment for AEs where no alternative treatment is available)
- Major elective surgical procedures

- Phototherapy
- Regular tanning in a bed/booth from 4 weeks prior to randomization and throughout the study
- Receipt of live attenuated vaccines is disallowed 30 days prior to first dose of IP, during IP administration, and for 12 weeks after last dose of IP
- Receipt of inactive/killed vaccinations (eg, inactive influenza) is allowed provided they are not administered within 1 week before/after any IP administration; additionally, it is recommended to rotate the next IP site injection to a site distant from the vaccine site injection
- Any marketed or investigational biologic (monoclonal or polyclonal antibody) is not allowed within 4 months or 5 half-lives (whichever is longer) prior to randomization, during the treatment period, and is not ideally recommended within 4 months or 5 half-lives (whichever is longer) after the last dose of the IP
- Other IPs for 30 days or 5 half-lives (whichever is longer) prior to randomization and during the study period
- New moisturizers containing additives including ceramide, hyaluronic acid, urea, or filaggrin degradation products may not be initiated after screening.

Participants should not receive allergen immunotherapy on the same day as the IP administration.

6.6 Dose Modification

Modification of the dose (benralizumab or placebo) is not permitted.

6.7 Intervention After the End of the Study

After the end of the study, the participant should be given standard of care therapy according to local practice, at the discretion of the Investigator.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Participants who prematurely discontinue from IP will be asked to come in for all visits and complete the study assessments at the IPD/EOT visit.

Discontinuation from IP does NOT automatically lead to a complete withdrawal from the study. Participants discontinuing from IP are strongly encouraged to continue in the study up to the study completion (Visit 16, Week 60) as described in Section 7.1.1.

Participants will be discontinued from IP in the following situations:

- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment. The participant should always be asked about the reason(s) and presence of any AEs.
- AE that, in the opinion of the Investigator, contraindicates further dosing.
- Severe non-compliance with the CSP.
- Risk to participant as judged by the Investigator or AstraZeneca.
- Pregnancy.
- IP unblinding.
- Development of any of the following study-specific criteria for discontinuation:
  - Anaphylactic reaction to IP administration, in the opinion of the Investigator, requiring administration of epinephrine.
  - Development of helminth parasitic infestation requiring hospitalization.

Refer to the SoA (Table 3) and Section 7.1.1 (IPD visit) for data to be collected at the time of IPD and follow-up and for any further evaluations that need to be completed.

The reason for premature discontinuation of IP should be documented in the source documentation and recorded in the eCRF.

7.1.1 Procedures for Early Discontinuation of Study Intervention and at End of Study

A participant who decides to discontinue IP should always be asked about the reason(s) and the presence of any AEs. The reason for discontinuing treatment and the date of last IP administration should be recorded in the eCRF. Participants permanently discontinuing IP administration should be given locally available standard of care therapy, at the discretion of the Investigator. Discontinuation of IP will be registered in the IxRS.

See the SoA (Table 3) for data to be collected at the IPD visit and for any further evaluations to be completed.

7.1.1.1 Early Discontinuation of Study Intervention

All participants who prematurely discontinue IP should return to the study site for the IPD visit 4 weeks (± 7 days) after the last dose of IP for procedures, or as soon as feasible if this interval is missed (eg, if decision on discontinuation was made later), as specified in Table 3.

At the IPD visit, the participant will be offered the following options for further follow-up:

- Participants are encouraged to return to all scheduled site visits and perform all procedures (including PRO completion and blood draws), but without IP administration, until the end of the study (Visit 16).
- If the participant is unwilling or unable to attend the scheduled site visits until the end of the double-blind treatment period, he/she will be offered a follow-up option that includes monthly telephone contact instead. During follow-up telephone contact, the Investigator will collect information about concomitant medications, information on AD symptoms, and AE/SAE(s) (Section 8.3).

7.1.1.2 Discontinuation of Study Intervention upon Notification of Closure of Study

The IPD visit (4 weeks [± 7 days] after the last dose of IP) should be conducted for all ongoing participants within 3 months of notification from AstraZeneca of closure of the study (Section 7.2.1).

7.1.2 Procedures for Handling Incorrectly Enrolled or Randomized Participants

Participants who fail to meet the eligibility criteria should not, under any circumstances, be randomized or receive IP. Participants who are enrolled but subsequently found not to meet all the eligibility criteria must not be randomized and must be withdrawn (screen failed) from the study.

Where a participant does not meet all the eligibility criteria but is randomized in error, or incorrectly started on IP, the Investigator should inform the study physician or designee immediately, and a discussion should occur between the study physician and the Investigator regarding whether to continue or discontinue the participant from IP.

If the agreed decision is to discontinue IP, participants should be encouraged to remain in the study and continue to be followed-up until the end of the study (ie, Week 60).

The decision to discontinue/continue IP must be appropriately documented, including rationale, particularly if the agreed decision is to continue IP treatment.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

- At the time of withdrawal from the study, if possible, the IPD visit should be conducted. See the SoA (Table 3) for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent/assent for disclosure of future information, AstraZeneca may retain and continue to use any data collected before such a withdrawal of consent/assent.

If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent/assent. If he/she requests withdrawal of consent/assent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent/assent and local regulations. The Investigator must document the decision on use of existing samples in the site study records and inform the AstraZeneca representative.

Participants who withdraw from the study will return the handheld electronic PRO device.

7.2.1 Discontinuation or Suspension of the Whole Study Program

If AstraZeneca decides to prematurely terminate or suspend the study, the Investigator and regulatory authorities should receive written notification of the reasons for the premature termination or suspension. The Investigator will immediately notify the decision to the participants and, if relevant, give appropriate medical treatment, take necessary measures, and document these in the source notes.

There are no pre-specified stopping rules or criteria for this study.

7.3 Lost to Follow-up

A participant will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site.

To prevent a participant being lost to follow-up, it is recommended that the study sites maintain up-to-date contact details for participants, including next of kin or other emergency contacts (if allowed by national regulation).

The Investigator should educate the participant on the importance of maintaining contact with the Investigator/study site throughout the study.

The following actions must be taken if a participant fails to return to the site for required study visits:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule.
- Repeated attempts must be made to regain contact with the participant or next of kin/emergency contact by repeat telephone calls, emails, and/or certified letter. These contact attempts should be documented in the participant's medical record.

Efforts to reach the participant should continue until the end of the study.

The participant will be classified as lost to follow-up only if he/she has failed to return for the required study visits and his/her vital status remains unknown at the end of the study (ie, Week 60), despite all above listed efforts. For the primary analysis purposes, a participant will be classified as lost to follow-up if he/she has failed to return for the required study visits and his/her vital status remains unknown at the time of primary DBL (ie, after the Week 16 visit).

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 3).

The Investigator will ensure that data are recorded on the eCRFs. The Web Based Data Capture system will be used for data collection and query handling.

The Investigator ensures the accuracy, completeness, legibility, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Immediate safety concerns should be discussed with the AstraZeneca representative immediately upon occurrence or awareness to determine if the participant should continue or discontinue IP.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood test, echocardiography, biopsy, etc.) and obtained before signing of the ICF may be utilized for

screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Note: for laboratory assessments, if not all laboratory kits are available at a given visit, the Investigator should contact the Study Physician to confirm whether assessment is critical or may be postponed until supplies are available.

8.1 Efficacy Assessments

8.1.1 Investigator Global Assessment

The IGA is an instrument used in clinical studies to rate the severity of AD globally, based on a 5-point scale ranging from 0 (clear) to 4 (severe). The IGA uses clinical characteristics of erythema, infiltration, papulation, oozing, and crusting as guidelines for the overall severity assessment. The validated IGA scale for AD will be completed by the investigator on an electronic device supplied to the site according to the SoA (Table 3) to capture these key measures of AD disease activity and describe the overall appearance of AD lesions (Table 7).

Table 7 Investigator Global Assessment Score

Score	Morphological description
0 – Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 -- Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 -- Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 -- Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 -- Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

8.1.2 Eczema Area and Severity Index

The EASI is a validated tool used in clinical practice and clinical trials to assess the severity and extent of AD (Hanifin et al 2001). The EASI including percentage body surface area (BSA) affected by AD will be assessed according to the SoA (Table 3). The EASI is a composite index with scores ranging from 0 to 72. Four AD disease characteristics (erythema, thickness [induration, papulation, edema], scratching [excoriation], and lichenification) will each be assessed by the investigator or designee at visits specified in the SoA (Table 3). The severity score is assessed on a scale of 0 (absent) to 3 (severe) in each of 4 body regions (head, trunk, upper limbs, and lower limbs). In addition, the area of AD involvement will be assessed as a percentage by body area in the 4 anatomic areas and converted to a score of 0 to

6. In each body region, the area is expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%).

The percentage of participants achieving a 50% reduction from baseline in EASI score (EASI-50), 75% reduction from baseline in EASI score (EASI-75), 90% reduction from baseline in EASI score (EASI-90), and 100% reduction from baseline in EASI score (EASI-100) will be calculated from the total EASI scores.

The EASI will be completed by the investigator on an electronic device supplied to the site, which will calculate the domain and total scores for the subject.

8.1.3 Scoring Atopic Dermatitis

SCORing Atopic Dermatitis (SCORAD) is a clinical tool for assessing the severity of AD that evaluates the extent and intensity of AD lesions, in addition to subjective symptoms (Kunz et al 1997). There are 3 components to the assessment: A = extent or affected body surface area, B = severity, and C = subjective symptoms. The extent of AD is assessed as a percentage of each defined body area (see Section 8.1.4) and reported as the sum of all areas, with a maximum score of 100% (assigned as “A” in the overall SCORAD calculation). The severity of 6 specific symptoms of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/lichenification, dryness) is assessed using the following scale: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points, assigned as “B” in the overall SCORAD calculation). Subjective assessment of itch and sleeplessness is recorded for each symptom by the participant or relative on a visual analogue scale (VAS), where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20. This parameter is assigned as “C” in the overall SCORAD calculation. The maximum total score is 103, with higher values indicating more severe disease. SCORAD will be assessed at the visits specified in the SoA (Table 3) and will be completed on the electronic device supplied to the site.

A suitable area of non-lesional skin will be designated at screening for SCORAD assessments of skin dryness at Visit 1. To allow for the assessment of skin dryness, moisturizers should not be applied to the designated area for ≥ 8 hours before visits when SCORAD will be assessed. These instructions should be explained to participants at Visit 1.

8.1.4 Body Surface Area Involvement of Atopic Dermatitis

Body surface area affected by AD will be assessed for each section of the body using the Palmar method with rule of nine. The possible highest score for each region is: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%], and will be reported as a percentage of all major body sections combined. Participants will undergo this assessment at time points according to the SOA (Table 3). The BSA affected scoring will also be calculated on the electronic device that is supplied to the site.

8.1.5 Skin Photography

Clinical skin photography is a method to capture and document images of the skin. To evaluate alternative methods of clinical assessments, skin photography will be used in this study. Full body photographs will be taken as outlined in the photography manual and according to the SoA (Section 1.3).

At visits when clinical skin photography is to be performed and assessed before the Investigator sees the participant for the study visit, the photographs should be taken by a trained site personnel and not by the Investigator performing efficacy assessments on the participant. The site Investigator will then review the photographs and perform the clinical efficacy assessments (IGA, EASI, SCORAD, and BSA) based on review of the photographs. The Investigator photograph assessment will be recorded in the eCRF. The same site Investigator should then see the participant and perform the usual in-person visit assessments including the in-person assessment of efficacy parameters and document the data. The first assessments (based on skin photography) should not be altered even if differences are observed after assessing the participant in person. The final in-person Investigator assessment documented should reflect the Investigator's overall clinical judgment. Photographic equipment will be provided to the sites.

8.1.6 Patient-reported Outcomes

Participants will complete all patient-reported outcomes (PRO) assessments using a handheld device. The handheld device will be the only accepted source of PRO data.

The Investigator will ensure that participants are properly trained on the use of this device and the importance of completing assessments as scheduled.

The handheld PRO device will be programmed at Visit 1 with reminder alarms for the daily diary. Study site staff will be able to adjust alarms for specific participant needs as needed. The participant will be required to complete a training module (at the site) before taking the device home.

The Investigator or designee will be responsible for ensuring that the participant is completing the daily diary and follow-up as necessary to minimize missing data. Participant compliance should be checked weekly (at a minimum) to ensure that the participant is completing the assessments as scheduled. Monitoring of participant compliance with completion of the diary is especially critical between Visit 1 and Visit 2 to ensure that the participant meets applicable criteria for randomization. If the participant does not meet the randomization requirements, the device will be deactivated and retained at the site for future use.

Review of participant compliance with the assessment schedule, completion of any available assessments, and logging of the visit on the handheld device should be completed prior to other study procedures.

Compliance with the assessment schedule should be completed weekly throughout the study and follow-up with participants via phone and at the visits. Compliance review is required to ensure sufficient data are available for supporting the primary endpoint of this study.

The timing and frequency for each PRO is provided in Table 3.

8.1.6.1 Peak Pruritus Numeric Rating Scale

The Peak Pruritus Numeric Rating Scale is a one-item daily assessment of the worst itch the patient experienced over the past 24 hours. The score ranges from 0 to 10, with 0 being "no itch" and 10 being "worst itch imaginable."

8.1.6.2 Patient-Oriented Eczema Measure

The Patient-Oriented Eczema Measure (POEM) is a 7-item assessment of AD symptoms (itchiness, sleep disturbance, bleeding, weeping, cracking, flaking, and dryness) that characterizes severity as a function of symptom frequency. The participant responds to each question by selecting the approximate number of days during the past week when they experienced the symptom (no days, 1 to 2 days, 3 to 4 days, 5 to 6 days, or every day).

For scoring, the frequency is converted to a 0 to 4 scale, with "no days" being 0 and "every day" being 4. The seven items are summed, resulting in a score ranging from 0 to 28 (Table 8). Higher scores represent more severe AD symptoms.

Table 8 Patient-Oriented Eczema Measure Score Bands

Score range	Clinical interpretation
0 to 2	Clear or almost clear
3 to 7	Mild atopic dermatitis
8 to 16	Moderate atopic dermatitis
17 to 24	Severe atopic dermatitis
25 to 28	Very severe atopic dermatitis

8.1.6.3 Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) is a 10-item assessment of dermatology-specific health-related quality of life in participants age 17 and older (Finlay and Khan 1994). Participants are asked to rate their symptoms and the impact of their symptoms on several domains: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Both the overall score and domain scores will be calculated.

The DLQI will only be administered to participants who are age 17 or older at Visit 1.

8.1.6.4 Children's Dermatology Life Quality Index

The Children's Dermatology Life Quality Index (CDLQI) is a 10-item assessment of dermatology-specific health-related quality of life in children and adolescents ages 5 to16 (Lewis-Jones and Finlay 1995). Participants are asked to rate their symptoms and the impact of their symptoms on several domains: symptoms and feelings, leisure, school and holidays, personal relationships, sleep, and treatment. Both the overall score and domain scores will be calculated.

The CDLQI will only be administered to participants who are age 16 or younger at Visit 1.

8.1.6.5 Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a mental health assessment comprising 7 items on anxiety and 7 items on depression. All questions are rated on a 0 to 3 scale, with higher scores representing worse mental health; scores for the 2 subscales thus range from 0 to 21. Scores between 0 and 7 are considered normal. Scores between 8 and 10 are possible cases of anxiety/depression. Scores 11 or greater are considered likely cases of anxiety/depression.

8.1.6.6 Patient Global Impression of Severity

The Patient Global Impression of Severity (PGI-S) is a single item assessment of the participant's perception of overall symptom severity at the time of completion. The assessment uses a 6-point categorical response scale (ranging from "no symptoms" to "very severe").

8.1.6.7 SF-36 (Version 2), Acute Recall

The Short Form 36-item Health survey Version 2 (acute recall) (SF-36v2) is a 36-item, self-report survey of functional health and well-being, with a 1-week recall period. Responses to 35 of the 36 items are used to compute an 8-domain profile of functional health and well-being scores. The remaining item, referred to as the 'Health Transition' item, asks participants to rate how their current state of health compared to their state of health 1 week ago and is not used to calculate domain scores. The 8-domain profile consists of the following subscales: Physical Functioning (PF), Role Limitations due to Physical Health (RP), Bodily Pain (BP), General Health Perceptions (GH), Vitality (VT), Social Functioning (SF), Role Limitations due to Emotional Problems (RE), and Mental Health (MH). Psychometrically-based physical and mental health component summary scores (PCS and MCS, respectively) are computed from subscale scores to give a broader metric of physical and mental health-related quality of life.

Two types of thresholds have been developed for interpretation of SF-36v2 scores. The first type is suitable for comparing group mean scores and is generally referred to as the minimal clinically important difference. The second type is suitable for interpreting change at the

individual level and is referred to as the responder threshold or responder definition; threshold values for the SF-36v2 scale and summary measures are provided in Table 9.

Table 9 Threshold Values for the SF-36v2 Scale and Summary Measures

Threshold	SF-36v2 score									
	PCS	MCS	PF	RP	BP	GH	VT	SF	RE	MH
Group difference	2	3	3	3	3	2	2	3	4	3
Individual change	3.4	4.6	4.3	3.4	6.2	7.2	6.2	6.9	4.5	6.2

BP, Bodily Pain; GH, General Health Perceptions; MCS, mental health component summary; MH, Mental Health; PCS, physical component summary; PF, Physical Functioning; RE, Emotional Problems; RP, Role Limitations due to Physical Health; Short Form 36-item Health Survey Version 2; VT, Vitality.

8.1.6.8 European Quality of Life-5 Dimensions

The European Quality of Life-5 Dimensions (EQ-5D) questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty.

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

CCI

[redacted]

8.1.7 Patient-Reported Experience

Participants will be asked to respond in writing (free text) to 3 open-ended questions about their experience with AD and their study intervention. The assessment will be conducted during the site visits specified in the SoA (Table 3), using a provisioned tablet to access the secure web form.

Data from the free text collection will be used for exploratory descriptive analysis using machine learning technologies. Due to the qualitative nature of the data and the analysis, the results will be presented in a separate report (not in the Clinical Study Report [CSR]) and the data will not be entered into the study database.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 3).

8.2.1 Clinical Safety Laboratory Assessments

Table 10 lists the clinical safety laboratory tests to be performed. Refer to the SoA (Table 3) for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the Laboratory Manual and the SoA (Table 3).

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at the site as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.5.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units, and reference ranges) will be recorded in the participant's medical records.

The clinical chemistry, hematology, and urinalysis will be performed at a central laboratory.

Instructions for sample collection, processing, storage, and shipment are provided in the central laboratory manual.

Table 10 Laboratory Safety Variables

Clinical chemistry		Hematology	Urinalysis
Alkaline phosphatase	Gamma-GT (gamma-glutamyl transpeptidase)	Hematocrit	Appearance
ALT (alanine aminotransferase)	Glucose	Hemoglobin	Blood
AST (aspartate aminotransferase)	Phosphorus	Mean corpuscular volume (MCV)	Color
BUN (blood urea nitrogen)	Potassium	Platelet count	Ketones
Calcium	Sodium	Red blood cell (RBC) count	Microscopy including White blood cell (WBC)/high power field (HPF), RBC/HPF
Chloride	Total bilirubin	WBC count (absolute and differential) [a]	pH
CO_2 (carbon dioxide) [b]	Uric acid		Specific gravity
Creatinine	Creatine kinase		

[a] Eosinophil, basophil, and monocyte counts will be redacted from the central laboratory reports starting from Visit 2 (refer to Section 6.3.2).

[b] Measured as bicarbonate.

8.2.1.1 Pregnancy Tests

The following tests are applicable to female participants only and will be conducted in accordance with the schedules provided in the SoA (Table 3).

- Serum beta-human chorionic gonadotropin (HCG): To be performed for all female participants at Visit 1 except for those who are NOT of childbearing potential as defined in inclusion criterion 12. This test is to be sent to and analyzed at the central laboratory.

- FSH: To be performed at Visit 1 only for female participants < 50 years who have been amenorrhoeic for ≥ 12 months prior to the planned date of randomization to confirm postmenopausal status. This test is to be sent to and analyzed at the central laboratory; all females should be treated as pre-menopausal until results are received from the central laboratory.
- Urine HCG (dipstick): To be performed locally at the study site before each IP administration (starting at Visit 2 through the EOT), and at IPD visits for all female participants except for those who are NOT of childbearing potential as defined in inclusion criterion 12. A positive urine test result must be confirmed with serum beta-HCG.

8.2.1.2 Serology

Hepatitis B surface antigen and hepatitis C antibody tests will be assessed in accordance with the SoA (Table 3); tests are to be performed at the central laboratory.

In case of positive result of hepatitis B surface antigen or hepatitis C virus antibody, additional testing (eg, hepatitis C ribonucleic acid [RNA] polymerase chain reaction test) may be performed.

HIV-1 and HIV-2 antibodies (along with p24 Antigen): To be performed only at screening; test to be performed at the central laboratory.

Instructions for sample collection, processing, storage, and shipment are provided in the laboratory manual.

8.2.2 Physical Examinations

Physical examinations (complete or brief), including height and weight, will be conducted in accordance with the schedule provided in Table 3. Baseline data will be collected at the randomization visit (Visit 2) before administration of the first dose of IP. Any new findings or aggravated existing abnormalities, judged as clinically significant by the Investigator, will be reported as an AE as described in Section 8.3.5.

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

The brief physical examination will include an assessment of the general appearance, head and neck (including eyes/conjunctivitis, nose), abdomen, cardiovascular, and respiratory system. For the brief physical examination, only information on whether the assessment was performed or not is to be recorded.

Weight measurements will be performed in light clothing and without shoes and will be recorded in kilograms.

8.2.3 Vital Signs

Pre-dose vital signs (pulse rate, blood pressure, respiratory rate, and body temperature) will be assessed in accordance with the SoA (Table 3).

It is recommended that vital signs are assessed before any interventional study procedures (blood test collection, IP administration).

Body temperature will be measured in Celsius in accordance with local standards.

Blood pressure and pulse measurements will be assessed while sitting with a completely automated device. Manual techniques will be used only if an automated device is not available. The pulse rate and blood pressure will be measured after the participant has been resting for at least 5 minutes in a quiet setting without distractions (eg, television, cell phones). The pulse rate should be obtained before blood pressure.

The respiration rate will be obtained after the participant has been resting for at least 5 minutes, by counting the number of breaths (how many times the chest rises) for 1 minute.

8.2.4 Electrocardiograms

Single 12-lead electrocardiogram (ECG) will be obtained locally during screening (Table 3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals. The ECG results will be interpreted locally.

The Investigator or authorized delegate will be responsible for the overall interpretation and determination of clinical significance of any potential ECG findings. The ECG printouts will be signed and dated by the Investigator and stored at the study site. Any findings will be recorded in the eCRF.

ECG will be taken in the supine position, after the participant has been resting for at least 5 minutes. The assessment should be performed before interventions with the participant (eg, IP administration).

8.3 Adverse Events and Serious Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow up AEs refer to Section 8.3.2.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected starting from Visit 1, throughout the treatment period, and including the follow-up period last contact with participant.

Serious AEs will be recorded from the time the participant signs the ICF, throughout the duration of the study. All SAEs will be recorded and reported to the AstraZeneca representative within 24 hours, as indicated in Appendix B. The Investigator will submit any updated SAE data to the AstraZeneca representative within 24 hours of it being available.

If the Investigator becomes aware of a SAE with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, report the SAE to the AstraZeneca representative.

8.3.2 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

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

Adverse Event Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity

- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to the IP
- AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Description of AE
- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to (see definition of SAE in Appendix B 2)
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

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 IP?'

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.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other

signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the protocol-mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the investigational product, or are considered to be clinically relevant as judged by the Investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 Disease Under Study

Symptoms of disease under study are those which might be expected to occur as a direct result of AD (eg, erythema, induration/papulation, lichenification, oozing/crusting, pruritus). Events which are unequivocally due to AD should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the IP.

8.3.7 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site within one calendar day of initial receipt for fatal and life-threatening events and within 5 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but no later than 24 hours of when he or she becomes aware of it).

If the electronic data capture system is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

The reference document for definition of expectedness/listedness is the Investigator's Brochure for benralizumab.

For further guidance on the definition of an SAE, see Appendix B.

8.3.8 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the AstraZeneca representative unless the pregnancy is discovered before the study participant has received any IP.

If a pregnancy is reported, the Investigator should inform the AstraZeneca representative within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

8.3.8.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed-up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representative within one day (ie, immediately but no later than 24 hours of when he or she becomes aware of it).

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (Section 8.3.7) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.3.9 Device Constituent Deficiencies

- In a combination drug-device IP [redacted] the Device Constituent deficiency is an inadequacy of a device constituent with respect to its identity, quality, durability, reliability, safety, or performance. These deficiencies include malfunctions, use errors, and information supplied by the manufacturer.
- Serious adverse device effect (SADE) is defined as any Device Constituent Deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
- For device constituent deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
- A remedial action is any action other than routine maintenance or servicing of a device constituent where such action is necessary to prevent recurrence of a device constituent deficiency. This includes any amendment to the device constituent design to prevent recurrence.
- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the device constituent deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

8.3.10 Serious Adverse Device Effect Reporting

NOTE: There are additional reporting obligations for device constituent deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to device constituents being used in clinical studies.

- Any device constituent deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device constituent deficiency.
- The sponsor will review all device constituent deficiencies and determine and document in writing whether they could have led to an SAE. These device constituent deficiencies

will be reported to the regulatory authorities and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) as required by national regulations.

8.3.11 Medication Error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the AstraZeneca representative within one day (ie, immediately but no later than 24 hours of when he or she becomes aware of it).

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within one (initial fatal/life-threatening or follow-up fatal/life-threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (Section 8.3.1) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix B.

8.3.12 Management of Investigational Product-related Drug Reactions

Appropriate drugs, such as epinephrine, H_1 and H_2 antihistamines, and corticosteroids, as well as medical equipment to treat acute anaphylactic reactions must be immediately available when IP is administered and study site personnel must be trained to recognize and treat anaphylaxis (Lieberman et al 2010). Details on anaphylaxis management are provided in Appendix E.

Anaphylaxis will be defined as a serious reaction that is rapid in onset and may cause death (Sampson et al 2006). Anaphylaxis typically manifests as 1 of 3 clinical scenarios:

1 The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue, or both and at least one of the following:
   (a) respiratory compromise; or
   (b) reduced blood pressure or symptoms of end-organ dysfunction; or
2 Two or more of the following that occur rapidly after exposure: involvement of the skin/mucosal tissue, respiratory compromise, reduced blood pressure or associated symptoms and/or persistent gastrointestinal symptoms; or
3 Reduced blood pressure after exposure.

Further details on the clinical criteria for defining anaphylaxis and immune complex disease are provided in Appendix E 2.

Participants will have had a pre-assessment (ie, vital signs) prior to IP administration. Participants should be observed in line with clinical practice after each IP administration for the appearance of any acute drug reactions.

Serum tryptase or other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local laboratory at the discretion of the Investigator.

8.4 Overdose

For this study, any administration greater than 200 mg of benralizumab will be considered an overdose.

There is no specific treatment for an overdose with benralizumab. If overdose occurs, the participant should be treated supportively with appropriate monitoring as necessary.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the case report form (CRF) and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca IP occurs in the course of the study, then the Investigator or other site personnel inform the AstraZeneca representative immediately, or no later than 24 hours of when he or she becomes aware of it.

The AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply, see Section 8.3.2. For other overdoses, reporting must occur within 30 days.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples, refer to Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent/assent and local requirements, after which they will be destroyed/repatriated.

- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented/assented for future analyses.
  - PK samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate

the analytical method. Any results from such analyses may be reported separately from the CSR.

- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.5.1 Pharmacokinetics

All PK samples will be collected before administration of IP according to the SoA (Table 3).

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the AstraZeneca and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

For the PK analysis, it is important that the date, time, and location of each SC injection is recorded for each participant.

Instructions for sample collection, processing, storage, and shipment are provided in the Laboratory Manual.

Full details of the analytical method used will be described in a separate Bioanalytical Validation Report.

8.5.1.1 Determination of Drug Concentration

Samples for determination of benralizumab concentration in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate report. Only samples from the benralizumab treatment arm will be analyzed.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.5.2 Immunogenicity Assessments

Blood samples for determination of ADA in serum will be assayed at the discretion of AstraZeneca by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods used will be described in a separate report.

ADA samples may also be further tested for characterization of the ADA response.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

8.5.3 Pharmacodynamics

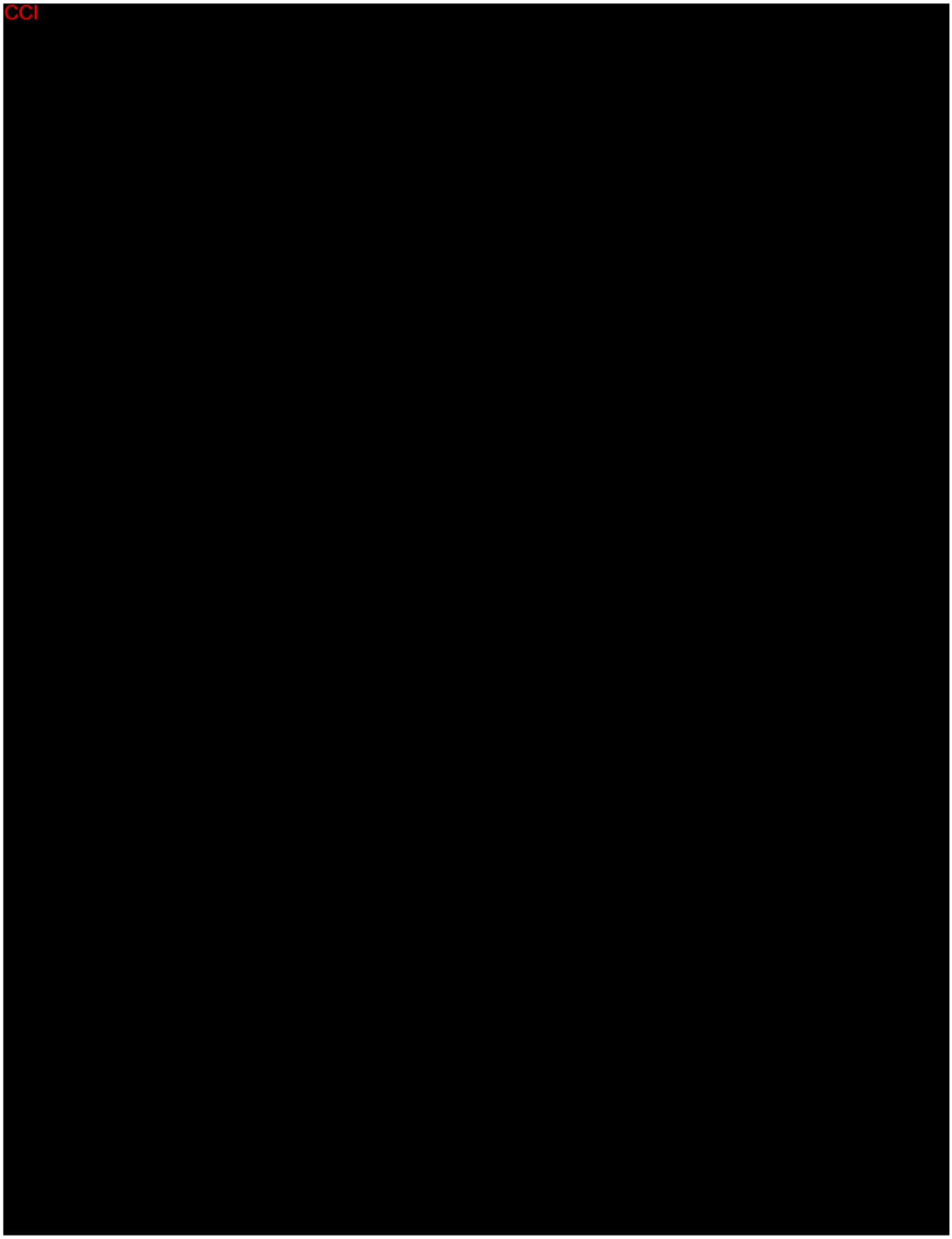
Blood and tissue eosinophil and basophil levels are an important marker of the PD effect of benralizumab and blood levels will be assessed as part of the hematology safety testing (Section 8.2.1). CCI [redacted]

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

CCI [redacted]

CCI



CCI

Detailed instructions for collection of these samples are provided in the Laboratory Manual.

8.6.2 Collection of Additional Biomarker Samples

CCI

- CCI [redacted]

Detailed instructions for collection of these samples are provided in the Laboratory Manual.

8.6.3 Storage, Re-use and Destruction of Biomarker Samples

CCI [redacted]

8.7 Optional Genomics Initiative Sample

CCI [redacted]

8.8 Healthcare Resource Utilization

AD-related healthcare resource utilization information will be collected by the Investigator, or designee, in accordance with the SoA (Table 3) and recorded in the appropriate eCRF module. Protocol-mandated procedures, tests, and encounters are not included.

At randomization, retrospective AD-related healthcare resource utilization information will be collected with a one-year recall period. At all subsequent visits, AD-related healthcare resource utilization information will be collected with a recall period of 'since last scheduled visit'.

The data collected may be used to conduct exploratory economic analyses and include:

- Number and duration of hospitalization (length of stay, overall and by wards [eg, general ward, intensive care unit])
- Number and type of diagnostic and therapeutic tests and procedures
- Number of outpatient medical encounters and interventions (including GP, specialists, or emergency room visits, and medications)

Note: Cases of hospitalization occurring after signing of the ICF must be reported as an SAE (Section 8.3).

9 STATISTICAL CONSIDERATIONS

The primary DBL will occur after all randomized participants have completed the initial 16-week treatment period. The final DBL will occur when all participants have completed the 52-week treatment period and/or the IPD/end-of-treatment/Week 60 follow-up visit. An additional analysis may be performed between the primary and final DBLs, to report data accumulating during the extension part of the study if needed to support end of Phase 2 decision making. Participants and investigators will remain blinded to the dosing regimens until the final DBL.

The CSR will be based on the final DBL and will include all data for the study.

9.1 Statistical Hypotheses

The primary endpoint is the proportion of participants with IGA 0/1 (ie, clear or almost clear) and a decrease in IGA of 2 or more points at Week 16, relative to baseline. The null hypothesis is: the proportion of participants on benralizumab 30 mg Q4W is equal to the proportion of participants on placebo. Whereas, the alternative hypothesis is: the proportion of participants on benralizumab 30 mg Q4W is not equal to the proportion of participants on placebo. That is,

H_0: Difference in proportions (benralizumab 30 mg Q4W – placebo) = 0

H_1: Difference in proportions (benralizumab 30 mg Q4W – placebo) ≠ 0

The first and third key secondary endpoints are derived from the EASI and they are: the proportion of patients with EASI-75 at Week 16; and the proportion of participants with EASI-90 at Week 16. The second key secondary endpoint is the proportion of participants with an improvement of 4 or more points in peak pruritus weekly score at Week 16, relative to baseline. For each of these endpoints, the null hypothesis is: the proportion of participants on benralizumab 30 mg Q4W is equal to the proportion of participants on placebo. Whereas, the alternative hypothesis is: the proportion of participants on benralizumab 30mg Q4W is not equal to the proportion of participants on placebo. That is,

H_0: Difference in proportions (benralizumab 30 mg Q4W – placebo) = 0

H_1: Difference in proportions (benralizumab 30 mg Q4W – placebo) ≠ 0

For the primary and key secondary endpoints, the primary estimand will be based on the full analysis set (Table 12). Intercurrent events will consist of participants who withdraw from the study or require rescue therapy (defined in Section 6.5.3). The primary estimand will regard these participants as non-responders from the time such events occur up to Week 16. A participant with missing data at a specific time point will also be considered as a non-responder at that time point.

Hypothesis testing for the primary and key secondary endpoints will be based on a 2-sided test and carried out using a 5% significance level. If a p-value is less than 0.05, the treatment effect favors benralizumab 30 mg Q4W and the decision will be to reject the null hypothesis (H_0) and the alternative hypothesis (H_1) will be accepted.

A hierarchical testing procedure will be used to control the overall Type I error rate at 5% across the primary and key secondary endpoints (Section 9.4.2). The variables will be tested sequentially in the following order using a 2-sided test and a 5% significance level:

1 Proportion of participants with IGA 0/1 (ie, clear or almost clear) and a decrease in IGA of 2 or more points at Week 16, relative to baseline
2 Proportion of participants with EASI-75 at Week 16
3 Proportion of participants with an improvement of 4 or more points in peak pruritus weekly score at Week 16, relative to baseline
4 Proportion of participants with EASI-90 at Week 16

9.2 Sample Size Determination

As a minimum, approximately 160 participants will be recruited into the study and will be randomized to one of the following treatment sequences in a ratio of 1:1:2 (respectively):

- **Benralizumab 30 mg Q4W** until Week 16, followed by an extension period with **benralizumab 30 mg Q4W** administered until Week 52 (n = 40)
- **Benralizumab 30 mg Q4W** until Week 16, followed by an extension period with **benralizumab 30 mg Q8W** administered until Week 52 (n = 40)
- **Placebo Q4W** until Week 16, followed by an extension period with **benralizumab 30 mg Q4W** administered until Week 28, and then **benralizumab 30 mg Q8W** administered until Week 52 (n = 80).

For the initial 16-week treatment period, the aim is to recruit a minimum of 80 participants into the placebo group and a minimum of 80 participants into the benralizumab 30 mg Q4W

group. (Note that participants who receive benralizumab 30 mg Q4W during the first 16 weeks will be grouped together and considered as a single treatment group.)

To identify responding subpopulations, the randomization will be stratified by age (≥ 12 to < 18 years and ≥ 18 years) and baseline blood eosinophils (< 300 cells/μL, ≥ 300 cells/μL). In total, the aim is to recruit a minimum number of participants per strata across the treatment groups as outlined in Table 11.

Table 11 Randomization Stratification

	Baseline blood eosinophils	
	< 300 cells/μL	**≥ 300 cells/μL**
Adolescents (≥ 12 to < 18 years), n	30	50
Adults (≥ 18 years), n	30	50

n, number

The study will continue to recruit participants until the minimum number of participants per strata is achieved, up to a maximum of 200 patients in total. The purpose of this method of recruitment is to ensure that a broad distribution of participants is recruited across the range of ages and blood eosinophil levels to allow potential identification of responding subpopulations and appropriate cut-offs for future studies, if necessary.

The sample size calculations that follow are based on the primary endpoint, ie, the proportion of patients with an IGA 0/1 and a decrease in IGA of ≥ 2 points relative to baseline. The calculations are associated with differences between benralizumab 30 mg Q4W and placebo at Week 16 during the initial double-blind, placebo-controlled phase of the study (Figure 2). For the primary analysis, the sample size calculation will power the study to detect a difference between benralizumab 30 mg Q4W and placebo in the overall population. Additional calculations have been provided to ensure that the study is adequately powered to detect treatment differences and consistency of effect in potential subgroups, should efficacy be limited to a subset of the population.

Primary analysis: In the overall population, a minimum of 80 participants per treatment group will provide a high level of power (> 95%) to detect a 30% difference between benralizumab 30 mg Q4W and placebo for the primary endpoint. This calculation is based on a 2-sided test and a 5% significance level and assumes a response rate of 40% for benralizumab 30 mg Q4W and 10% for placebo.

Subgroup analyses: As a benchmark, a minimum of 35 participants per treatment will provide at least 80% power to detect a 30% difference between benralizumab 30 mg Q4W and placebo. (As for the primary analysis, these calculations are based on a 2-sided test and a 5%

significance level, and assumes the same response rates for benralizumab 30 mg Q4W and placebo.) Thus, there is a high probability of detecting differences between treatments in the baseline blood eosinophils ≥ 300 cells/μL subgroup (with 50 participants per treatment), in the adult subgroup (with 40 participants per treatment), and in the adolescent subgroup (with 40 participants per treatment). Note that in the baseline blood eosinophils < 300 cells/μL subgroup, 30 participants per treatment group will provide an adequate amount of data to explore treatment differences, and will allow different cut-offs between 'low' and 'high' eosinophils at baseline to be assessed.

Assessing consistency of effect: Consistency of effect will be assessed between adult and adolescent participants in the overall population and in any identified subgroup for baseline blood eosinophils. By aiming for 25 adults and 25 adolescents per treatment in the baseline blood eosinophils ≥ 300 cells/μL subgroup, the probability of detecting consistent effects between adults and adolescents is high. That is, assuming the true increase in response rate between benralizumab 30 mg Q4W and placebo is 30%, there is > 85% chance of observing a treatment difference for adolescents of at least half of the treatment difference observed for adults.

9.3 Populations for Analyses

The populations for purposes of analyses are defined in Table 12:

Table 12 Populations for Analyses

Population	Description
All participants analysis set	All participants who sign the ICF
Full analysis set	The full analysis set will comprise all randomized participants who receive at least one dose of IP, irrespective of their protocol adherence and continued participation in the study. Participants will be analyzed according to their randomized treatment irrespective of whether or not they were prematurely discontinued, according to the ITT principle. Data for participants who withdraw consent/assent to participate in the study will be included up to the date of permanent discontinuation.
Safety analysis set	The safety analysis set will comprise all participants who receive at least one dose of IP. Erroneously-treated participants (eg, those randomized to treatment A but actually given treatment B) are accounted for in this analysis set by assigning them to the treatment they actually received. A participant who receives at least one dose of active IP will be classified as active and included in the active IP treatment group/sequence. Safety and ADA data will be based on this analysis set and for whom any post-dose data are available.

Table 12 Populations for Analyses

Population	Description
Pharmacokinetic analysis set	All participants who received benralizumab and from whom PK blood samples are assumed not to be affected by factors such as protocol violations (eg, received wrong dose) and who had at least one quantifiable serum PK observation post first dose. All PK summaries will be based on this analysis set.
Placebo-to-benralizumab extension analysis set	All participants who received benralizumab at the start of the extension period who were previously on placebo.

ADA, Anti-drug antibodies; ICF, Informed consent/assent form; IP, Investigational product; ITT, Intent-to treat; PK, Pharmacokinetic.

9.4 Statistical Analyses

A comprehensive statistical analysis plan (SAP) will be developed and finalized prior to the primary DBL and will include a more technical and detailed description of the statistical analyses described below. The SAP will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. Any deviations from this plan will be reported in the CSR.

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

All personnel involved in the analyses of the study will remain blinded until the primary DBL and protocol deviations are identified.

Analyses will be performed by AstraZeneca or its representatives.

Categorical variables will be summarized using frequency and percentages, where the denominator for calculation is the underlying analysis set population unless otherwise stated.

Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate.

All point estimates will be presented together with 95% confidence intervals. Nominal p-values, corresponding to a 2-sided test, will be presented for comparisons between treatments. Methods for controlling multiplicity across the primary and key secondary endpoints are discussed in Section 9.4.6.

9.4.1 General Considerations

The primary analysis will be based on the initial 16-week, double-blind, placebo-controlled phase of the study, and will compare 2 treatment groups comprising all participants

randomized to benralizumab 30 mg Q4W until Week 16 (n = 80) and all participants randomized to placebo until Week 16 (n = 80).

The primary estimand will be based on participants in the full analysis set (Table 12) and will be used for the analysis of primary and key secondary endpoints. The set of incurrent events for this estimand consists of participants who withdraw from the study and participants who require rescue therapy (refer to Section 6.5.3). The primary estimand will regard these participants as non-responders from the time such events occur up to Week 16. The amount of missing data for this study is expected to be low, as participants who prematurely discontinue IP will be asked to come in for all visits and complete all study assessments up to the end of the study. Any participant with missing data at a specific time point will be considered as a non-responder at that time point.

Additional estimands will be specified in the SAP for the primary and key secondary endpoints to carry out sensitivity analyses for assessing the robustness of results. These sensitivity analyses will explore different methods for handling intercurrent events and different assumptions for missing data. Estimands for secondary, exploratory, and tertiary endpoints will also be specified in the SAP, which will include how intercurrent events will be handled for continuous endpoints. Sensitivity analyses may be carried out for specific secondary endpoints, if deemed necessary to strengthen conclusions drawn from the primary and key secondary endpoints. Full details will be provided in the SAP.

Full details of the analyses and methods to be used for the extension period will be provided in the SAP.

Demography and baseline characteristics will be summarized by treatment for the Full Analysis Set (FAS). If there are major differences between the FAS and safety analysis set, the summaries will also be repeated and presented for the safety analysis set.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint

Proportion of Patients with Skin Clearance at Week 16 Using the IGA Data

The primary endpoint is a binary response that classifies a participant's skin clearance at Week 16 using the IGA score. Participants will be classified as responders if IGA 0/1 (ie, clear or almost clear) and they have a decrease in IGA of 2 or more points relative to baseline. Otherwise, participants will be classified as non-responders.

For the primary analysis, a logistic regression model will be fitted to the primary endpoint using a logit link function. The model will include treatment group and baseline covariates for age (adolescents; adults) and blood eosinophils (< 300 cells/μL; ≥ 300 cells/μL). Sensitivity analyses may also explore the effect of including baseline covariates such as severity of

disease (moderate; severe), presence of staphylococcus aureus (absent; present) and asthma comorbidity (yes; no). The model will be used to estimate the proportion of responders for benralizumab and placebo, the difference between these proportions (benralizumab – placebo) and an odds ratio, with corresponding 95% confidence limits. A p-value, corresponding to a 2-sided test, will be presented to compare the benralizumab and placebo treatment groups. Note that if the logistic regression model does not converge to a solution due to low response rates in certain strata, these data will be analyzed using a Cochran–Mantel–Haenszel test.

To support this analysis, the observed proportion of responders will be summarized using descriptive statistics by treatment group and each scheduled visit up to Week 16. Full details will be provided in the SAP.

9.4.2.2 Key Secondary Endpoints

Proportion of Patients with Skin Clearance at Week 16 Using the EASI Data

The first and third key secondary endpoints are binary responses that classify a participant's skin clearance at Week 16 using the EASI:

- EASI-75 response rate: Participants will be classified as responders if they achieve at least a 75% reduction from baseline in their EASI score at Week 16. Otherwise, participants will be classified as non-responders.
- EASI-90 response rate: Participants will be classified as responders if they achieve at least a 90% reduction from baseline in their EASI score at Week 16. Otherwise, participants will be classified as non-responders.

The statistical analysis described for the primary analysis will be carried out for these key secondary endpoints. To support this analysis, the observed proportion of responders will be summarized for each endpoint using descriptive statistics by treatment group and each scheduled visit up to Week 16. Full details will be provided in the SAP.

Proportion of Patients with Itch at Week 16, Using the Peak Pruritus Numerical Rating Scale (NRS) Data

The second key secondary endpoint is a binary response that will classify a participant as a responder if there is an improvement of 4 or more points in peak pruritus weekly score at Week 16 relative to baseline. Otherwise, participants will be classified as a non-responder. (Note that daily peak pruritus scores are averaged to give a weekly score.)

The statistical analysis described for the primary analysis will be carried out for this key secondary endpoint. To support this analysis, the observed proportion of responders will be summarized using descriptive statistics by treatment group and each scheduled visit up to Week 16. Full details will be provided in the SAP.

Note that a hierarchical testing procedure will be used to control the overall Type I error rate at 5% across the primary and key secondary endpoints. Refer to Section 9.4.6 for more details.

9.4.2.3 Secondary Endpoints

Proportion of Patients with Skin Clearance at Week 16 Using the EASI Data

Two additional binary responses that classify a participant's skin clearance at Week 16 will be derived from the EASI:

- EASI-50 response rate: Participants will be classified as responders if they achieve at least a 50% reduction from baseline in their EASI score at Week 16. Otherwise, participants will be classified as non-responders.
- EASI-100 response rate: Participants will be classified as responders if they achieve at least a 100% reduction from baseline in their EASI score at Week 16. Otherwise, participants will be classified as non-responders.

The statistical analysis described for the primary analysis will be carried out for each of these endpoints. (The p-values will be nominal, as secondary objectives are not controlled for multiplicity and do not appear in the testing hierarchy.) To support this analysis, the observed proportion of responders will be summarized for each endpoint using descriptive statistics by treatment group and each scheduled visit up to Week 16. Full details will be provided in the SAP.

Assessing Changes in Atopic Dermatitis at Week 16 Using the EASI

The EASI is a continuous outcome that will be completed at the visits specified in the SoA (Table 3) during the initial 16-week treatment period. This endpoint will be analyzed by a Mixed Model Repeated Measures (MMRM) model.

The model will include change from baseline as the dependent variable (derived for each participant and every scheduled visit up to Week 16); baseline as a continuous covariate; treatment, age (adolescents; adults), baseline blood eosinophils (< 300 cells/μL; ≥ 300 cells/μL) and visit as categorical covariates; treatment-by-visit as an interaction term. An unstructured variance-covariance matrix will be used to model within-subject errors, and the Kenward-Roger approximation will be used to estimate denominator degrees of freedom and to adjust standard errors. (If the model fails to converge, alternative variance-covariance models will be tried in the following order: Toeplitz, first-order regressive, compound symmetry.) For each visit, the model will be used to estimate the mean change from baseline for each treatment group and the difference versus placebo, with corresponding 95% confidence limits. A p-value, corresponding to a 2-sided test, will be presented to compare the benralizumab and placebo treatment groups at each visit. (The p-values will be nominal, as secondary objectives are not controlled for multiplicity and do not appear in the testing hierarchy.)

The distributional assumptions of the MMRM model will be checked by examining plots of residuals. If the residuals suggest that it is unreasonable to assume that data follow a Normal distribution (eg, data are skewed and the constant variance assumption is not met), alternative models will be explored. For example, data may be log transformed prior to fitting the model, or a non-parametric method may be deemed more appropriate.

To support this analysis, observed means and mean changes from baseline will be summarized using descriptive statistics by treatment group and each scheduled visit up to Week 16. Full details will be provided in the SAP.

Assessing Itch at Week 2, Using the Peak Pruritus Numerical Rating Scale (NRS) Data

Daily peak pruritus scores are continuous outcomes that will be averaged for each participant to give a value at baseline and values for Week 1 through to Week 16 (inclusive) during the initial 16-week treatment period. The statistical analysis described above for the EASI will be carried out for this secondary endpoint, where the same MMRM model will be fitted to these data. To support this analysis, observed means and mean changes from baseline will be summarized using descriptive statistics by treatment group and each timepoint up to Week 16. Full details will be provided in the SAP.

Assessing Skin Severity at Week 16, Using the Patient Orientated Eczema Measure data

The POEM is a continuous outcome that will be completed at the visits specified in the SoA (Table 3) during the initial 16-week treatment period. The statistical analysis described above for the EASI will be carried out for this secondary endpoint, where the same MMRM model will be fitted to these data. To support this analysis, observed means and mean changes from baseline will be summarized using descriptive statistics by treatment group and each scheduled visit up to Week 16. Full details will be provided in the SAP.

Assessing Quality of Life at Week 16, Using the Dermatology Life Quality Index and the Children's Dermatology Life Quality Index

The DLQI and CDLQI are continuous outcomes that will be completed by participants aged > 16 years and ≤ 16 years (respectively) at the visits specified in the SoA (Table 3) during the initial 16-week treatment period. The statistical analysis described above for the EASI will be carried out for each of these secondary endpoints, where the same MMRM model will be fitted to DLQI and CDLQI separately. To support these analyses, observed means and mean changes from baseline will be summarized for DLQI and CDLQI using descriptive statistics by treatment group and each scheduled visit up to Week 16. Full details will be provided in the SAP.

Assessing Atopic Dermatitis at Week 16, Using the SCORAD Index

SCORAD is a continuous outcome that will be completed at the visits specified in the SoA (Table 3) during the initial 16-week treatment period. The statistical analysis described above for the EASI will be carried out for this secondary endpoint, where the same MMRM model

will be fitted to these data. To support this analysis, observed means and mean changes from baseline will be summarized using descriptive statistics by treatment group and each scheduled visit up to Week 16. Full details will be provided in the SAP.

Assessing the Efficacy of Q8W Relative to Q4W Dosing Out to Week 52

The long-term efficacy of the Q8W dosing regimen will be assessed against the Q4W dosing regimen as the benchmark. The efficacy endpoints described above will be assessed until Week 52, where trends over time will be assessed for the 3 treatment sequences described in Section 4.2.

The focus of this analysis will assess results at Week 52 for participants that (i) remain on benralizumab 30 mg Q4W throughout the study and (ii) switch from benralizumab 30 mg Q4W to benralizumab 30 mg Q8W at Week 16. The third group of participants that receive placebo followed by benralizumab at Week 16 will also be presented in the analyses; however, they will not be formally compared against the other 2 treatment sequences. Results observed at Week 52 will be interpreted relative to changes already observed at Week 16 to assess if preliminary efficacy appears to be maintained with either treatment regimen.

Primarily, long-term efficacy will be assessed using the EASI, which is a continuous endpoint measured at baseline and at scheduled visits during the study until Week 52 (Table 3). Change from baseline values will be derived for every scheduled visit up to Week 52 and analysed by an MMRM model, which will include the 3 treatment sequences as a categorical covariate. Similar analyses may be performed for additional efficacy endpoints. Full details will be provided in the SAP.

9.4.2.4 Tertiary/exploratory Endpoints

Analyses for exploratory objectives will be specified in the SAP or in an exploratory analysis plan.

9.4.3 Safety Analyses

Safety analyses will be performed using the safety analysis set. Analyses will be presented for the overall study period divided by the 3 treatment sequences and presented separately for the first 16 weeks comparing the single benralizumab group with placebo.

Participants will be analyzed according to the treatment they received.

In general, the baseline value for statistical analysis is the last non-missing value prior to administration of the first dose of IP. Details will be described in the SAP.

Adverse Events

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) that will have been released for execution at AstraZeneca/designee.

Safety data will be presented using descriptive statistics unless otherwise specified in the SAP.

Adverse events will be presented for each treatment by system organ class and preferred term, including the number and percentage of participants reporting at least one event, number of events and exposure-adjusted rates, where appropriate.

An overview of AEs will be presented for each treatment, including the number and percentage of participants with any AE, AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP.

Separate AE tables will be provided taking into consideration the relationship as to IP assessed by the Investigator, maximum intensity, seriousness, death and events leading to discontinuation of IP, as well as other action taken related to IP.

Key participant information will be presented for participants with AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP.

An AE listing for the safety analysis set will cover details for each individual AE.

Full details of AE analyses will be provided in the SAP.

Treatment Emergent

The following events are considered treatment emergent:

- Adverse events with an onset date on or after the first dose of IP
- Worsening of pre-existing events on or after first dose of IP

Clinical Laboratory Safety Assessments

Laboratory data for hematology and clinical chemistry will be summarized. The frequency of changes with respect to normal ranges between baseline and each post-treatment time point will be tabulated. Frequencies of clinically noteworthy values (defined in the SAP) occurring during the clinical study will also be given. Shifts from normal to abnormal between baseline and each post-baseline time point will be evaluated for urinalysis.

Vital Signs

Vital sign parameters will be presented for each treatment. Summary statistics for continuous variables cover n, mean, standard deviation, Minimum, Q1, median, Q3, and Maximum.

Frequency tables cover number and percentage of participants in the respective category.

For each scheduled post-baseline visit, descriptive statistics for all vital sign parameters will be presented for observed values and change from baseline.

Changes in vital signs will be examined at each visit. Frequencies of clinically noteworthy values (defined in the SAP) occurring during the clinical study will be presented.

Details of vital sign analyses will be provided in the SAP.

Physical Examination

Shifts from normal to abnormal between baseline and follow-up will be evaluated for the physical examination.

9.4.4 Immunogenicity Analyses

Anti-drug antibodies to benralizumab will be summarized using descriptive statistics at each visit by treatment. The ADA titres-time profiles of benralizumab may be generated. The impact of ADA on PK and eosinophil level will be assessed. The potential association of ADA with safety and efficacy will be evaluated. Further details will be provided in the SAP.

9.4.5 Other Analyses

Pharmacokinetic and PD exploratory analyses will be described in the SAP, or in an exploratory SAP, which will be finalized before DBL.

9.4.5.1 Skin Photography

To support clinical efficacy assessments, skin photography will be performed and these results will be compared with in-person completed clinical assessments.

Treatment effects for efficacy endpoints when informed by photography assessments may be compared to those based on in-person efficacy assessments. Concordance between photography efficacy assessments and in-person assessments for a given endpoint/visit will be summarized as appropriate. Details will be specified in the SAP.

9.4.6 Methods for Multiplicity Control

A hierarchical testing procedure will be used to control the overall Type I error rate at 5% across the primary and key secondary endpoints. The variables will be tested sequentially in the following order using a 2-sided test and a 5% significance level:

1 Proportion of participants with IGA 0/1 (ie, clear or almost clear) and a decrease in IGA of 2 or more points at Week 16, relative to baseline
2 Proportion of participants with EASI-75 at Week 16
3 Proportion of participants with an improvement of 4 or more points in peak pruritus weekly score at Week 16, relative to baseline
4 Proportion of participants with EASI-90 at Week 16

If the treatment comparison for (1) is statistically significant, testing will proceed to (2). If the treatment comparison for (2) is statistically significant, testing will proceed to (3). If the treatment comparison for (3) is statistically significant, testing will proceed to (4). If, at any point in this hierarchy, a null hypothesis cannot be rejected at the 5% significance level in favor of benralizumab, further testing will stop, and no subsequent null hypotheses will be rejected.

9.4.7 Sensitivity Analyses

Sensitivity analyses will be explored to assess the robustness of treatment effects for the primary and key secondary endpoints. Different missing data mechanisms (eg, values missing at random and values missing not at random) will be considered to assess the robustness of the treatment effect for these endpoints. The use of multiple imputation approaches will be considered. Full details of the sensitivity analyses will be specified in the SAP and documented prior to the primary DBL.

9.4.8 Subgroup Analysis

For the primary and secondary efficacy variables, subgroup analyses will be conducted to explore the consistency of the overall estimated treatment effect and will include (but not limited to) age and baseline blood eosinophils. Subgroup analyses will include assessing different cut-offs for baseline blood eosinophil levels to understand if benralizumab is effective in different responding subpopulations. Details of these analyses will be provided in the SAP.

9.5 Interim Analyses

No formal interim analysis is planned for the study.

The first set of analyses will be run at the primary DBL, which will occur after all randomized participants have completed the initial 16-week treatment period. The final set of analyses will be produced at the final DBL, which will occur when all participants have completed the 52-week treatment period and/or the IPIPD/end-of-treatment/Week 60 follow-up visit. An additional analysis may be performed between the primary and final DBLs to report data accumulating during the extension part of the study if needed to support end of phase 2

decision making. Participants and investigators will remain blinded to the dosing regimens until the final DBL.

9.6 Data and Safety Monitoring Board

An independent DSMB will be utilized for this study. The DSMB will provide oversight, with particular focus on the adolescent participants, to ensure safe and ethical conduct of the study. For details on the rationale for and the remit of the committee, refer to Appendix A 5.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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