Clinical Study Protocol	
Study Intervention	Benralizumab
Study Code	D325AC00002
Version	4.0
Date	26 April 2022

A Multinational, Randomized, Double-blind, Parallel-group, Placebo-controlled Study to Investigate the Use of Benralizumab as a Treatment Option for Patients with Bullous Pemphigoid (FJORD)

Sponsor Name: AstraZeneca AB

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Regulatory Agency Identifier Number(s):

European Clinical Trials Database (EudraCT) number: 2020-000287-32; 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: D325AC00002

Amendment Number: 3

Study Intervention: Benralizumab.

Study Phase: 3

Short Title:

A study to investigate the use of benralizumab in patients with bullous pemphigoid (FJORD).

Safety Physician Name and Contact Information will be provided separately

International Co-ordinating investigator

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	26 Apr 2022
Amendment 2	17 May 2021
Amendment 1	30 November 2020
Original Protocol	24 June 2020

Amendment 3 (26 APR 2022)

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 decrease participant and site burden and to simplify the protocol. Other changes were made for alignment with the updated company protocol template.

Section # and name	Description of change	Brief rationale	Substantial/ Non-substantial
Title Page	The local amendment number changed to 3 (Protocol Version 4).	Updated to reflect the correct version number of this protocol.	Non-substantial
1.3 Schedule of Activities CCI [redacted]	CCI [redacted]	These assessments were removed to reduce participant and site burden.	Non-substantial
1.3 Schedule of Activities	Table updated to reflect CCI [redacted] will only be performed at Screening and Visit 13.	To reduce participant and site burden.	Non-substantial
	Table updated to reflect that samples for pharmacokinetics, ADA and CCI [redacted] at unscheduled visits will only be collected if the visit occurs for BP relapse.	Testing updated as these are only needed if the participant experiences relapse.	Non-substantial

Section # and name	Description of change	Brief rationale	Substantial/ Non-substantial
	Hepatitis B and C testing added to the local laboratory testing.	Omitted in error.	Non-substantial
	Neutralizing antibodies added to immunogenicity testing.	Omitted in error.	Non-substantial
	Footnote added for distribution of handheld device and instruction on use to clarify that the AstraZeneca study physician will have the discretion to exempt participants with certain medical conditions (eg, BP lesions of the fingers/hand, neurologic condition affecting fingers/hand, visual impairment) from use of the handheld device for off-site PRO assessments. All participants will use the tablet for onsite PRO assessments.	Updated conditions for exemption based on patient centricity. This will not impact the study endpoints.	Non-substantial
	Urinalysis (dipstick) removed	To reduce participant burden.	Non-substantial
	CCI [redacted]	To reduce participant burden, CCI [redacted] will no longer be performed except in previously enrolled participants.	Non-substantial
	Reduced urine pregnancy testing requirements to quarterly, rather than every visit. All relevant sections updated with new guidance.	For clarification and to reduce participant/site burden.	Non-substantial
3. Objectives and Endpoints	CCI [redacted]		Non-substantial
	[redacted]		Non-substantial
5.1 Inclusion Criteria	Addition of inclusion Criterion 6 to be able to complete PRO	Updated conditions for exemption based on patient centricity. This	Non-substantial

Section # and name	Description of change	Brief rationale	Substantial/ Non-substantial
	assessments on a tablet and on a handheld device, with some participants being exempted from completing home PROs on the handheld device upon agreement with the AstraZeneca physician (eg, if the patient has a medical condition such as BP lesions of the fingers/hand, a neurologic condition affecting fingers/hand, or severe visual impairment).	will not impact the study endpoints.	
	Criterion 8 was updated to specify that participants must have a negative pregnancy test at Screening only.	Updated to align with benralizumab safety data and internal guidance for testing.	Non-substantial
5.2 Exclusion Criteria	Criterion 1 was updated to remove the list of medications that could potentially induce Bullous pemphigoid (BP).	Text amended to simplify the exclusion criterion language.	Non-substantial
	Criterion 2 was replaced with the following “Comorbid disease that in the Investigator's judgement might interfere with the evaluation of the IP or safety of the participant.”	Text amended to simplify the language in the exclusion criteria.	Non-substantial
	Criterion 3a was updated to specify that only participants with in situ carcinoma of the cervix had to be treated and have been in remission for 12 months.	Text amended as risks with superficial cancers have not been identified.	Non-substantial
	Criterion 3b added so participants with superficial basal cell or squamous skin cancers can be enrolled.	Text amended as risks with superficial skin cancers have not been identified.	Non-substantial
	Assent removed from Criterion 3a and 3b (now renumbered as 3c).	Text amendment as this is an adult only study.	Non-substantial
	Criterion 6 was updated to remove urinalysis and include electrocardiogram.	To reduce participant burden and to include relevant assessments following on from the removal of Criterion 7.	Non-substantial.
	Criterion 7 was removed.	Relevant assessments are included in updated Criteria 2 and 6.	Non-substantial

Section # and name	Description of change	Brief rationale	Substantial/ Non-substantial
	Criterion 11 was updated to specify that participants that are on stable therapy for at least 3 months before randomization that intend to stay on treatment throughout the study with marketed biologics that are not likely to interfere with the assessment of safety and/or efficacy of benralizumab may participate in the study.	Updated to align with the updated project specific safety requirements for the benralizumab development program.	Non-substantial
	Criterion 18 was updated to clarify that only participants already enrolled in another interventional clinical trial including IP and devices will be excluded.	To clarify the types of research projects that could confound the interpretation of the study.	Non-substantial
	Exclusion Criterion 20 updated to specify that a urine pregnancy test must be performed at Visit 1 only.	For clarification and to reduce participant/site burden.	Non-substantial
	New Criterion 21 added to specify that participants with cognitive function conditions (eg, dementia) who cannot complete PROs will be excluded.	To further clarify that participants must be able to understand and complete PRO assessments independently.	Non-substantial
6.1 Study Intervention Administered	Requirement for urine pregnancy test prior to each administration of IP was removed.	For clarification and to reduce participant/site burden.	Non-substantial
6.1.2 Investigational Product Administration Re-scheduling	Removal of febrile participants as a condition for not administering and rescheduling of IP.	Updated based on the safety profile of benralizumab.	Non-substantial
	Text updated to remove pregnancy testing for recommendations when IP dosing needs to be postponed or rescheduled.	For clarification and to reduce participant/site burden.	Non-substantial
6.1.3 Medical Devices	New section added.	Section added to include the use of a medical device.	Non-substantial
6.5 Concomitant Therapy	Text on recording prednisolone/prednisone use using the handheld PRO device was updated.	To clarify the use of the handheld device for the recording of concomitant prednisolone/prednisone use.	Non-substantial

Section # and name	Description of change	Brief rationale	Substantial/ Non-substantial
6.5.2 Restrictions	Updated to specify that only oral antimicrobial agents with anti-inflammatory properties are disallowed and removal of angiotensin-converting enzyme inhibitors, penicillamine, furosemide, and phenacetin from disallowed medication.	The listed concomitant medications that were restricted are not associated with drug-induced BP and based on literature support does not require restriction during the trial.	Non-substantial
	Text updated to allow COVID related prevention and treatment.	Treatments may be necessary during the trial and will not impact participant's efficacy or safety evaluations.	Non-substantial
CCI		Protocol updated to reduce participant and site burden.	Non-substantial
(8.1.2) Other Findings Supportive of Steroid-sparing Benefit	Section has been removed.	Section removed as participants will be receiving steroids during the trial.	Non-substantial
8.1.2 Patient-reported Outcomes	Text updated to clarify that otherwise eligible participants may be enrolled if the AstraZeneca study physician agrees to exempt the participant from handheld device usage due to certain medical conditions (eg, BP skin lesions on the fingers/hands or, neurological impairment affecting fingers/hands).	Text updated to ensure that otherwise eligible participants should be enrolled.	Non-substantial
8.2.4 Clinical Safety Laboratory Assessments	Urinalysis removed.	These assessments are not required for safety monitoring.	Non-substantial
	Mean corpuscular volume and red blood cell count removed.	These assessments are not required for safety monitoring.	Non-substantial
8.2.4.1 Pregnancy Tests	Urine HCG dipstick pregnancy testing modified to reflect updated pregnancy testing schedule.	For clarification and to reduce participant/site burden.	Non-substantial

Section # and name	Description of change	Brief rationale	Substantial/ Non-substantial
8.3.11 Medical Device Deficiencies and Appendix I Medical Device AEs, ADEs, SAEs, SADEs, USADEs and Medical Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies	New sections added.	To ensure compliance with new regulatory requirements.	Non-substantial
8.5.2.1 Anti-drug Antibodies	Text regarding neutralizing antibodies has been included at the end of paragraph.	Text included to indicate that neutralizing antibodies may be assessed on ADA positive samples.	Non-substantial
8.6.1.2 Tissue Histology and Immunostaining	Text updated to remove skin biopsy collection at time of disease control.	Text updated to reduce participant burden.	Non-substantial
9.4.3.3 Clinical Safety Laboratory Assessments	Urinalysis of shifts from normal to abnormal between baseline and each post-baseline time point removed.	These assessments are not needed since there are no urinary safety parameters with the IP.	Non-substantial
9.4.6.1 Patient Reported Outcomes	Text regarding analyses of the Peak Pruritus NRS inserted after second paragraph.	Text included to indicate that analyses of the Peak Pruritus NRS endpoint will be completed in the subset of patients able to use the handheld device.	
9.4.6.5 Longer Term Potential Steroid-sparing Benefits of Benralizumab	Section deleted.	'To evaluate the longer-term steroid-sparing benefit of benralizumab' was removed from Table 4 and therefore related sections have also been removed.	
CCI [redacted]	This section was deleted from the protocol.	Exploratory analysis will be in the SAP for assessments performed previous to this amendment.	Non-substantial

Section # and name	Description of change	Brief rationale	Substantial/ Non-substantial
Appendix K Protocol Amendment History	Updated with details for Protocol Amendment 2.	To align with protocol template and procedures.	Non-substantial

AE, adverse event; ADE, adverse device effect; BP, Bullous pemphigoid; IP, investigational product; IPD, investigational product discontinuation; NRS, Numeric Rating Scale; SADE, serious adverse device effect; SAE, serious adverse event; SAP, statistical analysis plan; USADE, unanticipated serious adverse device effect.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A Multinational, Randomized, Double-blind, Parallel-group, Placebo-controlled Study to Investigate the Use of Benralizumab as a Treatment Option for Patients with Bullous Pemphigoid (FJORD).

Short Title:

A study to investigate the use of benralizumab in patients with bullous pemphigoid (FJORD)

Rationale:

Benralizumab is a humanized, afucosylated cytolytic monoclonal antibody that binds to the human interleukin-5 receptor alpha subunit (IL-5Rα) on eosinophils and basophils. The absence of fucose in the Fc domain of benralizumab results in high affinity for FcγRIIIa receptors on immune effector cells such as natural killer cells, leading to apoptosis of eosinophils and basophils through enhanced antibody-dependent cell-mediated cytotoxicity. The pharmacodynamic response to benralizumab dosing is eosinophil depletion. Bullous pemphigoid (BP) is an autoimmune blistering disorder. The disease primarily occurs in the elderly, may last for several years, and tends to recur despite currently available treatment. Eosinophils are central to the pathology of BP. It is proposed that by depleting eosinophils in the blood and skin of patients with BP, benralizumab treatment could help achieve disease remission and maintain disease control, prevent relapses, allow tapering of oral corticosteroid (OCS) usage, and reduce corticosteroid load. The aim of this study is to investigate the use of benralizumab as treatment for patients with symptomatic BP.

Objectives and Endpoints:

The primary and secondary objectives and associated endpoints are detailed in Table 1. The primary and secondary efficacy objectives are based on the double-blind, placebo-controlled phase of the study. For tertiary/exploratory objectives and endpoints, see Section 3 of the protocol.

Table 1 Primary and Secondary Objectives

Objective	Estimand descriptions/endpoints
Primary	
To compare the clinical efficacy of benralizumab with placebo in participants with symptomatic BP	• Population: Full analysis set • Endpoint: A binary response, whereby a responder is defined as a participant who is in complete remission while off OCS for ≥ 2 months at Week 36. Otherwise, a participant is a non-responder • Intercurrent events: Participants who receive restricted medications or withdraw from the study will be considered as non-responders from the time such events occur up to Week 36. • Summary measure: Difference in proportion of participants who are responders between benralizumab and placebo at Week 36.
Secondary	
To compare the effect of benralizumab with placebo on supportive measures of clinical efficacy in participants with symptomatic BP up to Week 36	• Key secondary [a]: Proportion of participants who remain relapse-free up to Week 36. • Key secondary [a]: Cumulative OCS exposure (mg/kg) from baseline to Week 36. • Key secondary [a]: Change from baseline in BPDAI activity score at Week 36. • Key secondary [a]: Change from baseline in BPDAI-Pruritus score at Week 36. • Proportion of participants in sustained complete/partial remission on minimal OCS/off OCS for at least 2 months at Week 36. • Cumulative time (weeks) in complete remission off OCS from baseline to Week 36. • Proportion of participants off OCS by Week 36. • IGA score at Week 36 • Change from baseline in IGA score at Week 36
To compare the effect of benralizumab with placebo on clinical efficacy in participants with symptomatic BP up to Week 16	• Key secondary [a] Cumulative OCS exposure (mg/kg) from baseline to Week 16. • Proportion of participants who remain relapse-free up to Week 16. • Proportion of participants with any clinical benefit (eg, partial and complete remission during taper, with no steroid use, or with minimal steroid use [ie, < 0.1 mg/kg/day]) at Week 16. • Time to disease control, OCS dose (mg/kg) at disease control and time to the end of the consolidation phase. • Change from baseline in BPDAI activity score at Week 16. • Change from baseline in BPDAI-Pruritus score at Week 16.

Table 1 Primary and Secondary Objectives

Objective	Estimand descriptions/endpoints
To estimate the PK and immunogenicity of benralizumab in participants with BP	• Serum benralizumab concentration • ADA
Safety	
To compare the safety and tolerability of benralizumab with placebo in participants with symptomatic BP	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

Estimands for the key secondary endpoints are detailed in Section 9. All other estimands will be detailed fully in the Statistical Analysis Plan.

ADA, anti-drug antibodies; AE, adverse event; BP, bullous pemphigoid; BPDAI, Bullous Pemphigoid Disease Area Index; IGA, Investigator Global Assessment; IP, investigational product; OCS, oral corticosteroids; PK, pharmacokinetics.

Overall Design:

This is a multinational, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 study to assess the efficacy and safety of a benralizumab 60 mg loading dose followed by repeat dosing of subcutaneously (SC) administered benralizumab 30 mg versus placebo in adult participants with symptomatic BP.

Disclosure Statement:

This is a Phase 3 parallel-group, placebo-controlled study with 2 double-blind treatment groups.

Number of Participants:

Approximately 190 participants will be enrolled/screened in order to achieve approximately 120 eligible study participants randomly assigned to study intervention.

Note: "Enrolled" is defined as a participant's agreement to participate in a clinical study following completion of the informed consent 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:

The study consists of a screening period, a randomized double-blind treatment period, and an open-label extension (OLE).

Following screening, eligible participants will be randomized 1:1 to receive either benralizumab or placebo every 4 weeks (Q4W) by SC injection during the initial 36-week, double-blind phase of the study. After randomization, participants will receive a loading dose of 60 mg benralizumab or placebo, administered as 2 SC injections. After 4 weeks, participants will receive 30 mg benralizumab or placebo Q4W until the end of the double-blind treatment period at 36 weeks. Participants will also receive OCS at 0.5 mg/kg/day (or higher if required) in addition to investigational product (IP) until BP disease control is achieved. The OCS dose can be increased, if necessary, to achieve disease control. The consolidation phase begins when disease control is achieved and continues until the time at which no new lesions or pruritic symptoms have developed for a minimum of 2 weeks and the majority of established lesions have healed (end of consolidation phase). At this point, participants will begin protocolled OCS tapering, with the aim to taper off OCS completely within 3 to 4 months (ie, 4 to 5 months from randomization).

After completion of the double-blind treatment period, all participants will have the option of entering an OLE period for at least 1 year, during which they will receive benralizumab 30 mg Q4W until study closure. During the OLE participants can receive OCS to address the BP relapse at the Investigator’s discretion, with the goal of tapering off the steroids to benralizumab monotherapy as soon as clinically indicated.

Data Monitoring Committee:

An Independent Data Monitoring Committee (IDMC) will be utilized for this study. Section A 5 provides more details on the rationale for the committee and its remit.

Since the benefit/risk profile for benralizumab is favorable in other diseases, AstraZeneca has not pre-specified study safety stopping criteria and leaves this to the IDMC as they monitor the study data and fulfill their role to make necessary recommendations on this matter, as outlined in the IDMC charter.

Statistical methods:

Sample size calculation

For the initial 36-week, double-blind, placebo-controlled phase of the study, the aim is to recruit 60 participants in the placebo group and 60 participants in the benralizumab group.

The sample size calculation was derived for the primary endpoint, the proportion of participants who are in complete remission while off OCS for ≥ 2 months at Week 36. Approximately 60 participants are needed per treatment group to detect a 30% difference between benralizumab and placebo with 90% power. The calculation is based on a 2-sided test and a 5% significance level and assumes a response rate of 50% for benralizumab and 20% for placebo.

A non-binding interim futility analysis will be performed by an IDMC when approximately 36 randomized participants (ie, when approximately 30% of the total amount of statistical information is available) have had the opportunity to complete at least 36 weeks of follow-up. By conducting the futility analysis the overall power will not be affected substantially.

Assessment of the first 36 weeks of treatment intervention

The primary efficacy analysis will be based on the initial 36-week, double-blind, placebo-controlled phase of the study and will compare benralizumab versus placebo. The primary endpoint is a binary response, whereby responders will be defined as participants who are in complete remission while off OCS for ≥ 2 months at Week 36. Otherwise, participants will be classified as non-responders. The primary estimand will be based on the full analysis set. Intercurrent events will consist of participants who receive restricted medications or withdraw from the study. The primary estimand will regard these participants as non-responders from the time such events occur up to Week 36. A participant with missing data at a specific time point will also be considered as a non-responder at that time point. Note that regardless of prior OCS use, participants who achieve complete remission while off OCS for ≥ 2 months at Week 36 will be classed as responders. For example, if participants who require an increase in OCS dose, or need to restart their OCS having had their disease controlled previously, satisfy the criteria for the primary endpoint at Week 36, they will be considered as responders.

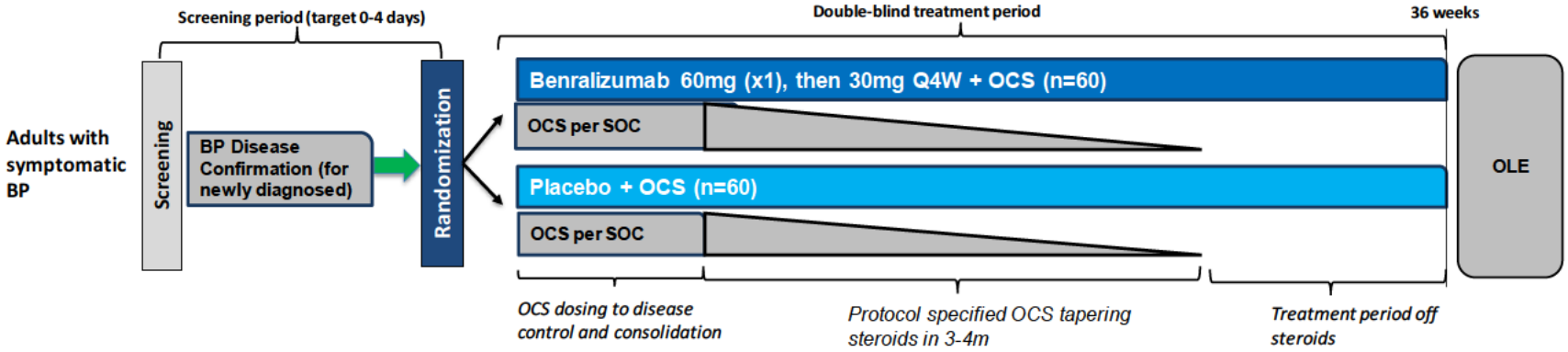
For the primary analysis, a logistic regression model will be fitted to the primary endpoint using a logit link function. The model will include treatment, baseline disease severity (moderate; severe) and time of BP diagnosis (ie, participants with newly diagnosed BP versus participants with a previous diagnosis of BP who have relapsed) as categorical covariates. (The effect of adding further covariates into the model, such as age and region, may also be assessed as a sensitivity analysis.) The model will be used to estimate the proportion of responders for benralizumab and placebo, the difference between these proportions (benralizumab – placebo), a rate ratio 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.

There are 5 key secondary endpoints, which are supportive measures of clinical efficacy. They include: proportion of participants who remain relapse-free up to Week 36; cumulative OCS exposure (mg/kg) from baseline to Week 36; change from baseline in bullous pemphigoid disease area index (BPDAI) activity score at Week 36; change from baseline in BPDAI-Pruritus score at Week 36, and cumulative OCS exposure (mg/kg) from baseline to Week 16.

1.2 Schema

Figure 1 Study Design



BP, bullous pemphigoid; m, months; n, number of participants randomized; OCS, oral corticosteroids; OLE, open-label extension; Q4W, every 4 weeks; SOC, standard of care.

1.3 Schedule of Activities

The Schedule of Activities (SoA) at each visit for this study is provided in Table 2. Details of the schedule of at-home and site visit patient-reported outcome (PRO) assessments are provided in Table 3.

Table 2 Schedule of Activities

Study period	Screen-ing	Double-blind treatment period												OLE			IPD/ EOT[c]	FU (12 wks after last dose of IP)	UNS[d]	Details in CSP section
Visit	**V1**	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	**V 8**	**V 9**	**V10**	**V11**	**V 12**	**V13/ EOT[a]**	**Every 4 wks (V14 to V22)[b]**	**V 19**	**Every 12 weeks (From V23)**				
Week (Wk)		**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40-72**	**60**	**From Week 76**				
Visit window (days)	**(Target 0-4 days)**	**± 3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**		
General Procedures																				
Informed consent	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
Record concomitant medications, including OCS dose and compliance check[e]	X	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

Table 2 Schedule of Activities

Study period	Screen-ing	Double-blind treatment period												OLE			IPD/ EOT[c]	FU (12 wks after last dose of IP)	UNS[d]	Details in CSP section
Visit	V1	V 2	V 3	V 4	V 5	V 6	V 7	V 8	V 9	V10	V11	V 12	V13/ EOT[a]	Every 4 wks (V14 to V22)[b]	V 19	Every 12 weeks (From V23)				
Week (Wk)		0	2	4	6	8	12	16	20	24	28	32	36	40-72	60	From Week 76				
Visit window (days)	(Target 0-4 days)	± 3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7		
Disease Measurements																				
Disease state, BPDAI, IGA, and CCI	X	X	X	X	X	X	X	X	X	X	X	X	X	CCI						Sections 8.1.1.1, 8.1.1.2, 8.1.1.3, and 8.1.1.4
CCI								X					X	X[f]						Section 8.1.1.5
		X											X							Section 8.1.1.6
Healthcare resource utilization		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.1.1.7
PRO Procedures																				
Distribution of handheld device and instruction on use[h]		X																		Section 8.1.2

Table 2 Schedule of Activities

Study period	Screen-ing	Double-blind treatment period												OLE			IPD/ EOT[c]	FU (12 wks after last dose of IP)	UNS[d]	Details in CSP section
Visit	**V1**	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	**V 8**	**V 9**	**V10**	**V11**	**V 12**	**V13/ EOT[a]**	**Every 4 wks (V14 to V22)[b]**	**V 19**	**Every 12 weeks (From V23)**				
Week (Wk)		**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40-72**	**60**	**From Week 76**				
Visit window (days)	**(Target 0-4 days)**	**± 3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**		
Review OCS usage and compliance with at-home PRO assessments[h] (Table 3)			X	X	X	X	X	X	X	X	X	X	X	X	X				X	Section 8.1.2
Compliance with at home PRO assessments[h].			X	X	X	X	X	X	X	X	X	X	X	X	X				X	Section 8.1.2
BPDAI-Pruritus, AB-QoL, and EQ-5D-5L	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.1.2
Select countries only: informed consent for qualitative patient interview sub-study	X[i]																			Section 8.1.2.6

Table 2 Schedule of Activities

Study period	Screen-ing	Double-blind treatment period												OLE			IPD/ EOT[c]	FU (12 wks after last dose of IP)	UNS[d]	Details in CSP section
Visit	**V1**	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	**V 8**	**V 9**	**V10**	**V11**	**V 12**	**V13/ EOT[a]**	**Every 4 wks (V14 to V22)[b]**	**V 19**	**Every 12 weeks (From V23)**				
Week (Wk)		**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40-72**	**60**	**From Week 76**				
Visit window (days)	**(Target 0-4 days)**	**± 3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**		
Select countries only: qualitative patient interview sub-study [j]	X										X				From Weeks 60 to 76					Section 8.1.2.6
Safety Assessments																				
AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3
Complete physical exam [k]	X												X				X	X		Section 8.2.1
Brief physical exam including weight [l]		X	X	X	X	X	X	X	X	X	X	X			X				X	Section 8.2.1
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X	X	Section 8.2.2
ECG	X																			Section 8.2.3
Local Laboratory Assessments																				
Hematology and Clinical chemistry	X [m]																			Section 8.2.4

Table 2 Schedule of Activities

Study period	Screen-ing	Double-blind treatment period												OLE			IPD/ EOT[c]	FU (12 wks after last dose of IP)	UNS[d]	Details in CSP section
Visit	**V1**	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	**V 8**	**V 9**	**V10**	**V11**	**V 12**	**V13/ EOT[a]**	**Every 4 wks (V14 to V22)[b]**	**V 19**	**Every 12 weeks (From V23)**				
Week (Wk)		**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40-72**	**60**	**From Week 76**				
Visit window (days)	**(Target 0-4 days)**	**± 3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**		
HIV express test	X																			Section 8.2.4.2
Hepatitis B and C serology [m]	X																			Section 8.2.4.2
Urine pregnancy test in FOCBP [n]	X						X			X			X[b]							Section 8.2.4.1
Confirmatory BP diagnostic testing	X[o]																			Section 5.1
Central Laboratory Assessments																				
Hematology and Clinical chemistry	X [m]						X						X		X		X	X	X[p]	Section 8.2.4
Hepatitis/HIV screening	X																			Section 8.2.4.2
HbA1c		X					X			X			X		X		X [q]	X [q]		Section 8.2.4

Table 2 Schedule of Activities

Study period	Screen-ing	Double-blind treatment period												OLE			IPD/ EOT[c]	FU (12 wks after last dose of IP)	UNS[d]	Details in CSP section
Visit	V1	V 2	V 3	V 4	V 5	V 6	V 7	V 8	V 9	V10	V11	V 12	V13/ EOT[a]	Every 4 wks (V14 to V22)[b]	V 19	Every 12 weeks (From V23)				
Week (Wk)		0	2	4	6	8	12	16	20	24	28	32	36	40-72	60	From Week 76				
Visit window (days)	(Target 0-4 days)	± 3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7		
FSH	X																			Section 8.2.4.1
PK sample		X	X	X	X[r]			X		X			X		X		X		X[s]	Section 8.5.1
ADA/nAb		X		X[r]				X		X			X		X		X		X[s]	Section 8.5.2
CCI		X																		Section 8.7.1
Exploratory Biomarkers																				
Whole blood (including CCI and eosinophil count), serum and plasma for biomarkers		X	X[t]					X					X				X		X[s]	Section 8.6.1.1

Table 2 Schedule of Activities

Study period	Screen-ing	Double-blind treatment period												OLE			IPD/ EOT[c]	FU (12 wks after last dose of IP)	UNS[d]	Details in CSP section
Visit	V1	V 2	V 3	V 4	V 5	V 6	V 7	V 8	V 9	V10	V11	V 12	V13/ EOT[a]	Every 4 wks (V14 to V22)[b]	V 19	Every 12 weeks (From V23)				
Week (Wk)		0	2	4	6	8	12	16	20	24	28	32	36	40-72	60	From Week 76				
Visit window (days)	(Target 0-4 days)	± 3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±7		
Skin biopsy for histology/ immunohisto-chemistry and CCI [e]	X[v]												X							Section 8.6.1.2
Medication Procedures																				
Benralizumab or Placebo administration		X		X		X	X	X	X	X	X	X	X[w]	X[b]	X	X[b]				Section 6

[a] For participants continuing in the OLE period, Visit 13 is the first treatment of the OLE period. If a participant chooses not to continue to the OLE period, the patient will be considered to have completed the study, the site will perform an EOT visit at Week 36, and the patient will return for a follow-up visit 12 weeks (+/- 7 days) after the last dose of IP, after which the participant exits the study.

[b] Benralizumab administration and vital signs tests will continue every 4 weeks, and urine pregnancy tests will continue every 12 weeks from Week 36 (Visit 13), during the open-label extension period until participant withdrawal or study closure.

[c] The IPD/EOT visit replaces the nearest regular visit: IPD/EOT visit procedures should be performed as soon as possible after the decision to discontinue IP has been made, and at the latest 4 weeks ± 7 days after the last dose of IP. For participants who discontinue IP and continue with study assessments during the double-blind treatment period, the end of treatment will be at Visit 13 (Week 36).

[d] The required assessments for this visit should continue to Week 72. Thereafter, they will continue at investigator's discretion.

[e] Investigator/delegate to record the OCS dose in the eCRF at each study visit and check compliance against participant-reported use between study visits for participants using a handheld device.

CCI [redacted]

[h] The AstraZeneca study physician will have the discretion to exempt participants with certain medical conditions (eg, BP lesions of the fingers/hand/neurologic condition affecting fingers/hand, visual impairment) from use of the handheld device for off-site PRO assessments. All onsite PRO assessments will however, be performed by all participants using the tablet.

[i] A separate consent for the qualitative interview sub-study is required. Interviews will only be performed with consenting patients from selected countries.

[j] Interview sub-study activities can only begin after the qualitative interview sub-study consent is given.

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

[l] Brief physical examination includes assessment of the following: weight, general appearance, skin, 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.

[m] Testing to be conducted at local laboratory, confirmation testing to be conducted by a central laboratory.

[n] A positive urine pregnancy test result must be confirmed with a serum pregnancy test.

[o] Confirmatory local testing is required for those who do not have a confirmed BP diagnosis.

[p] An unscheduled hematology and clinical chemistry should be performed if the visit is for relapse.

[q] If not conducted in the previous 3 months.

[r] Samples will be taken only at one time point, ie, at the visit when disease control has been achieved.

[s] Samples will be taken at an unscheduled visit if the visit is for relapse.

[t] Blood biomarkers will be collected only at one of the time points between Visits 4 and 6; ie, only at the visit that disease control has been achieved and before steroid taper is commenced.

[u] Skin biopsies will be taken from peri-lesional skin for histopathology and CCI [redacted] research.

[v] For participants without a confirmed diagnosis, no biopsy for CCI [redacted] is collected. In these participants, the biopsy will be for inclusion criteria confirmation at the local lab and immunohistochemistry for exploratory research.

[w] Benralizumab administration only; for participants who continue the study in the open-label extension.

AB-QoL, Autoimmune Bullous Disease Quality of Life; ADA, anti-drug antibodies; AE, adverse event; BP, Bullous pemphigoid; BPDAI, Bullous Pemphigoid Disease Area Index; CCI [redacted]; CSP, clinical study protocol; ECG, electrocardiogram; EOT, end of treatment; EQ-5D-5L, European Quality of Life-5 Dimensions; FOCBP, females of childbearing potential; FSH, follicle-stimulating hormone; FU, follow-up; HIV, human immunodeficiency virus; IGA, Investigator Global Assessment; IP, investigational product; IPD, investigational product discontinuation; nAb, neutralizing antibodies; OCS, oral corticosteroids; OLE, open-label extension; CCI [redacted]; PK, pharmacokinetics; PRO, patient-reported outcomes; SAE, serious adverse event; UNS, unscheduled; V, visit; Wks, weeks.

Table 3 Schedule of PRO Assessments

Instruments	Schedule
Peak Pruritus Numeric Rating Scale and OCS Usage	First assessment at site at V2, then at home every evening (17:00-23:59) starting the day after V2 at home thereafter until V22 (Week 72).[a]
BPDAI-Pruritus, AB-QoL, EQ-5D-5L	At site at every visit up to V22 (Week 72), and then every 12 weeks thereafter. At site at unscheduled, IPD, and follow-up visits.

[a] Participants will complete BPDAI-pruritus, AB-QoL, and EQ-5D-5L onsite using the tablet. Some participants may be exempted from completing the at home PRO assessments on the handheld device (ie, Peak Pruritus Numeric Rating Scale and OCS Usage) upon agreement with the AstraZeneca physician.

AB-QoL, Autoimmune Bullous Disease Quality of Life; BPDAI, bullous pemphigoid disease area index; EQ-5D-5L, European Quality of Life-5 Dimensions; IPD, investigational product discontinuation; OCS, oral corticosteroids; PRO, patient-reported outcomes; V, visit.

2 INTRODUCTION

2.1 Study Rationale

Benralizumab is a humanized, afucosylated cytolytic monoclonal antibody that binds to the human interleukin-5 receptor α subunit (IL-5Rα) on eosinophils and basophils. The absence of fucose in the Fc domain of benralizumab results in high affinity for FcγRIIIa receptors on immune effector cells such as natural killer cells, leading to apoptosis of eosinophils and basophils through enhanced antibody-dependent cell-mediated cytotoxicity (Kolbeck et al 2010, Laviolette et al 2013). The pharmacodynamic response to benralizumab dosing is eosinophil depletion. Benralizumab has been or is being investigated in eosinophil-driven diseases including asthma, chronic obstructive pulmonary disease (COPD), hypereosinophilic syndrome (HES), nasal polyposis, eosinophilic chronic rhinosinusitis, eosinophilic granulomatosis with polyangiitis, and eosinophilic esophagitis. The direct eosinophil-depleting ability of benralizumab is effective in eosinophilic asthma (Bleecker et al 2016, FitzGerald et al 2016) and steroid-dependent asthma (Nair et al 2017), and it may show benefit in HES (Kuang et al 2019). In patients with eosinophilic asthma, benralizumab treatment leads to near-complete depletion of blood eosinophils and a reduction of annual asthma exacerbation rates (Bleecker et al 2016, FitzGerald et al 2016).

Bullous pemphigoid (BP) is a rare disease mainly affecting the elderly. The etiology of BP is frequently unknown (Amber et al 2018a, Venning and Wojnarowska 1995). The incidence of BP worldwide is 6 to 7 new cases per million persons per year in the general population. In those aged over 80 years old, the incidence rises to 150 to 330 per million persons per year (Schmidt and Zillikens 2013). Bullous pemphigoid is associated with significant morbidity and increased mortality secondary to increased risk of secondary infections, comorbid conditions, and serious side effects from high-dose steroids and immunosuppressants. Comorbid conditions with an increased frequency in patients with BP include multiple sclerosis, Parkinson’s disease, Alzheimer's disease, stroke, and diabetes (Kibsgaard et al 2017). Common causes of mortality in patients with BP include sepsis, cardiovascular disease, and cerebrovascular accident (Joly et al 2002).

Eosinophils play a central role in the pathophysiology of BP and present a potentially promising therapeutic target (de Graauw et al 2017). This is supported by a pilot study of bertilimumab, an antibody against the eosinophil chemoattractant eotaxin-1, that suggested the drug may be efficacious for treating patients with BP; 9 treated patients in the study showed rapid and durable improvement in disease activity with a mean 81% reduction in disease activity and lower doses of prednisone used than in a standard BP regimen (Lee et al 2018).

Initial evidence of benralizumab’s eosinophil-depleting effect in skin was observed in 2 clinical studies. In a Phase 2 study performed in 4 patients with HES with dermatological involvement, blood and tissue eosinophils were absent in 2 of the patients who received

benralizumab and had skin biopsies performed (Kuang et al 2019). Eosinophil reduction was associated with clinical improvement and the ability to taper background therapy. The second study, a small single-blinded, placebo run-in study in 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 studies provide further evidence of benralizumab's significant eosinophil-depleting capabilities in the skin and suggest that benralizumab will also be effective for the treatment of BP. A short-term study with mepolizumab, a drug that indirectly depletes eosinophils, has also been investigated for the treatment of BP (Simon et al 2020). Efficacy of mepolizumab with 4 doses over 16 weeks was not demonstrated; the authors concluded that mepolizumab did not significantly affect tissue eosinophil infiltration and noted that insufficient control of tissue eosinophils by mepolizumab has also been observed in other studies (Simon et al 2020). Learnings from the mepolizumab study and evidence of benralizumab mechanism of action in skin helped inform the design of this Phase 3 study in adult patients with BP.

Results from these studies suggest benralizumab could treat other conditions characterized by eosinophilia, such as BP. By depleting eosinophils in the blood and affected skin of patients with BP, benralizumab treatment could help achieve remission off oral corticosteroid (OCS) therapy, achieve disease control, prevent relapses, allow tapering of OCS usage, and reduce corticosteroid load.

The aim of this randomized, double-blind, placebo-controlled, parallel-group, multinational Phase 3 study is to investigate the use of benralizumab as a treatment for patients symptomatic with BP.

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

2.2 Background

2.2.1 BP Disease and Current Approaches to Disease Management

Bullous pemphigoid is an autoimmune blistering disorder characterized by immunoglobulin E (IgE) and/or immunoglobulin G (IgG) autoantibodies against BP180 and/or BP230, 2 structural proteins of the hemidesmosomes (a junctional adhesion complex in the skin). The autoimmune response against BP180 and BP230 results in damage to the dermal-epidermal junction, which manifests clinically as tense blisters, erythema, and erosions on the skin (Amber et al 2018a, Schmidt and Zillikens 2013). Before blisters develop, there is frequently a prodromal phase lasting for weeks or months during which patients experience itching and sometimes skin lesions (Bernard and Antonicelli 2017, Schmidt and Zillikens 2013).

Eosinophils are central to the pathology of BP. They are involved in the blister formation mediated by anti-BP180 IgE antibodies (Amber et al 2018b), and blood eosinophil count has been associated with disease severity (Kridin 2018). Patients with BP have high levels of blood and tissue eosinophils and markers of eosinophilic activation, particularly in and around blisters (Amber et al 2018b, Kridin and Ludwig 2018, Morshed et al 2012). Degranulated eosinophils, extracellular eosinophil granules, and free granule proteins are present within the bullous lesions in BP, and the eosinophil chemoattractant eotaxin-1 has been found in lesions and blister fluid. Findings on skin biopsies of developing lesions have shown that eosinophil degranulation precedes blister formation, and eosinophil granule proteins can cause significant keratinocyte detachment from matrix in vitro (Amber et al 2018c). These findings indicate that eosinophil infiltration and degranulation contribute to lesion formation and are not merely a consequence of tissue damage (Kridin 2018).

The disease primarily occurs in the elderly, may last for several years, and tends to recur even with currently available treatment (Amber et al 2018a, Williams et al 2017).The main treatment goals in BP are to treat the skin eruptions and itching, reduce the risk of recurrence, and improve patients' quality of life. Additionally, limiting the side effects associated with corticosteroid treatment is of particular importance in the patient population with BP as these patients are predominantly elderly and have significant comorbid conditions.

The first-line treatment for BP is high-potency topical corticosteroids, but few patients achieve disease control on topical corticosteroids alone. Oral corticosteroids are used when disease control cannot be achieved with topical corticosteroids, when the affected areas are extensive, or when preferred by the patient (Feliciani et al 2015, Venning et al 2012). Oral corticosteroids are highly effective for controlling BP; in one study, disease control was achieved in 91% of patients at 3 weeks after initiating therapy (Joly et al 2002). However, the BP relapse rate after remission is high (27% to 53% [Wang et al 2018]), and steroid toxicity is one of the most common causes of iatrogenic illness associated with chronic diseases. The risks for adverse effects are both dose- and duration-dependent and can affect many organ systems. Adverse effects can include osteoporosis-related fractures, serious infections, diabetes, gastrointestinal bleeding, and cataracts (Schäcke et al 2002).

Adjunct therapies are used to reduce corticosteroid dependency, in patients with severe or refractory disease, and in patients who do not tolerate corticosteroids. These therapies include immunosuppressants (eg, mycophenolate mofetil, azathioprine, and methotrexate), anti-inflammatory agents (eg, tetracyclines with nicotinamide/dapsone), and biologic immunotherapies (eg, intravenous [IV] immunoglobulin and rituximab), although there is limited evidence of efficacy and limited guidance on the optimal use of these therapies (Feliciani et al 2015, Venning et al 2012).

Both BP and its only well-established treatment—corticosteroids—are associated with significant morbidity and mortality. An unmet need therefore remains for new treatments in particular, treatments that could enable a reduction of corticosteroid use, achieve remission, and prevent relapses.

2.3 Benefit/Risk Assessment

The efficacy and safety of benralizumab have been established in patients with asthma. Previous studies have shown that the overall safety profile of benralizumab in severe asthma patients is similar to placebo for exposures up to approximately one year (Bleecker et al 2016 and FitzGerald et al 2016). The most commonly reported adverse events (AEs) 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. Longer-term safety studies have been conducted in asthma patients who completed one of the predecessor studies for up to an additional one year (adults) and 2 years (adolescents). In general, the safety results were commensurate with the predecessor studies (Busse et al 2013). Safety and tolerability data from the Phase 2a study of benralizumab in patients with chronic spontaneous urticaria (CSU) showed that benralizumab was well-tolerated, with no AEs attributable to treatment with benralizumab (Bernstein and Singh 2019). Similarly, safety and tolerability data from the Phase 2a study of benralizumab in patients with HES; (Kuang et al 2019) showed that benralizumab had comparable rates of AEs observed between active and placebo groups. No new safety signals for benralizumab were identified in these studies and the safety profile of benralizumab was similar to that in the asthma pivotal studies.

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

Serious infections have been reported in patients using benralizumab. However, 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 following benralizumab administration 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.

Based on benralizumab´s mechanism of action and evidence of benefit in other eosinophil-driven diseases (asthma and HES) and the Phase 2a study in CSU, there is a potential for benralizumab to provide benefits in patients with BP. Expected benefits of benralizumab over placebo include clinically significant reduction in disease relapse in patients with BP and with a potentially reduced corticosteroid load. In addition, there is extensive safety data already available, and therefore, the benefit/risk profile in patients with BP 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.

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 4 lists the objectives of this study and the endpoints for each objective. The primary and secondary efficacy objectives are based on the double-blind, placebo-controlled phase of the study.

Table 4 Objectives and Endpoints

Objective	Estimand descriptions/Endpoints
Primary	
To compare the clinical efficacy of benralizumab with placebo in participants with symptomatic BP	• Population: Full analysis set. • Endpoint: A binary response, whereby a responder is defined as a participant who is in complete remission while off OCS for ≥ 2 months at Week 36. Otherwise, a participant is a non-responder. • Intercurrent events: Participants who receive restricted medications or withdraw from the study will be considered as non-responders from the time such events occur up to Week 36. • Summary measure: Difference in proportion of participants who are responders between benralizumab and placebo at Week 36.

Table 4 Objectives and Endpoints

Objective	Estimand descriptions/Endpoints
Secondary	
To compare the effect of benralizumab with placebo on supportive measures of clinical efficacy in participants with symptomatic BP up to Week 36	• Key secondary [a]: Proportion of participants who remain relapse-free up to Week 36. • Key secondary [a]: Cumulative OCS exposure (mg/kg) from baseline to Week 36. • Key secondary [a]: Change from baseline in BPDAI activity score at Week 36. • Key secondary [a]: Change from baseline in BPDAI-Pruritus score at Week 36. • Proportion of participants in sustained complete/partial remission on minimal OCS/off OCS for at least 2 months at Week 36. • Cumulative time (weeks) in complete remission off OCS from baseline to Week 36. • Proportion of participants off OCS by Week 36. • IGA score at Week 36 • Change from baseline in IGA score at Week 36
To compare the effect of benralizumab with placebo on clinical efficacy in participants with symptomatic BP up to Week 16	• Key secondary [a] Cumulative OCS exposure (mg/kg) from baseline to Week 16. • Proportion of participants who remain relapse-free up to Week 16. • Proportion of participants with any clinical benefit (eg, partial and complete remission during taper, with no steroid use, or with minimal steroid use [ie, < 0.1 mg/kg/day]) at Week 16. • Time to disease control, OCS dose (mg/kg) at disease control and time to the end of the consolidation phase. • Change from baseline in BPDAI activity score at Week 16. • Change from baseline in BPDAI-Pruritus score at Week 16.
To estimate the PK and immunogenicity of benralizumab in participants with BP	• Serum benralizumab concentration • ADA
Safety	
To compare the safety and tolerability of benralizumab with placebo in participants with symptomatic BP	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

Table 4 Objectives and Endpoints

Objective	Estimand descriptions/Endpoints
	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
Tertiary/exploratory	
To explore the effect of benralizumab versus placebo on patient-reported, health-related, quality of life, measures in participants with symptomatic BP	• Changes in Peak Pruritus Numeric Rating Scale • Change from baseline at Week 36 for: ° AB-QoL ° EQ-5D-5L
CCI [redacted]	
To explore the effect of benralizumab versus placebo on healthcare resource utilization in participants with symptomatic BP	• Assessment of all-cause and BP-related healthcare resource utilization over 36 weeks including annualized rate of hospitalizations, length of hospital stay, office visits, emergency room visits, tests and procedures.
CCI [redacted]	
	• Changes in AB-QoL • Changes in EQ-5D-5L
CCI [redacted]	• Skin histology and immunohistochemistry • CCI [redacted] and serum and plasma biomarkers
[redacted]	• Skin histology and immunohistochemistry • CCI [redacted] and serum and plasma biomarkers
CCI [redacted]	
To characterize the patient's experience with the disease and study treatment through qualitative interviews (sub-study)	• Qualitative interviews to characterize the patient's experience with the disease and treatment received

[a] Estimands for the key secondary endpoints are detailed in Section 9. All other estimands will be detailed fully in the Statistical Analysis Plan.

CCI [redacted]

AB-QoL, Autoimmune Bullous Disease Quality of Life; ADA, anti-drug antibodies; AE, adverse event; BMI, body mass index; BP, bullous pemphigoid; BPDAI, Bullous Pemphigoid Disease Area Index; CCI; EQ-5D-5L, European Quality of Life-5 Dimensions; IGA, Investigator Global Assessment; IP, investigational product; OCS, oral corticosteroids; CCI; PK, pharmacokinetics; CCI

4 STUDY DESIGN

4.1 Overall Design

This is a multinational, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 study to assess the efficacy and safety of repeat dosing of benralizumab in adult participants with symptomatic BP. The study consists of a screening period (Section 4.1.1), a randomized double-blind treatment period (Section 4.1.2), and an open-label extension (OLE) (Section 4.1.3). The double-blind treatment period for each participant will last for 36 weeks.

The primary database lock (DBL) will occur when all randomized participants have had the opportunity to complete at least 36 weeks of follow-up. The final DBL will occur when all participants have completed the OLE period. Additional locks, between the primary and final DBLs, may be performed to report data accumulated during the OLE period to support decision making.

For an overview of the study design see Figure 1. For details of objectives and endpoints, see Section 3. For a detailed list of procedures at each period see Table 2.

4.1.1 Screening Period

After obtaining informed consent, all participants will enter a screening period. The screening period is targeted to last 0 to 4 days depending upon the study assessment requirements (eg, there may be delays beyond 4 days awaiting confirmatory biopsy and serology results). During the screening period, participants may continue their topical or oral corticosteroids; however, any topical corticosteroids will need to be discontinued at randomization.

The following will occur during this period:

- Assessment of participant eligibility based on inclusion/exclusion criteria
- Assessment of BP
- Recording of medical history and concomitant medications
- Clinical and laboratory evaluations, including biopsies

4.1.2 Double-blind Treatment Period

Approximately 120 eligible participants will be randomized 1:1 at baseline (Visit 2), to receive either benralizumab or placebo every 4 weeks (Q4W) by subcutaneous (SC) injection.

The randomization will be stratified by disease severity and time of BP diagnosis (participants with newly diagnosed BP; participants with a previous diagnosis of BP who have relapsed). Bullous pemphigoid disease area index (BPDAI) activity score will be used to assess disease severity, whereby participants with a score greater than or equal to 56 points will be classified as severe. The double-blind treatment period for each participant will last for 36 weeks.

Participants will receive a loading dose of either 60 mg benralizumab or placebo, administered as 2 SC injections at Visit 2. After 4 weeks, participants will receive 30 mg benralizumab or placebo Q4W per their initial randomization until the end of the double-blind treatment period. Starting at Visit 2, participants will also receive OCS 0.5 mg/kg/day until BP disease control is achieved. In participants who do not achieve disease control, the OCS dose can be increased (eg, 0.75 mg/kg; (Feliciani et al 2015) to achieve disease control. The steroid doses and time necessary to achieve disease control of BP may vary between participants.

After participants have achieved disease control and the end of the consolidation phase has been reached (see Table 6 for definitions of disease control and consolidation phase), participants will begin OCS tapering according to a protocolled taper regimen. This period is expected to allow sufficient effect of benralizumab on systemic eosinophil depletion to facilitate steroid tapering. For details on prednisolone/prednisone tapering see Section 6.5.1. The steroid taper will continue according to the protocolled schedule until relapse or until corticosteroid treatment is completely tapered off. The steroid taper schedule will direct participants to reduce their steroid dose by 20% per week until it reaches 10 mg per day. After that, the dose should be reduced by 2.5 mg every other week until completely tapered off or until BP relapse. The aim will be to taper participants off steroids completely within 3 to 4 months (ie, 4 to 5 months from randomization). An example of how the protocolled tapering schedule would be applied for participants of different body weights, and OCS doses achieving disease control is provided in Appendix F.

Participants who relapse during the double-blind period (which includes during the protocolled taper regimen) will be treated with OCS along with their continued randomized treatment to control BP symptoms as necessary. If the relapse occurs during the steroid tapering period, the OCS dose may be increased to the previous dosage that symptoms were controlled (Feliciani et al 2015). Further attempts to taper steroids will be based on the Investigator's judgment; however, it is recommended to follow the protocolled OCS taper schedule (Section 6.5.1). Participants who prematurely discontinue IP will be asked to complete all visits and study assessments up to Week 36.

4.1.3 Open-label Extension

After completion of the double-blind treatment period, all participants will have the option of entering an OLE period, during which they will receive benralizumab 30 mg Q4W for at least 1 year. Assessments will be conducted according to the SoA (Table 2). During the OLE

participants can receive corticosteroids (topical and/or oral) for BP relapse at the Investigator's discretion, with the goal of tapering off the steroids to benralizumab monotherapy as soon as clinically indicated. If in the opinion of the Investigator, a participant requires the addition of immunosuppressants, the participant will discontinue benralizumab and will withdraw from the OLE. Participants will be asked to complete the follow-up visit assessment 12 weeks after their last dose according to the SoA (Table 2). Participants may additionally be asked to allow future contact to provide follow-up clinical details regarding their health and information on disease state.

4.1.4 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 (GCP), 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 for the mitigation procedures (note, in the case of verbal consent, the Informed Consent Form (ICF) should be signed at the participant's next contact with the study site).
- Re-screening: Additional re-screening 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 H.

4.2 Scientific Rationale for Study Design

As detailed in Section 2, the central role of eosinophilia in the pathophysiology of BP suggests that a direct eosinophil-depleting approach, as provided by benralizumab, may prove beneficial in the treatment of BP. There are several lines of evidence that indicate eosinophils are central to the disease pathology of BP (Amber et al 2018b, Messingham et al 2019).

This is a Phase 3 study designed to evaluate the efficacy and safety of benralizumab in the treatment of participants with BP.

This study's inclusion/exclusion criteria are designed to capture a population appropriate for treatment with benralizumab. For inclusion in the study, participants should be candidates for systemic corticosteroid therapy based on the extent or seriousness of their disease. The study will include participants with classic, predominantly cutaneous BP. Participants with drug-induced BP, a small subset of BP participants; will be excluded as the initial treatment approach in these participants is discontinuation of the offending drug.

The study's randomized, double-blind, placebo-controlled, parallel-group treatment period is designed to demonstrate the efficacy and safety of benralizumab.

The primary endpoint chosen is to assess the effect of benralizumab on sustained disease remission. This endpoint was chosen based on outcome measures recommended by the consensus statement (Murrell et al 2012) and feedback from a panel of clinical experts on BP who were consulted on the feasibility of using benralizumab as a treatment for BP and on the optimal study design. While OCS are the only well-established treatment for BP and highly effective for achieving disease control, the relapse rate is high on tapering and discontinuation, and OCS are associated with significant morbidity and mortality. The overall treatment goal in participants with BP is to reduce the dose of OCS and associated side effects while maintaining disease control. The ability of participants to taper steroids and achieve complete remission off steroids (the proposed primary variable) and the proportion of participants who have relapsed after tapering steroid therapy (the first key secondary variable) are therefore clinically important outcomes in this participant population. Both are accepted endpoints for BP studies (Murrell et al 2012). The key secondary variables, proportion of participants who remain relapse-free up to Week 36, cumulative OCS exposure (mg/kg) up to Week 16 and up to Week 36, and change in BPDAI activity and pruritus scores at Week 36, will also provide an opportunity to assess benralizumab's efficacy in participants with symptomatic BP.

The OLE will provide an opportunity to assess long-term safety and tolerability, in addition to assessing efficacy of benralizumab monotherapy, and to ensure that all participants who complete the double-blind treatment period can have access to treatment with benralizumab.

4.3 Justification for Dose

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 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 depletions for both the Q8W and Q4W dosing regimens. Treatment with benralizumab 30 mg Q4W has also been shown to reduce blood and tissue eosinophilia in tissues 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).

Patients with BP have peripheral blood and tissue eosinophilia and elevated eosinophils in tissue (Kridin 2018). Data is available for benralizumab pharmacokinetics (PK) in blood, lung tissue and bone marrow (Laviolette et al 2013), but not in skin. As the skin compartment is thicker than lung tissue and not as vascular skin tissue may follow different PK and may benefit from a higher initial dose. This strategy aligns with other biologics in skin diseases where a higher initial dose is indicated to ensure skin partitioning in an efficient manner. Efficient delivery of drug to diseased tissue is paramount in this disease given the acute and marked symptomatology.

The PK of benralizumab are well-characterized (Wang et al 2017), and benralizumab is expected to demonstrate consistent PK across different disease populations. According to Population PK modeling in asthma patients, a loading dose of 60 mg benralizumab followed by 30 mg benralizumab Q4W SC will result in greater exposure and rapid partitioning into the skin to ensure eosinophil depletion, maximizing the potential of disease control in patients with BP. Post loading dose, the more frequent regimen, 30 mg Q4W, was selected to maintain eosinophil depletion in BP patients, as there is high eosinophil burden in blood and skin.

The safety and tolerability of a range of doses of benralizumab have been demonstrated. In Phase 3 asthma studies, over 3500 patients have received 30 mg doses of benralizumab. In Phase 2 and 3 studies in patients with COPD, 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 for 52 weeks (refer to the Investigator Brochure for details). In clinical trials in COPD using the 100 mg dose, tolerability was demonstrated in 450 patients aged 65 years to 74 years old and 166 patients aged over 75 years old received benralizumab.

Therefore, the proposed dosing regimen for benralizumab in this study is 60 mg loading followed by 30 mg SC Q4W.

4.4 End of Study Definition

The end of study is defined as the last expected visit/contact of the last participant undergoing the study. A participant is considered to have completed the study when he/she has completed his/her last scheduled visit/telephone contact.

As participants may be offered the opportunity to participate in an OLE (Section 4.1.3) of at least 1 year after completing the double-blind period of the study on IP, the end of study is planned to be when the last randomized participant completes 1 year in the OLE.

However, as AstraZeneca may choose to extend the OLE period, this decision will determine when the end of the study is declared. Notification of closure of the study will be communicated to sites at least 3 months in advance of the end of study, unless faster termination is warranted (eg, emergence of a safety concern).

After the end of the study, participants should be given standard-of-care therapy, at the discretion of their treating physician, per local practice.

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 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/Age

1 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

2 Adult participants ≥ 18 years of age at the time of signing the ICF.

Type of Participant and Disease Characteristics

3 Participants must have clinical features of BP (eg, urticarial or eczematous or erythematous plaques, bullae, pruritus) at the screening visit and confirmed diagnosis with histology, direct immunofluorescence, and serology at randomization. Required for inclusion:

   (a) Histology.

   (b) Positive direct immunofluorescence (from skin biopsy) (IgG and/or C3 at the basement membrane zone).

   (c) AND at least one of the following serologic assessments positive (all assessed from participant's blood sample):

      (i) indirect immunofluorescence (IgG on the roof of salt- split skin).

      (ii) positive serology on ELISA for BPAG1 (230-kd).

      (iii) positive serology on ELISA for BPAG2 (180-kd).

4 BPDAI activity score ≥ 24 at the screening and randomization visits.

5 Candidate for systemic corticosteroid therapy.

6 Able to complete PRO assessments on a tablet and on a handheld device. Some participants may be exempted from completing home PROs on the handheld device upon agreement with the AstraZeneca physician (eg, if the patient has a medical condition such as BP lesions of the fingers/hand, a neurologic condition affecting fingers/hand, or severe visual impairment).

Sex

7 Male or female.

Reproduction

8 Female participants capable of having children must meet both of the following conditions ([a] and [b]):

(a) Have a negative urine pregnancy test at Screening and

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

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

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

  (iii) Intrauterine device.

  (iv) Intrauterine hormone-releasing system.

  (v) Bilateral tubal occlusion.

  (vi) 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).

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

(c) 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 amenorrhoeic for ≥ 12 months prior to the planned date of randomization without an alternative medical cause. The following age-specific requirements apply:

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

  (ii) Females ≥ 50 years old will be considered postmenopausal if they have been amenorrhoeic 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 Forms of BP other than classic, predominantly cutaneous BP: eg, mucous membrane BP, epidermolysis bullosa acquisita, Brunsting-Perry BP, p200 BP, p105 BP, BP with concomitant pemphigus vulgaris, and drug-induced BP.

2 Comorbid disease that in the Investigator's judgement might interfere with the evaluation of the IP or safety of the participant. This includes any disorder that in the opinion of the Investigator is not stable (eg, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, psychiatric, or major physical impairment).

3 Current or history of malignancy within 5 years before the screening visit with the following exceptions:

   (a) Participants treated for in situ carcinoma of the cervix who have completed curative therapy and are in remission for at least 12 months prior to signing the informed consent and

   (b) Participants with superficial basal cell or squamous skin cancer.

   (c) 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 was obtained.

4 History of anaphylaxis to any biologic therapy or vaccine.

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

6 Any clinically significant abnormal findings in physical examination, vital signs, electrocardiogram (ECG), hematology, or clinical chemistry during screening, 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.

7 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 screening 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.

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

Prior/Concomitant Therapy

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

Other Exclusions

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

11 Receipt of any marketed or investigational biologic within 4 months or 5 half-lives prior to the date informed consent is obtained, whichever is longer. Participants on stable therapy for at least 3 months before randomization who intend to stay on treatment throughout the study with marketed biologics that are not likely to interfere with the assessment of safety and/or efficacy of benralizumab (eg, for the treatment of osteoporosis, migraine, pain, diabetes, obesity, ocular, cardiovascular, or metabolic diseases) can participate in the study.

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

13 Receipt of live attenuated vaccines 30 days prior to the date of randomization.

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

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

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

17 Previous randomization in the present study.

18 Concurrent enrollment in another interventional (eg, investigational drug or device) clinical trial.

19 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

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

(a) A urine pregnancy test must be performed for FOCBP at Visit 1. A positive urine test result must be confirmed with a serum pregnancy test. If serum test is positive, the participant should be excluded.

21 Participant is unable to complete PRO assessments because of cognitive function (eg, dementia).

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 8b, Section 5.1.

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

5.4 Screen Failures

Screen failures are defined as participants who consent 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, participant 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. Re-screening of a participant for any reason will also be allowed only upon approval of the AstraZeneca representative 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 (with the exception of biopsy) 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, both provided in a prefilled syringe.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

Descriptions of the IPs are provided in Table 5.

Table 5 Investigational Products

	Study intervention	
	Benralizumab	**Placebo**
Dosage formulation	Benralizumab [CCI] mg/mL solution ([CCI] mM L-histidine/L-histidine hydrochloride monohydrate, [CCI] M trehalose dihydrate, and [CCI] % w/v polysorbate [CCI] pH [CCI] for injection in APFS, [CCI] mL fill volume	Matching placebo solution ([CCI] mM L histidine/L-histidine hydrochloride monohydrate, [CCI] M trehalose dihydrate and [CCI] % (w/v) polysorbate [CCI], pH [CCI]) for injection in an APFS, [CCI] mL fill volume
Route of administration	Subcutaneous injection	Subcutaneous injection
Dosing instructions	Benralizumab active solution will be administered subcutaneously to participants by healthcare professionals using an APFS	Placebo solution will be administered subcutaneously to participants by health care professionals using an APFS
Use	Experimental	Placebo-comparator
IMP and NIMP	IMP	IMP
Sourcing	AstraZeneca	AstraZeneca
Packaging and labeling	Study intervention will be provided in an APFS. Each syringe will be labeled in accordance with GMP Annex 13 and per country regulatory requirement.	Study intervention will be provided in an APFS. Each syringe will be labeled in accordance with GMP Annex 13 and per country regulatory requirement.

APFS, accessorized prefilled syringe; 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.

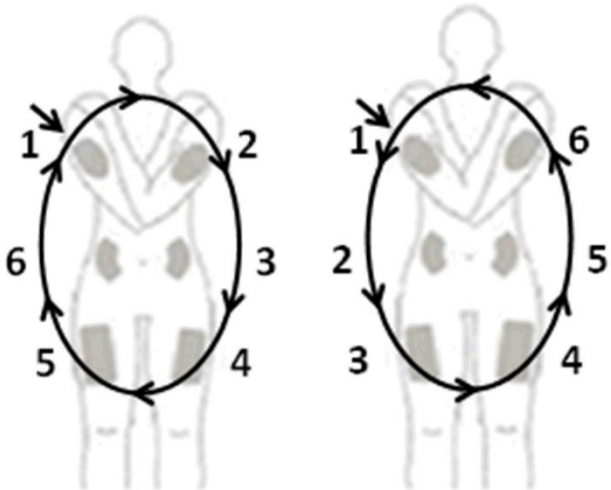
Prior to each IP administration:

- Investigator, or designee, will evaluate the participant's condition for potential contraindications for dosing (Section 6.1.2).
- Investigator, or designee, will assess the injection site as per standards of medical care.

IP Administration

Benralizumab or matching placebo will be administered SC initially as a 60 mg loading dose, and 30 mg Q4W after 4 weeks. Participants will receive the loading dose as 2 single injections via the accessorized prefilled syringe (APFS) by the Investigator, or designee; a single SC injection will be administered for subsequent doses thereafter. The 2 injections for the loading dose will be administered at the same anatomical site with a distance of at least 3 cm between the 2 injections. 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. If a particular injection site is not favorable for the participant and/or Investigator, a separate site may be used. The site, as well as the reason for not using the suggested site, is to be documented. Suggested injection site rotation sequence is presented below (Figure 2). 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, should be recorded in the appropriate section of the eCRF.

Figure 2 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.

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

The participant should be observed on-site 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 rescheduled 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 IV antimicrobials, antivirals, or antifungals until it is confirmed by the Investigator that the infection has resolved.
- 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 AstraZeneca representative 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 IP administration) are still performed within the visit window.

Rescheduled IP dose can then be administered at an unscheduled visit. 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 rescheduled 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 AstraZeneca representative 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. Discontinuation procedures are described in Section 7.1.1.

6.1.3 Medical Devices

1 The AstraZeneca manufactured medical device (or medical device manufactured for AstraZeneca by a third party) provided for use in this study is a prefilled syringe (Status, FDA Approved/CE Marked).

2 Instructions for medical device use are provided in the Investigational Product Instructions for Use manual.

3 All medical device deficiencies (including malfunction, use error and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.11) and appropriately managed by the sponsor.

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 2). The IP will be supplied to the site in kits with an APFS 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
- Damaged syringe/cartridge

Damaged or temperature excursed IP should be documented using an Interactive Voice Response System/Interactive Web Response System (IxRS) (refer to IxRS manual and the Pharmacy Manual for further details).

All IP (ie, benralizumab and matching-placebo) must be stored in a secure, environmentally controlled, and monitored (manual or automated) area, in the original outer container. The IP (ie, benralizumab and matching-placebo) must be kept under conditions specified on the label (refrigerated between 2°C to 8°C [36°F to 46°F], protected from light and must not be frozen), with access limited to the Investigator and authorized site staff. The temperature should be monitored on a daily basis and documented in the temperature-monitoring log.

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 APFS device, 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. The randomization will be stratified by disease severity (moderate; severe) and time of BP diagnosis (participants with newly diagnosed BP; participants with a previous diagnosis of BP who have relapsed). BPDAI activity score will be used to assess disease severity, whereby participants with a score greater than or equal to 56 points will be classified as severe. 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 re-screened under certain conditions (Section 5.4.1).

If a participant withdraws from the study, then his/her enrollment/randomization code cannot be reused unless the participant is re-screened. 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, AstraZeneca representative, and investigational site staff. Neither the participant nor any of the Investigators or AstraZeneca/AstraZeneca representative 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.

Benralizumab is available only as a 30 mg dose in a prefilled syringe. At Visit 2, the 60 mg loading dose requires 2 SC injections and all participants will receive 2 injections to maintain the blind at this visit. At Visit 3 through to the end of study, participants will receive one SC injection.

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 IxRS company
- The AstraZeneca supply chain department
- Patient 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 (CRO) 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

Participants on active benralizumab treatment are expected to have lower eosinophil and basophil blood counts than participants on placebo based on its established mechanism of action. Procedures to prevent unblinding based on eosinophil and basophil counts will be in place during the double-blind treatment period:

- Screening hematology assessments will initially be conducted by a local laboratory and confirmation will be conducted by a central laboratory. Post-randomization, AstraZeneca, AstraZeneca representative, study site personnel, and participants will be blinded to the eosinophil, basophil, and monocyte counts. The absolute eosinophil, basophil, and monocyte counts and percentages will be redacted from the hematology reports provided to the investigational sites; absolute neutrophils and absolute lymphocytes will be provided.
- 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 and the AstraZeneca representative.

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 (refer to the IxRS manual and the unblinding plan).

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 the AstraZeneca representative, without revealing the participant's treatment randomization to the 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 emergency room). As soon as possible, the Investigator should first contact the Safety 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 study treatments 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 2). 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

The Investigator must be informed as soon as possible about any medication(s) taken from the time of screening until the end of the study. 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 as follows:

- Background OCS
- All other medications used 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)

For corticosteroids (prednisolone/prednisone), the dose must be recorded as well as all dose changes. Specific guidance on the dose /adjustment of dose of OCS is provided in Section 6.5.1. In order to monitor compliance, participants will use the at home handheld PRO device to record the daily dose of prednisolone/prednisone (Table 3). The OCS dosage recorded in the eCRF will be the source for analysis.

6.5.1 Oral Corticosteroids and Tapering

The background medication OCS (prednisolone/prednisone) is not regarded as an IP.

During the double-blind treatment period, participants will be treated with IP and OCS until BP disease control is achieved (Figure 1). If participants were applying topical corticosteroids prior to randomization, the topical corticosteroids will be discontinued at randomization. The OCS dose will target 0.5 mg/kg/day to achieve disease control. In participants who do not achieve disease control, the OCS dose can be increased (eg, 0.75 mg/kg; Feliciani et al 2015) to achieve disease control. Participants will begin protocolled OCS tapering at the end of the consolidation phase (see Table 6 for definitions of disease control and consolidation phase). The recommended steroid taper schedule will direct participants to reduce their steroid dose by 20% per week until it reaches 10 mg per day. After that, the dose should be reduced by 2.5 mg every other week until completely tapered off or until BP relapse. The aim will be to taper participants off steroids completely within 3 to 4 months (ie, 4 to 5 months from randomization), if the participant does not relapse during the taper. If participants experience clinically significant AEs or are at a high risk of experiencing these AEs related to OCS

therapy, the Investigator will have the option to start taper sooner or taper the participant off the OCS more rapidly. An example tapering schedule is provided in Appendix F.

Participants who have a relapse (as defined in Table 6) during steroid taper may increase their OCS dose to the previous dosage where symptoms were controlled prior to relapse occurrence. The intention of determining the lowest effective OCS dose is to provide information to the Investigator for use during any subsequent tapering. Participants who have a relapse after tapering completely off steroids, will be restarted on steroids with dosing at the Investigator's discretion.

During the OLE, participants can receive corticosteroids (topical and/or oral) for BP relapse at the Investigator's discretion, with the goal of tapering off the steroids to benralizumab monotherapy as soon as clinically indicated.

Participants who are treated with OCS and then tapered can be at risk for acute adrenal insufficiency. The possibility of acute adrenal insufficiency should be considered, according to the guidance in Appendix G, in any acutely unwell participant undergoing withdrawal of chronic systemic corticosteroid treatment. Assessment of hypothalamic-pituitary-adrenal axis integrity may be performed, according to standard of care, at the discretion of the Investigator.

If the Investigator is considering addition of an immunosuppressant for the treatment of BP relapse, a discussion with the designated study physician should occur to review study options which may include discontinuation of IP. If in the opinion of the Investigator, a participant requires the addition of immunosuppressants for control of relapse, the participant will discontinue IP administration. Participants who are in the double-blind period will be asked to complete all visits and study assessments up to Week 36. Participants who are in the OLE will withdraw from the study and will be asked to complete the study assessments for the final follow-up visit as outlined in the SoA (Table 2).

While OCS compliance will be captured daily on the handheld device (unless exempted), the main source of data for analysis of OCS-related endpoints will be saved in the eCRF.

6.5.2 Restrictions

Use of any of the following concomitant treatments will not be permitted throughout the study duration, unless otherwise specified. If a participant should require or receives restricted medication, there should be a discussion between the Investigator and the AstraZeneca representative study physician to establish whether discontinuation of IP is required.

Restricted concomitant treatments are as follows:

- Immunosuppressive medication (other than for recurrent relapse at the Investigator's discretion or for treatment of AEs where no alternative treatment is available)

- Dipeptidyl peptidase-4 inhibitors or Immuno-Oncology therapies
- Oral antimicrobial agents with anti-inflammatory properties (eg, Tetracycline antibiotics, dapsone, erythromycin)
- Topical immunosuppressive medications
- Topical corticosteroids after randomization during the double-blind treatment period
  - Topical corticosteroids will be permitted during the OLE at the Investigator's discretion
  - Topical corticosteroids for non-BP related dermatological conditions (eg, poison ivy) may be permitted for short term use (approximately 7 calendar days)
- Receipt of live attenuated vaccines is disallowed 30 days prior to first dose of IP, during IP administration, and for 12 weeks after the 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 during the treatment period and is ideally not recommended within 12 weeks after the last dose of the IP. Participants on stable therapy for at least 3 months before randomization who intend to stay on treatment throughout the study with marketed biologics that are not likely to interfere with the assessment of safety and/or efficacy of benralizumab (eg, for the treatment of osteoporosis, migraine, pain, diabetes, obesity, ocular, cardiovascular, or metabolic diseases) can participate in the study (AstraZeneca should be informed when COVID prevention or treatment is utilized).
- Other IPs during the study duration or within 12 weeks after the last dose of benralizumab/placebo.

It is recommended that 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 discontinuing from IP are strongly encouraged to continue in the study up to the end of the double-blind treatment period (Visit 13/Week 36) as described in Section 7.1.1. The IP discontinuation (IPD) visit should be done 4 weeks (± 7 days) after the last dose of IP. Participants who discontinue IP can continue in the study until Visit 13/Week 36.

Discontinuation from IP does NOT automatically lead to a complete withdrawal from the study.

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.
  - New or active malignancy.
  - If after randomization, the result of the central laboratory HIV test is positive.

Refer to the SoA (Table 2) 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 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. Participants who discontinue IP at any time will be allowed to modify their background therapy and still be followed at study visits. Discontinuation of IP will be registered in IxRS.

See the SoA (Table 2) for data to be collected at the IPD visit and for any further evaluations to be completed.

7.1.1.1 Discontinuation of Study Intervention

All participants who prematurely discontinue IP should return to the study site for an 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 described in Table 2. The IPD visit replaces the nearest scheduled visit after IP discontinuation.

The participant will be offered the following options for further follow-up:

- In the double-blind treatment period if a participant discontinues prior to 36 weeks, he/she is encouraged to return to all scheduled site visits and perform all procedures/blood draws, but without IP administration, until the end of the double-blind treatment period (Visit 13, Week 36). The participant should attend the IPD visit and follow-up visit (12 weeks after the last dose of IP). Ideally, during this time, all ePRO assessments should continue at home; otherwise, participants will return the ePRO device at the IPD visit.
- In the OLE period, if a participant discontinues at any time, he/she should attend the IPD visit 4 weeks after discontinuation, as well as the follow-up visit (12 weeks after the last dose of IP).
- If the participant is unwilling or unable to attend the scheduled site visits until the end of the study, 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 disease state (Section 8.1), BP symptoms, and AE/SAE(s) (Section 8.3). The participant will be encouraged to attend the follow-up visit at the study site, if feasible.

7.1.1.2 Discontinuation of Study Intervention Upon Notification of Closure of Study

The end of treatment visit (4 weeks [± 7 days] after the last dose of IP) and follow-up visit (12 weeks after last dose) 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 AstraZeneca representative study physician immediately, and a discussion should occur between the AstraZeneca representative study physician and the Investigator regarding whether to continue or discontinue the participant from IP.

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, behavioral, 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, both the IPD visit and the follow-up visit should be conducted. See the SoA (Table 2) for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

If the participant withdraws consent for disclosure of future information, AstraZeneca may retain and continue to use any data collected before such a withdrawal of consent.

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. If he/she requests withdrawal of consent 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 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 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 safety 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, 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.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 2). PRO assessment schedules are summarized in 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 (Table 2), 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 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 (Table 2).

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 Clinician-reported Outcome Assessments

Investigators will complete clinician-reported outcome assessments during site visits in accordance with the SoA (Table 2). It is strongly encouraged to have the clinician-reported outcome assessments be performed by the same Investigator at each site to minimize variability in the assessments. The following assessments will be completed by the Investigator or designee: BP disease state (Section 8.1.1.1), BPDAI (Section 8.1.1.2), IGA (Section 8.1.1.3), CCI [redacted] CCI [redacted] and healthcare resource utilization (Section 8.1.1.7).

Patient-reported outcomes assessments will be completed by the participants using an electronic PRO device (Section 8.1.2).

8.1.1.1 Bullous Pemphigoid Disease State

Investigators will be asked to make a clinical assessment of the participants to determine their BP disease state (ie, active disease, disease control, end of consolidation phase, remission, and relapse) from baseline (Visit 2) until the end of the double-blind period, during the OLE, and then in addition at the IPD, and follow-up visit. The BP disease state will be considered "active disease" until one of the disease states in Table 6 is achieved.

At each visit, investigators will be required to assess a participant's outcome measures, including the states defined in Table 6. The outcome measure will be documented in the eCRF.

Table 6 Definitions for Bullous Pemphigoid Outcome Measures

Outcome measure	Definition [b]
Disease control/beginning of consolidation phase	The time at which new lesions cease to form and established lesions begin to heal, or pruritic symptoms start to abate
End of consolidation phase	Time at which no new lesions have developed for a minimum of 2 weeks and approximately 80% of lesions have healed and pruritic symptoms are minimal
Sustained partial remission on minimal steroid [a]/off steroid therapy	The presence of transient new lesions that heal within 1 week while the participant is on minimal steroid therapy or off steroid therapy for at least 2 months
Sustained complete remission on minimal steroid [a] /off steroid therapy	The absence of new or established lesions or pruritus while the participant is on minimal steroid therapy/ off steroid therapy for at least 2 months
Relapse	The appearance of 3 or more new lesions per month (blisters, eczematous lesions, or urticarial plaques) or at least one large (> 10 cm diameter) eczematous lesion or urticarial plaques that do not heal within 1 week, or the extension of established lesions or daily pruritus in participants who have achieved disease control

[a] Minimal steroid therapy is defined as less than or equal to 0.1 mg/kg/d of prednisone or equivalent

Definitions as per Murrell et al 2012

Disease Control/Consolidation Phase

During the first 8 weeks of the study, participants will be assessed every 2 weeks for disease control (see Table 6 for definition). When disease control is achieved, this marks the beginning of the consolidation phase. The end of the consolidation phase is the point that corticosteroid tapering will be initiated and documented in the eCRF.

BP Remission

BP remission (see Table 6 for definition) will be assessed at each study visit per the SoA (Table 2). Remission can be partial or complete and can occur off steroid therapy or on minimal steroid therapy.

BP Relapse

In the event of a suspected BP relapse (see Table 6 for definition), the participant should attend an unscheduled visit. A BPDAI evaluation will be conducted at the time of the relapse, or as soon as possible afterwards.

Investigators will be required to record details pertaining to each relapse event in the eCRF from baseline (Visit 2) until IPD visit/end of treatment and follow-up visit. Details should include the BPDAI activity and pruritus score and the required intervention(s), eg, OCS dose increase, the OCS dose at the time of relapse, addition of immunosuppressive therapy or requirement for hospitalization. Participants who require the addition of OCS after taper or an increase in the dose of OCS will be defined as having a relapse.

The management of participants who relapse will be according to standard of care. See Section 6.5.1 for further details. The participant's relapse is managed with the addition of OCS and tapering should be recommended as soon as the relapse has been appropriately controlled as per current guidelines (Feliciani et al 2015). In case of a relapse during steroid tapering, the OCS dose may be increased to the previous dosage that symptoms were controlled. For recurrent relapses the OCS dosing regimen and tapering schedule will be at the Investigator's discretion. If the participant requires therapy other than OCS (eg, immunosuppressants), the study treatment may need to be discontinued but this should be discussed with the study physician prior to decision making. In the event that discontinuation of IP is required, the participant will still be asked to continue with the study assessments until the end of the double-blind period at Week 36. For relapse during OLE, the use of topical and/or oral corticosteroids and the schedule of taper will be at the discretion of the Investigator; however, it is recommended to follow the protocol taper schedule. The goal of therapy will be to taper off steroids to benralizumab monotherapy as soon as clinically indicated. In the event that the Investigator will need to control relapse with an immunosuppressant in the OLE, the participant will be withdrawn from the study and will not receive further benralizumab therapy. Participants may additionally be asked to allow future contact to provide follow-up clinical details regarding their health and information on disease state.

8.1.1.2 Bullous Pemphigoid Disease Area Index

Bullous Pemphigoid Disease Area Index is a clinician completed tool that is used for independent disease severity assessment to measure disease extent in BP (Wijayanti et al 2017).

The Investigator will be required to complete the BPDAI on a tablet at screening (Visit 1), randomization (Visit 2), and then at each visit until the end of the double-blind treatment period, at the time of presentation with relapse or suspected relapse, at unscheduled visit, and at IPD/end of treatment and follow-up visit.

During the subsequent OLE (if applicable), the Investigator is required to complete BPDAI Q4W, at unscheduled visits (eg, in the event of a relapse), and at the IPD/end of treatment and follow-up visit.

The BPDAI tool computes 2 scores: total BPDAI activity and total BPDAI damage. The total BPDAI activity score (0 to 360) is the arithmetic sum of the 3 subcomponents – cutaneous blisters/ erosions, cutaneous urticaria/erythema, and mucosal blisters/ erosions. The total BPDAI damage score (0 to 12) is the arithmetic sum of the items rated regionally for damage caused by more permanent features such as post-inflammatory hyperpigmentation, scarring and other. BPDAI quantifies lesion number and size thresholds. Lesions are rated based on the regions affected. BPDAI gives additional weighting to areas of the skin primarily affected in BP, such as the limbs, and less emphasis to scalp and face. The BPDAI total activity and BPDAI damage give an indication of disease activity, with higher scores indicating greater disease activity or damage.

8.1.1.3 Investigator Global Assessment

An IGA scale uses clinical characteristics to assess overall disease severity at any given time point. This scoring system allows clinicians to rate skin disease activity by general overall impressions. This IGA scale uses key signs of BP with ordinal levels of severity. The IGA is a 5-point categorical scale ranging from 0 (clear) to 4 (severe) with higher scores indicating greater disease activity or damage (Table 7). The IGA uses clinical characteristics based on the number of lesions, blisters, erosions, erythema and number of anatomical locations. The IGA scale will be completed at the site by the investigator according to the SoA (Table 2).

Table 7 IGA Scores and Descriptions

Score	Description
0 – Clear	No skin lesions
1 – Almost Clear	Very few small skin lesions
2 – Mild	Few skin lesions
3 – Moderate	Multiple lesions in > 1 anatomical area OR any large erosive area
4 - Severe	Extensive skin lesions/erosive areas

Note: Examples of skin lesions include blisters, small round erosions, and erythema.

8.1.1.7 Healthcare Resource Utilization

Broad-based all-cause and BP-related healthcare resource utilization information will be collected by the Investigator, or designee, in accordance with the SoA (Table 2) and recorded in the appropriate eCRF module. Protocol-mandated procedures, tests, and encounters are not included.

At randomization, retrospective all-cause and BP-related healthcare resource utilization information will be collected with a one-year recall period. At all subsequent visits, all-cause and BP-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 medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days or length of stay, including duration by wards [eg, intensive care unit])
- Outpatient medical encounters and interventions (including specialist visits, General Practitioner visits, home health care visits, and emergency room visits, etc.)
- Number and type of diagnostic and therapeutic tests and procedures

CCI [redacted]

8.1.2 Patient-reported Outcomes

Participants will complete all PRO assessments using provisioned devices. All participants will complete PROs on the tablet at onsite visits. Daily PROs are completed on the handheld device at home. If the Investigator believes that the participant has a medical condition (eg, BP skin lesions on the fingers/hand, neurologic condition affecting the fingers/hand, or severe visual impairment), then an exemption from at-home PROs may be requested from the AstraZeneca study physician prior to the screening visit.

The Investigator will ensure that participants are properly trained on the use of the handheld PRO device and the importance of completing at-home assessments as scheduled. Compliance should be checked weekly (at a minimum) to ensure that the participant is completing the assessments as scheduled, including a check of the daily oral steroid doses taken. The Investigator or designee will be responsible for monitoring participant adherence with the daily assessments and follow up as necessary.

The at-home handheld device will be programmed at Visit 2 with reminder alarms for the daily questionnaires. 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 before taking the device home.

Participants must bring the at-home handheld device to every visit.

Confirmation of the visit in the PRO system, completion of at-site PRO assessments, and review of participant compliance with at-home PRO assessments should be completed prior to other study procedures. The timing and frequency for each PRO is provided in Table 3. The handheld device will be returned to the study site at Visit 22 (Week 72) or at the IPD visit for participants who prematurely discontinue from IP and are unwilling/unable to continue with visit procedures.

8.1.2.1 Peak Pruritus Numeric Rating Scale

The Peak Pruritus Numeric Rating Scale (NRS) is a one-item assessment that asks participants to rate the intensity of their worst itch during the past 24 hours. The scale ranges from 0 (no itch) to 10 (worst itch imaginable).

The participant will complete the Peak Pruritus NRS on a provisioned handheld device at home according to the schedule in Table 3.

8.1.2.2 Corticosteroid Medication Usage

The participant will be asked to report the dosage of OCS taken over the past 24 hours.

The participant will complete the Corticosteroid Medication Usage question on a provisioned handheld device at home according to the schedule in Table 3.

Patient-reported corticosteroid use and dosage will be checked at each clinic visit/telephone contact visit. This check should include a review of compliance with the prescribed OCS dose between each visit and/or tapering of dose, as described in Section 6.5.1.

8.1.2.3 Bullous Pemphigoid Disease Area Index Pruritus

The BPDAI-Pruritus is a separate component of the BPDAI that asks the participant to grade the severity of pruritus over the past 24 hours, the past week, and the past month. For each recall period, severity of pruritus is rated on an NRS ranging from 0 for no itch to 10 for maximal itching. The three scores are then summed for a total score ranging from 0 to 30.

The participant will complete the BPDAI-Pruritus on a tablet at the site as per schedule of assessments (Table 2).

8.1.2.4 Autoimmune Bullous Disease Quality of Life Questionnaire (AB-QoL)

The AB-QoL is a 17-item assessment of the health-related quality of life impact of autoimmune bullous diseases, including BP. The recall period is one week. The participant will complete the AB-QoL on a tablet at the site as per schedule of assessments (Table 2).

8.1.2.5 European Quality of Life-5 Dimensions (EQ-5D-5L)

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

The 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 visual analog scale, 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.

The participant will complete the EQ-5D-5L on a tablet at the site as per schedule of assessments (Table 2).

8.1.2.6 Qualitative Patient Interview Sub-study

Participants who complete the ICF in select languages, and one primary caregiver (if applicable), will be invited to participate in a qualitative patient interview sub-study. Up to 34 participants (or participant-caregiver dyads) will be enrolled in the sub-study. The

sub-study consists of interviews at 3 timepoints (prior to treatment/early treatment, end of double-blind treatment, and after at least 6 months of OLE). The interviews will be non-interventional and will collect data on participants' experiences with BP and the study treatment, and the participants' conceptions of meaningful change on some of the PROs used in this study. If a caregiver can participate, the caregiver's perspective will be included to better understand the familial and social burdens of the disease. Interviews will be conducted remotely (eg, by telephone) at a time convenient for the participant and/or caregiver; they will not be conducted during the course of a site visit. The duration of each interview will be approximately 90 minutes.

A detailed description of sub-study procedures is available in the Qualitative Patient Interview Sub-Study Manual.

Participants will be introduced to the sub-study during the informed consent process using the participant communication materials attached to the Qualitative Patient Interview Sub-study Manual. Interested participants and/or caregivers will consent specifically for this sub-study (participation in this sub-study is optional and independent from the main study). Participants and/or caregivers will be contacted according to procedures described in the Qualitative Patient Interview Sub-study Manual.

Each sub-study participant will be interviewed at the following timepoints:

- Prior to treatment/early treatment: between Week 0 and Week 4, to capture experiences before starting study treatment and/or in the first month of study treatment
- End of double blind: between Week 28 and Week 36, to examine participants' experiences during study treatment
- Open-label extension: between Week 60 and Week 76, to examine participants' experiences with BP in the open label period

During each interview, participants (and caregivers, if applicable) will be asked a set of open-ended questions. The interview discussion guide is provided as an appendix to the Qualitative Patient Interview Sub-study Manual.

The interview will be audio recorded with the participant's permission (and caregiver's permission, if applicable), confirmed verbally prior to the start of the interview. The recordings will be transcribed, and transcripts will be coded using qualitative data analysis software.

Participants' and caregivers' confidentiality and personal information will be protected throughout the sub-study to the same standard as all other coded data in the study.

Due to the qualitative nature of the data and the analysis, the results will be presented in a separate report (ie, not in the Clinical Study Report [CSR]) and the data (transcriptions) will not be entered into the study database. No identifiable data will be reported.

AstraZeneca will follow standard procedures for handling AE reporting involving these participants (as described in Appendix B). At the beginning and end of each interview, participants will be advised to report any AE to the Investigator or designee.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 2).

8.2.1 Physical Examinations

Physical examinations (complete or brief), including height and weight, will be conducted in accordance with the schedule provided in Table 2. Baseline measurements will be assessed at screening (Visit 1) or the randomization visit (Visit 2) before 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: height and weight, general appearance, skin, head and neck (including eyes, ears, nose, mouth, and throat), lymph nodes, abdomen, musculoskeletal (including spine and extremities), cardiovascular, respiratory, and neurological systems.

The brief physical examination will include an assessment of the following: weight, general appearance, skin, 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.

8.2.2 Vital Signs

Pre-dose vital signs (pulse rate, blood pressure, respiratory rate, and body temperature) will be assessed in accordance with the SoA (Table 2).

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 one minute.

8.2.3 Electrocardiograms

Single 12-lead ECG will be obtained locally during screening (Table 2) 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).

8.2.4 Clinical Safety Laboratory Assessments

Table 8 lists the clinical safety laboratory tests to be performed. Refer to the SoA (Table 2) 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 2).

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, and hematology assessments will be performed at a central laboratory, and at both local and central laboratories at Visit 1.

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

Table 8 Laboratory Safety Variables

Clinical chemistry		**Hematology**
Alkaline phosphatase	Gamma-GT (gamma-glutamyl transpeptidase)	Hematocrit
ALT (alanine aminotransferase)	Glucose	Hemoglobin
AST (aspartate aminotransferase)	Phosphorus	
BUN (blood urea nitrogen)	Potassium	Platelet count
Calcium	Sodium	
Chloride	Total bilirubin	WBC count (absolute and differential) [a]
CO_2 (carbon dioxide) [b]	Uric acid	HbA1c [c]
Creatinine	Creatinine kinase	
Cholesterol, total		

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

[b] Measured as bicarbonate.

[c] Refer to the schedule of assessments (Table 2) for details of HbA1c.

8.2.4.1 Pregnancy Tests

The following tests are applicable to female participants only and will be conducted in accordance with the SoA (Table 2).

- 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 human chorionic gonadotropin (HCG; dipstick): To be performed locally at the study site according to the SoA for all female participants except for those who are NOT of childbearing potential as defined in inclusion criterion 7(c). A positive urine pregnancy test result must be confirmed with a serum pregnancy test (beta-HCG).

8.2.4.2 Serology

Hepatitis B surface antigen and hepatitis C antibody tests will be assessed in accordance with the SoA (Table 2). The testing may be performed at the study site for participants who require immediate results for randomization, however this will also require confirmatory tests sent to the central laboratory. The test to be performed at the central laboratory for all other participants.

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): Local HIV express test will be performed at Visit 1 to inform eligibility; the sample from Visit 1 will also be sent to the central laboratory. If, after randomization, the result of the central laboratory HIV test is positive, the participant will be discontinued from treatment.

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

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 see 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 participant 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 or designee 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 an 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 investigational product?'

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

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 IP, 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, dose adjustment or 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 BP (eg, pruritus, eczematous lesions, urticarial plaques, blisters/bulla, mucosal lesions). Events which are unequivocally due to BP 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, fetal death, stillbirth, congenital anomalies, 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 representatives within 1 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 Medication Error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs 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 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.

8.3.10 Device Constituent Deficiencies

- In a combination drug-device IMP (eg, APFS), 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.

8.3.11 Medical Device Deficiencies

Medical devices are being provided for use in this study as prefilled syringes are being utilized to deliver the IMP under study. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of medical device deficiency that occur during the study with such medical devices.

The definition of a Medical Device deficiency can be found in Appendix I.

NOTE: Incidents and deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Appendix I of the protocol.

8.3.11.1 Time Period for Detecting Medical Device Deficiencies

- Medical device incidents or malfunctions of the medical device will be detected, documented, and reported during all periods of the study in which the medical device is used.

- If the investigator learns of any medical device deficiency at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting Medical Device Deficiency is provided in Appendix I.

8.3.11.2 Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.3.11.3 Prompt Reporting of Medical Device Deficiencies to Sponsor

- Medical device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.
- The Medical Device Deficiency Paper Report Form will be sent to the sponsor by email or fax (PPD or PPD respectively).
- The sponsor will be the contact for the receipt of medical device deficiency reports.

8.3.11.4 Regulatory Reporting Requirements for Device Deficiencies

- The investigator will promptly report all medical device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of medical device deficiencies to the IRB/IEC.
- For further guidance on the definition of an SAE, see Appendix I.

8.3.12 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 IRBs/IECs as required by national regulations.

8.3.13 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 should 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 after each IP administration for the appearance of any acute drug reactions, in line with clinical practice.

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 dose of benralizumab greater than 200 mg 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 eCRF and on the Overdose eCRF module.

- An overdose without associated symptoms is only reported on the Overdose eCRF 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, see 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 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 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 according to the SoA (Table 2). Pharmacokinetic samples will be collected before administration of IP, except Week 2, as there is no IP administered at Week 2. Pharmacokinetic samples will also be collected at disease control if no IP administration has occurred.

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 Institutional Review Board (IRB)/Independent Ethics Committee (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 Bioanalytical Report.

The bioanalytical laboratory will have access to the randomization list (Section 6.3.2). The following samples will be analyzed:

Double-blind treatment period:

- PK samples from participants assigned to the benralizumab treatment group

Open-label extension period:

- PK samples at Visit 19 (Week 60) in the OLE period in all groups.

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

8.5.2.1 Anti-drug Antibodies

Blood samples for determination of ADA in serum will be collected as detailed in the SoA (Table 2) and 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. Neutralizing antibodies may be assessed on ADA positive samples. Samples will be collected according to the SoA (Table 2).

Other analyses may be performed to verify the stability of antibodies to benralizumab and/or further characterize the immunogenicity of benralizumab.

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 pharmacodynamic effect of benralizumab, and blood levels of these 2 types of cells will be assessed as part of the hematology safety testing (Section 8.2.4). Tissue eosinophil and basophil levels will be assessed as part of the biomarker evaluation (Section 8.6). Biomarkers thought to play a role in eosinophilic inflammation and/or BP pathogenesis may also be assessed as part of exploratory research (Section 8.6).

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

Mandatory collection of samples for exploratory biomarker research is a part of this study. Samples for exploratory biomarker research are required and will be collected from all participants in this study as specified in the SoA (Table 2).

Blood (whole blood, serum, and plasma) and skin tissue will be collected according to the SoA (Table 2) in order to evaluate the effect of benralizumab on CCI [redacted], inflammation, and immunological mechanisms related to the pathogenesis of BP.

Instructions for sample collection, processing, storage, and shipment are provided in the Laboratory Manual. Results from the exploratory biomarker analyses, if performed, will be reported separately from the CSR. (Investigators will not receive the results.)

8.6.1.1 Serum and Plasma

Serum and plasma samples will be collected according to the SoA (Table 2) to evaluate the pharmacology of benralizumab as well as biomarkers of eosinophil recruitment, activation, and survival (eg, absolute eosinophil count, IL-5, EDN, eotaxin). Additional markers of

cellular inflammation and/or activation may be assessed including, but not limited to, those associated with humoral autoimmunity (total serum IgE, IgG directed against auto-antigens BP-180 and/or BP-230), T cell subsets (eg, IL-13, IFN-gamma, IL-17), eosinophil granule proteins (eg, MBP, eosinophil peroxidase), epithelial cell damage (eg, TSLP, IL-25, IL-33), itch (IL-31), and pain (substance P). The results from such studies will not be reported in the CSR but in separate reports or publications as appropriate.

Instructions for sample collection, processing, storage, and shipment will be found in the Laboratory Manual.

8.6.1.2 Tissue Histology and Immunostaining

Skin biopsies will be collected at screening and Week 36 (as per SoA [Table 2]). Skin biopsies will be taken from peri-lesional skin for histopathology and CCI research. If lesions have resolved, skin biopsies will be taken at a site proximal to the previously peri-lesional site. If lesions persist, biopsies will be taken at peri-lesional sites proximal to the original peri-lesional site. Skin biopsies will be collected and processed locally at the clinical sites as described in detail in the Laboratory Manual. For participants without a confirmed diagnosis, no biopsy for CCI is collected. In these participants, the biopsy will be for inclusion criteria confirmation at the local lab and immunohistochemistry for exploratory research.

Staining of the biopsies will be conducted at an appropriate contract lab and/or at AstraZeneca. The skin biopsies will be stained for markers for the detection and enumeration of CCI

CCI

CCI

8.6.2 Storage, Re-use and Destruction of Biomarker Samples

Samples will be stored for a maximum of 15 years from the date of the last participant's last visit (end of study is defined in Section 4.4), after which they will be destroyed. The results of this biomarker research may be pooled with biomarker data from other studies to provide data for greater understanding of pathophysiology of BP and possible participant subsets.

Guidance regarding handling, transport, and destruction of human biological samples is provided in Appendix C.

CCI

[redacted]

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary endpoint is the proportion of participants who are in complete remission while off OCS for ≥ 2 months at Week 36. The null hypothesis is: the proportion of participants on benralizumab is equal to the proportion of participants on placebo. Whereas the alternative hypothesis is: the proportion of participants on benralizumab is not equal to the proportion of participants on placebo. That is:

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

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

There are 5 key secondary endpoints. The first key secondary endpoint is the proportion of participants who remain relapse-free up to Week 36. Relapse is defined as participants experiencing: 3 or more new lesions a per month (blisters, eczematous lesions, or urticarial plaques); or at least one large (> 10 cm diameter) eczematous lesion or urticarial plaques that do not heal within 1 week; or the extension of established lesions or daily pruritus in participants who have achieved disease control. The null hypothesis states: there is no difference in proportion relapse-free between benralizumab and placebo. The alternative hypothesis states: there is a difference in proportion relapse-free between benralizumab and placebo. That is:

H_0: Difference in proportions (benralizumab - placebo) = 0

H_1: Difference in proportions (benralizumab - placebo) $\neq 0$

The remaining 4 key secondary endpoints are continuous outcomes, and they are: cumulative OCS exposure (mg/kg) from baseline to Week 36; change from baseline in BPDAI activity score at Week 36; change from baseline in BPDAI-Pruritus score at Week 36; cumulative OCS exposure (mg/kg) from baseline to Week 16. For each of these endpoints, the null hypothesis is: the mean for benralizumab is equal to the mean for placebo. Whereas the alternative hypothesis is: the mean for benralizumab is not equal to the mean for placebo. That is:

H_0: Difference in means (benralizumab – placebo) = 0

H_1: Difference in means (benralizumab – placebo) $\neq 0$

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 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 who are in complete remission and have taken no OCS for ≥ 2 months at Week 36
2 Proportion of participants who remain relapse-free up to Week 36
3 Cumulative OCS exposure (mg/kg) from baseline to Week 36
4 Change from baseline in BPDAI activity score at Week 36
5 Change from baseline in BPDAI-Pruritus score at Week 36
6 Cumulative OCS exposure (mg/kg) from baseline to Week 16

9.2 Sample Size Determination

The sample size calculation was derived for the primary endpoint, the proportion of participants who are in complete remission while off OCS for ≥ 2 months at Week 36. Approximately 60 participants are needed per treatment group to detect a 30% difference between benralizumab and placebo with 90% power. The calculation is based on a 2-sided test and a 5% significance level and assumes a response rate of 50% for benralizumab and 20% for placebo.

There is limited evidence currently available from completed comparative BP trials to date to base the study size assumptions on. However, a mepolizumab Phase 2 trial with a similar

participant population, design, and steroid taper rate reported a low proportion who were relapse free up to 36 weeks (20% versus 33% for mepolizumab versus placebo; Simon et al 2020). From this study, the assumption that an expected remission rate off steroids at Week 36 would be low, at most 20%, was extrapolated. A 30% improvement in this remission rate was recommended by a panel of BP experts to be at the lower end of what may be clinically meaningful, and so was considered to be a conservative assumption.

A non-binding interim futility analysis will be performed by an Independent Data Monitoring Committee (IDMC) when approximately 36 randomized participants (ie, when approximately 30% of the total amount of statistical information is available) have had the opportunity to complete at least 36 weeks of follow-up. By conducting the interim analysis, the overall power will not be affected substantially. Full details are provided in Section 9.5.

9.3 Populations for Analyses

Analyses presented in the CSR will be based on the populations as defined in Table 9.

Table 9 Populations for Analysis

Population	Description
All participants analysis set	All participants screened for the study, to be used for reporting disposition and screening failures.
Full analysis set	All randomized participants who received at least 1 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 have prematurely discontinued, according to the ITT principle. Participants who withdraw consent to participate in the study will be included up to the date of their study termination.
Safety analysis set	The safety analysis set consists of all participants who have received 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 has on one or several occasions received active IP is classified as active. Safety, and ADA data will be based on this analysis set and for whom any post-dose data are available.
Pharmacokinetic analysis set	All participants who received at least one dose of 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 1 quantifiable serum PK observation post first dose. All PK summaries will be based on this analysis set.
OLE benralizumab analysis set	All participants who start or carry on receiving at least 1 dose of benralizumab after the end of the DB treatment period

ADA, anti-drug antibodies; DB, double-blind; IP, investigational product; ITT, intent-to-treat; OLE, open-label extension; 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. Any deviations from this plan will be reported in the CSR.

This section is a summary of the planned statistical analyses of the primary and 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 (CIs). 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 9.4.7.

9.4.1 General Considerations

The primary analysis will be based on the initial 36-week, double-blind, placebo-controlled phase of the study, and will compare all participants randomized to benralizumab until Week 36 against all participants randomized to placebo until Week 36.

Table 10 outlines the estimands which will be used for the primary analyses of the primary and key secondary endpoints, with additional detail on each endpoint in the sections below.

Table 10 Primary and Key Secondary Estimands

Statistical category	Treatment condition	Endpoint (Population)	Intercurrent event strategy	Population level summary (Analysis)
Primary objective: To compare the clinical efficacy of benralizumab with placebo in participants with symptomatic BP				
Primary	Treatment with benralizumab versus placebo, regardless of IP compliance; restricted medication use indicates treatment failure	Proportion of participants who are in complete remission while off OCS for ≥ 2 months at Week 36 (FAS)	• Treatment discontinuation – treatment policy • Rescue with OCS[a] – treatment policy • Restricted medication use – composite (non-responder) • Study withdrawal – composite (non-responder)	Odds ratio and difference in proportion of participants who are responders at Week 36 (logistic regression model)
Secondary objective: To compare the effect of benralizumab with placebo on supportive measures of clinical efficacy in participants with symptomatic BP up to Week 36/up to Week 16				
Key Secondary	Treatment with benralizumab versus placebo, regardless of IP compliance; rescue with OCS and restricted medication use indicate treatment failure	Proportion of participants who remain relapse-free up to Week 36 (FAS)	• Treatment discontinuation – treatment policy • Rescue with OCS[a] – composite (not relapse free) • Restricted medication use – composite (not relapse free) • Study withdrawal – composite (not relapse free)	Odds ratio and difference in proportion of participants remaining relapse free up to Week 36 (logistic regression model)
Key Secondary	Treatment with benralizumab versus placebo, regardless of IP compliance	Cumulative OCS exposure (mg/kg) from baseline to Week 36 and from baseline to Week 16 (FAS)	• Treatment discontinuation – treatment policy • Restricted medication use – effectiveness (includes OCS dosing up to occurrence of event) • Study withdrawal – effectiveness (includes OCS dosing up to occurrence of event)	Difference in mean cumulative OCS exposure (mg/kg) from baseline to Week 36 and from baseline to Week 16 (MMRM)

Table 10 Primary and Key Secondary Estimands

Statistical category	Treatment condition	Endpoint (Population)	Intercurrent event strategy	Population level summary (Analysis)
Key Secondary	Treatment with benralizumab versus placebo, regardless of IP compliance; rescue with OCS and restricted medication use indicate treatment failure	Change from baseline in BPDAI activity score at Week 36, change from baseline in BPDAI-Pruritus score at Week 36 (FAS)	• Treatment discontinuation – treatment policy • Rescue with OCS[a] – composite (LOCF) • Restricted medication use – composite (LOCF) • Study withdrawal – hypothetical (multiple imputation)	Difference in mean change from baseline in BPDAI activity score/BPDAI-Pruritus score at Week 36 (ANCOVA)

[a] Rescue with OCS is defined as needing to increase OCS dose after previously having achieved disease control.

ANCOVA, analysis of covariance; BP, bullous pemphigoid; BPDAI, bullous pemphigoid disease area index; FAS, full analysis set; IP, investigational product; LOCF, last observation carried forwards; MMRM, mixed-effect model for repeated measures; OCS, oral corticosteroids.

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.

Further estimands will be specified 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. Further description is given in Section 9.4.8 and will be fully specified in the SAP.

All analyses for the OLE endpoints will be descriptive, as no placebo-control data will be available for this period. Consequently, no hypothesis testing will be performed.

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

9.4.2 Efficacy Analyses

9.4.2.1 Primary Analysis Method

Proportion of participants who are in complete remission and have taken no oral corticosteroids for ≥ 2 months at Week 36

The primary endpoint is a binary response whereby participants will be classified as responders if they are in complete remission while off OCS for ≥ 2 months at Week 36. Otherwise, participants will be classified as non-responders.

The estimand strategy is outlined in Table 10 above. Intercurrent events (use of restricted medications, study withdrawal) are unfavorable outcomes and will be handled with a composite strategy whereby participants experiencing these events prior to Week 36 will be considered as non-responders in the analysis. Likewise, participants with missing data at Week 36 for any other reason will be considered as non-responders. However, for this endpoint, if a participant needs to increase OCS after previously achieving disease control but still tapers and achieves the remission criteria by Week 36, this will count as response in the analysis. It is considered unlikely that this situation would emerge often, but given the clinical relevance of still being able to achieve remission and that OCS use is built into the remission definition, it is considered appropriate to count this situation as response in the analysis.

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, baseline disease severity (moderate; severe) and time of BP diagnosis (ie, participants with newly diagnosed BP versus participants with a previous diagnosis of BP who have relapsed) as categorical covariates.

(Note that participants will be classified as severe based on a cut-off of 56 points for baseline BPDAI activity score.) The effect of adding further covariates into the model, such as age and region, may also be assessed as a sensitivity analysis if any potentially significant imbalances occur in the set of baseline characteristics.

The model will be used to estimate the proportion of responders for benralizumab and placebo, the difference between these proportions (benralizumab – placebo), a rate ratio (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 categories, the endpoint 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 36.

9.4.2.2 Analysis Methods for Key Secondary Efficacy Variables

Proportion of participants who remain relapse-free up to Week 36

The proportion of participants who remain relapse-free up to Week 36 will be analyzed as a binary response variable, where participants who remain relapse-free throughout the study up to Week 36 will be considered responders, but otherwise participants will be considered non-responders. Relapse is defined as the appearance of: 3 or more new lesions per month (blisters, eczematous lesions, or urticarial plaques); or at least one large (> 10 cm diameter) eczematous lesion or urticarial plaques that do not heal within 1 week; or the extension of established lesions or daily pruritus in participants who have achieved disease control.

The estimand strategy is outlined in Table 10 above. Intercurrent events of rescue use with OCS after having previously achieved disease control, restricted medication use, and study withdrawal are unfavorable outcomes and will be handled with a composite strategy whereby participants experiencing these events prior to Week 36 will be considered as non-responders (ie, not relapse-free) in the analysis. Likewise, participants with missing data at Week 36 for any other reason will be considered as not-relapse free.

For the primary analysis of the proportion of participants relapse-free at Week 36, a logistic regression model will be fitted using a logit link function. The model will include treatment, baseline disease severity (moderate or severe, with a BPDAI activity score of 56 points used as the threshold between moderate and severe) and time of BP diagnosis (ie, participants with newly diagnosed BP versus participants with a previous diagnosis of BP who have relapsed) as categorical covariates.

The model will be used to estimate the proportion who are relapse-free for benralizumab and placebo, the difference between these proportions (benralizumab – placebo), a rate ratio

(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 categories, the endpoint will be analyzed using a Cochran–Mantel–Haenszel test.

As supportive analyses to explore the timing of relapse events, the time to first BP relapse will also be analyzed, where time to first relapse is defined as the earliest time after randomization that any of the relapse criteria are met. This analysis will use a log-rank test stratified by baseline disease severity (moderate; severe) and time of BP diagnosis (ie, participants with newly diagnosed BP versus participants with a previous diagnosis of BP who have relapsed). A p-value, corresponding to a 2-sided test, will be presented to compare the benralizumab and placebo treatment groups. A Cox-proportional hazards model will be used to estimate the hazard ratio and its 95% CI. The median time to first relapse will be estimated from the Kaplan-Meier curves for the benralizumab and placebo treatment groups.

Cumulative OCS exposure (mg/kg) from baseline to Week 36 and from baseline to Week 16

Two cumulative OCS exposure endpoints are defined: the cumulative OCS exposure over the 36-week double-blind period, and the cumulative OCS exposure over the first 16 weeks of the study. Each of these endpoints will be assessed from a mixed-effect model for repeated measures (MMRM), examining each participant's cumulative OCS exposure in 4-week periods. The cumulative exposure over the 36 (and 16) weeks will be estimated as the sum over the relevant 4-week periods from the MMRM model. This analysis method was selected to utilize all available data in the situation of any participants dropping out prior to 36 weeks. This ensures that any such participants can still contribute to the analysis for the period they remain in the study, without needing to make potentially implausible imputation assumptions around future OCS exposures in these situations (eg, carrying forward a high last observation of 0.75 mg/kg/d, which would not be a feasible dose to maintain for a 36-week period).

As highlighted in Table 10, the intercurrent events of restricted medication use and study withdrawal will be handled with an effectiveness strategy, including all available data in the MMRM model until the occurrence of such events. As described above, this avoids needing to make potentially implausible imputation assumptions that a composite strategy would involve. Likewise, use of a treatment policy strategy is also not considered appropriate, as use of restricted medications would confound future OCS use. For example, if OCS were discontinued to receive another treatment due to lack of response or intolerability to OCS, the treatment policy approach would show a low cumulative OCS dose, which is a positive outcome and does not fairly represent the overall picture. Note that the list of intercurrent events does not include rescue with OCS (ie, increases in OCS dose after achieving disease

control), as by definition of the endpoint, increases in OCS dosing will be reflected in the cumulative OCS dose.

The model will include cumulative OCS exposure (mg/kg) as the dependent variable (calculated for each participant over 4 weekly intervals up to Week 36); treatment, 4 weekly interval, baseline disease severity and time of BP diagnosis as categorical covariates; treatment-by-4 weekly interval as an interaction term. The inclusion of baseline OCS dose as a covariate will also be considered. An unstructured variance-covariance matrix will be used to model within-participant 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 4 weekly interval and for the sum of the 4-weekly intervals over the whole of the 36-week treatment period, and for the sum of the 4-weekly intervals over the initial 16-week treatment period, the model will be used to estimate the mean cumulative OCS exposure (mg/kg) for each treatment group and the difference versus placebo, with corresponding 95% confidence limits. P-values, corresponding to 2-sided tests, will be presented to compare the benralizumab and placebo treatment groups for each interval, including the whole of the 36-week treatment period and the initial 16-week treatment period.

To support this analysis, observed means will be summarized using descriptive statistics by treatment group and each 4 weekly interval, are for the whole of the 36-week treatment period and the initial 16-week treatment period.

Change from baseline in BPDAI activity score at Week 36

BPDAI activity score is a continuous endpoint that will be completed at the visits specified in the SoA (Table 2) during the initial 36-week treatment period.

The estimand strategy is outlined in Table 10 above. For this endpoint, intercurrent events of rescue use with OCS after having previously achieved disease control and restricted medication use are considered unfavorable outcomes and will be handled with a composite strategy whereby participants experiencing these events prior to Week 36 will have their last observation prior to rescue/restricted medication use carried forward to Week 36. For participants who discontinue the study without having rescue or restricted medications, missing data at Week 36 will be imputed using multiple imputation based on participants who don’t have rescue/restricted medication use. Once these imputations are made, the available change from baseline in BPDAI score at Week 36 will then be analyzed using an analysis of covariance (ANCOVA) model.

The model will include change from baseline at Week 36 as the dependent variable, baseline BPDAI score as a continuous covariate, and treatment, baseline disease severity, and time of

BP diagnosis as categorical covariates. The model will be used to estimate the mean change from baseline at Week 36 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.

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 36. In addition, the cumulative distribution function of absolute changes from baseline in BPDAI activity score at Week 36 will also be plotted, to allow the treatment difference at various response thresholds to be explored. Responder analyses using minimal clinically important differences presented in the literature (Wijayanti et al 2017) may be presented, if appropriate.

Change from baseline in BPDAI-Pruritus score at Week 36

BPDAI-Pruritus score is a continuous endpoint that will be completed at the visits specified in the SoA (Table 2) during the initial 36-week treatment period. The statistical analysis described above for BPDAI activity score will be carried out for this endpoint, with the same estimand approach and the same ANCOVA 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 36. In addition, the cumulative distribution function of absolute changes from baseline in BPDAI-Pruritus score at Week 36 will also be plotted to allow the treatment difference at various response thresholds to be explored.

9.4.2.3 Analysis Methods for Secondary Efficacy Variables

Proportion of participants in sustained complete/partial remission on minimal OCS/off OCS for at least 2 months at Week 36

A supportive responder analysis will be performed where any participant who achieved complete or partial remission, while on minimal OCS or off OCS for at least 2 months at Week 36 will be defined as responders. The statistical methodology described for the primary analysis will be carried out for this endpoint.

Summaries of the different combinations of complete and partial remission, each on minimal OCS or off OCS, will also be produced to understand the distribution of these clinical benefit categories at visits throughout the study up to Week 36.

Cumulative time (weeks) in complete remission off OCS from baseline to Week 36

Cumulative time in complete remission while off OCS will be derived for each participant over the initial 36-week treatment period. These times will then be assigned to a set of ordered categories (which will include a category for no weeks in complete remission off OCS), to be

fully defined in the SAP. An ordered logistics regression model will be fitted to these categories, assuming proportional odds.

The model will include cumulative time as the dependent variable and treatment, baseline disease severity and time of BP diagnosis as categorical covariates. The model will be used to estimate an odds ratio, with 95% CIs.

Proportion of participants off OCS by Week 36

Participants will be defined as responders if they are off OCS by Week 36. Otherwise, participants will be classified as non-responders. The statistical methodology described for the primary analysis will be carried out for this endpoint. (The p-value 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 using descriptive statistics by treatment group and each scheduled visit up to Week 36.

IGA score at Week 36 and change from baseline in IGA score at Week 36

IGA score achieved (clear, almost clear, mild, moderate, severe) will be summarized using descriptive statistics by treatment group at each scheduled visit up to Week 36.

A responder analysis will be performed where participants will be classified as responders if they achieve IGA 0/1 (ie, clear or almost clear) at Week 36. Otherwise, participants will be classified as non-responders. The statistical methodology described for the primary analysis will be carried out for this endpoint (the p-value will be nominal, as secondary objectives are not controlled for multiplicity and do not appear in the testing hierarchy).

Number of points change from baseline in IGA score will be summarized, and a shift table comparing IGA score at baseline against IGA score achieved at Week 36 (and other visits throughout the study, as relevant) will be produced.

Proportion of participants who remain relapse-free up to Week 16

Referring to the statistical analysis for the proportion of participants who remain relapse-free up to Week 36, proportion of participants who remain relapse-free up to Week 16 will also be analyzed as a binary endpoint with a similar logistic regression model.

Proportion of participants with any clinical benefit at Week 16

To assess signs of clinical efficacy during the first 16 weeks of the study, the observed proportion of participants showing partial remission or complete remission at Week 16 will be summarized using descriptive statistics by treatment group. The summary will categorize each of these disease states into: during taper, with no steroids, and with minimal steroids (ie, < 0.1 mg/kg/day).

If a consistent message can be drawn across these categories and treatment groups, a supportive analysis will be carried out, whereby a participant will be classified as a responder if they show any clinical benefit (ie, partial remission or complete remission) during taper, with no steroids or with minimal steroid use at Week 16. Otherwise, a participant will be classified as a non-responder. This binary variable will then be analyzed using a logistic regression model with a logit link function. The model will include treatment, baseline disease severity and time of BP diagnosis as covariates. 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. (The p-value will be nominal, as secondary objectives are not controlled for multiplicity and do not appear in the testing hierarchy.)

Time to disease control, OCS dose at disease control and time to the end of the consolidation phase

Time to disease control, OCS dose at disease control and time to the end of the consolidation phase will be summarized using descriptive statistics by treatment group. The time to disease control and time to the end of the consolidation phase may also be grouped into ordered categories and summarized by treatment group. Statistical analysis and Kaplan Meier plots may be performed if appropriate. Full details will be provided in the SAP.

Change from baseline in BPDAI activity score at Week 16

Referring to the statistical analysis for change from baseline in BPDAI activity score at Week 36, the same analysis methods will be used for the change from baseline at Week 16 endpoint (the p-value at Week 16 will be nominal, as secondary objectives are not controlled for multiplicity and do not appear in the testing hierarchy).

Change from baseline in BPDAI-Pruritus score at Week 16

Referring to the statistical analysis for change from baseline in BPDAI-Pruritus score at Week 36, the same analysis methods will be used for the change from baseline at Week 16 endpoint (the p-value at Week 16 will be nominal, as secondary objectives are not controlled for multiplicity and do not appear in the testing hierarchy).

9.4.3 Safety Analyses

Summaries will be based primarily on the safety analysis set and focus on the initial 36-week treatment period. A key subset of these summaries will also be repeated for the entire study period and the OLE. Full details will be provided in the SAP.

9.4.3.1 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.

Adverse events will be presented for each treatment group by system organ class and preferred term, including the number and percentage of participants reporting at least 1 event, number of events and exposure-adjusted rates, where appropriate.

An overview of AEs will be presented for each treatment group, 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.

An additional table will present number and percentage of participants with most common AEs (frequency of ≥ 3%).

In accordance with the requirements of the Food and Drug Administration, a separate table will present non-serious AEs occurring in more than 5% of participants in any treatment group.

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.

9.4.3.2 Treatment Emergence

The following events are considered treatment emergent:

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

9.4.3.3 Clinical Safety Laboratory 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.

9.4.3.4 Vital Signs

Details of all vital signs analyses will be provided in the SAP. As an overview, descriptive statistics will be presented for observed and change from baseline values for all vital sign parameters, which include the continuous measures: systolic blood pressure, diastolic blood pressure, pulse rate, respiration rate and body temperature.

For each treatment group:

- The parameters will be summarized at each scheduled post-baseline visit and will include: number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate.
- The number and percentage of participants falling into specific vital signs categories (defined in the SAP) will be presented at each scheduled post-baseline visit in a frequency table.
- Changes in vital signs measurements will be examined at each scheduled post-baseline visit and clinically noteworthy values observed during the study (defined in the SAP) will be presented in a frequency table.

9.4.3.5 Body Weight

For each treatment group, descriptive statistics will be presented for observed and change from baseline values at each scheduled post-baseline visit and will include: n, mean, standard deviation, minimum, Q1, median, Q3 and maximum. Changes in body weight will be examined at each scheduled post-baseline visit and clinically noteworthy values observed during the study (defined in the SAP) will be presented in a frequency table.

9.4.4 Pharmacokinetic Analyses

The PK analyses will be performed at or under the guidance of AstraZeneca Research and Development. Benralizumab serum concentrations will be summarized using descriptive statistics at each scheduled visit for participants in the PK analysis set.

9.4.5 Immunogenicity Analyses

Anti-drug antibodies to benralizumab will be summarized using descriptive statistics by treatment group and each visit specified in the SoA (Table 2). The ADA titers-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. Full details will be provided in the SAP.

CCI [redacted]

9.4.6.1 Patient-reported Outcomes

Quality of life will be assessed using the AB-QoL total score and the EQ-5D-5L score at the visits specified in the SoA (Table 2). For each of these continuous endpoints, observed means and mean changes from baseline will be summarized using descriptive statistics by treatment group and each scheduled visit. To support these summaries, an MMRM model may be fitted to each of these outcome variables if deemed appropriate, following the details outlined in Section 9.4.2.2 for BPDAI activity score.

Itch will be assessed using the Peak Pruritus NRS and recorded every day from Visit 2 onwards by participants using a handheld device. Note that this endpoint is not collected during the screening period and so a baseline score will not be available. All changes will be assessed in an exploratory manner, relative to disease control. Analyses of the Peak Pruritus NRS endpoint will be completed in the subset of patients able to use the handheld device.

For each participant, if at least 4 non-missing daily assessments are available in a weekly period, a weekly mean score will be derived starting from the seventh day after disease control, by summing the daily score over the available assessment and dividing by the number of available assessments in that week. If there are less than 4 non-missing daily assessments included in the calculation of the weekly score, the weekly score is missing for that week. The weekly scores will be summarized by descriptive statistics for observed means and mean changes from disease control.

Binary endpoints will be derived using these weekly mean scores, whereby participants will be classified as a responder or a non-responder for each week using pre-specified clinically meaningful thresholds. As no threshold for a clinically relevant within-person response definition has been established for BP, the ≥ 2- to 4-point change threshold proposed for atopic dermatitis by Yosipovitch et al 2019 will be used for this study. Atopic dermatitis is an appropriate comparison point as it is another intensely pruritic inflammatory skin condition associated with eosinophilia (Jenerowicz et al 2007). Therefore, in the current study, a participant will be considered to have an improvement for a given week if a ≥ 2-point reduction versus disease control is observed and will be considered to have a worsening for a given week if a ≥ 2-point increase versus disease control is observed for the weekly mean score. However, depending on distribution of the data, other thresholds for response may be explored. The responder definition will be finalized and documented before unblinding.

Observed proportion of responders will be summarized using descriptive statistics by treatment group and week.

9.4.6.2 Healthcare Resource Utilization

BP-related healthcare resource utilization assessments will be completed at the visits specified in the SoA (Table 2). The set of assessments will include the frequency and duration of hospitalization, and frequency of office visits and emergency room visits. These endpoints

will be summarized using descriptive statistics for each treatment group, and will include an annualized rate of hospitalizations due to BP and an average length of hospital stay due to BP. To support these summaries, a negative binomial regression model may also be fitted to each of these endpoints if deemed appropriate.

9.4.6.3 Exploratory Biomarkers

To explore the mechanism of action of benralizumab and the predictive value of biomarker data with clinical outcomes, the following assessments will be carried out at the visits specified in the SoA (Table 2): skin histology and immunohistochemistry; CCI [redacted] CCI [redacted] serum and plasma biomarkers. Statistical analyses will be fully described in the SAP.

9.4.6.4 Effect of Benralizumab in the OLE

The effect of benralizumab will be explored in participants in the OLE period by assessing endpoints such as: CCI [redacted] Peak Pruritus NRS , AB-QoL and EQ-5D-5L. These endpoints will be summarized using descriptive statistics for each treatment group at pre-defined time points in the OLE period up to Week 72 of the study. Full details will be provided in the SAP.

9.4.7 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 who are in complete remission while off OCS for ≥ 2 months at Week 36 (primary endpoint)
2 Proportion of participants who remain relapse-free up to Week 36 (key secondary endpoint)
3 Cumulative OCS exposure (mg/kg) from baseline to Week 36 (key secondary endpoint)
4 Change from baseline in BPDAI activity score at Week 36 (key secondary endpoint)
5 Change from baseline in BPDAI-Pruritus score at Week 36 (key secondary endpoint)
6 Cumulative OCS exposure (mg/kg) from baseline to Week 16 (key secondary endpoint)

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 the treatment comparison for (4) is statistically significant, testing will proceed to (5). If the

treatment comparison for (5) is statistically significant, testing will proceed to (6). 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.

9.4.8 Sensitivity Analyses

Sensitivity analyses will be explored to assess the robustness of treatment effects for the primary and key secondary endpoints.

Alternative estimand approaches for handling intercurrent events will be explored including treatment policy approaches, or alternative imputation techniques for handling of treatment failure intercurrent events for continuous endpoints, if relevant.

For missing data due to study withdrawal of incomplete data for other reasons, 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, including dropout reason-based multiple imputation will be considered.

To examine the impact of missing data, including the impact of non-responder/not relapse free imputations due to study withdrawal, for the primary and first key secondary endpoint respectively, tipping point analyses may be performed. These analyses will systematically vary the assumptions about outcomes among the subsets of participants on the treatment arms who withdraw from the study early or have missing data at Week 36 for any other reason. Tipping point analyses are intended to identify the point at which the results would tip from statistically significant to not statistically significant. Thus, the tipping point analyses will only be performed if an endpoint achieves a nominally statistically significant result (ie, nominal p-value < 0.05).

Full details of all sensitivity analyses will be provided in the SAP.

9.4.9 Subgroup Analyses

Exploratory analyses will be carried out to assess the consistency of the treatment effect across key, pre-defined, subgroups. These analyses will focus on the primary endpoint, and they may be performed on key secondary endpoints if deemed appropriate. The list of subgroups will include, but may not be limited to: disease severity using baseline BPDAI to categorize participants; time of BP diagnosis (ie, participants with newly diagnosed BP versus participants with a previous diagnosis of BP who have relapsed); age; region; OCS dose at randomization; baseline blood eosinophils. Full details of all subgroup analyses will be described in the SAP, including hypotheses that will be tested and the covariates and interaction terms to be included in the statistical models.

9.5 Interim Analyses

A non-binding futility analysis will be carried out by the IDMC when approximately 36 randomized participants (ie, when approximately 30% of the total amount of statistical information is available) have had the opportunity to complete at least 36 weeks of follow-up. Recruitment will remain ongoing while the futility analysis is performed.

In the futility analysis, a predictive power-based hurdle will be used for the primary endpoint (remission whilst off OCS for at least 2 months by Week 36) such that, given the data accumulated to date, if there is low chance (CCI of achieving statistical significance at the final analysis if the study were to continue, then a stop decision for futility should be recommended. CCI
CCI
If a decision is made that the study should continue, the primary analysis will be performed when all randomized participants have had the opportunity to complete at least 36 weeks of follow-up. The sample size calculation described in Section 9.2 incorporates the small loss of power (< 2%) that results from performing the futility analysis to maintain the overall power at > 90%.

9.6 Data Monitoring Committee

An IDMC will be utilized for this study. Appendix A 5 provides more details on the rationale for an IDMC and the remit of the committee.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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