| **Clinical Study Protocol** | |
|---|---|
| Study Intervention | Benralizumab |
| Study Code | D3259C00001 |
| Version | 4 |
| Date | 31 May 2021 |

# A Phase 2b Multinational, Randomised, Double-blind, Parallel-group, 24-week Placebo-controlled Study with 28-week Extension to Investigate the Use of Benralizumab in Patients with Chronic Spontaneous Urticaria Who are Symptomatic Despite the Use of Antihistamines (ARROYO)

**Sponsor Name: AstraZeneca AB**

Legal Registered Address: AstraZeneca AB, 151 85 Södertälje, Sweden

Local Sponsor in Japan: AstraZeneca KK, 3-1 Ofuka-cho, Kita-ku, Osaka 530-0011, Japan

**Regulatory Agency Identifying Number(s):**

EudraCT number 2020-000169-17; IND 146828.

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:** D3259C00001

Amendment Number: 3

Study Intervention: Benralizumab

Study Phase: 2b

**Short Title:**

A phase 2b study to investigate the use of benralizumab in patients with chronic spontaneous urticaria who are symptomatic despite the use of antihistamines (ARROYO).

**Study Physician Name and Contact Information will be provided separately**

**International Co-ordinating Investigator:**

PPD

Charitéplatz 1
10117 Berlin, Germany

# PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| Amendment 3 | 31 May 2021 |
| Amendment 2 | 16 October 2020 |
| Amendment 1 | 11 June 2020 |
| Original Protocol | 20 January 2020 |

## Amendment 3 (31 May 2021)

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

## Overall Rationale for the Amendment:

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

| Section # and Name | Description of Change | Brief Rationale | Substantial/Non-substantial |
|---|---|---|---|
| Throughout | The term “medical monitor” was replaced by “study physician”. | To ensure consistency with the latest protocol template. | Non-substantial |
| Throughout | The term “congenital abnormalities” was amended to “congenital anomalies”. | To ensure consistency with the latest protocol template. | Non-substantial |
| Throughout | The term “women” was amended to “females”. | To ensure consistency throughout the protocol. | Non-substantial |
| Throughout | Minor editorial changes. | To ensure consistency with the latest protocol template. | Non-substantial |
| Title Page | The local amendment number changed to 3. | Updated to reflect the correct amendment number of this protocol version. | Non-substantial |
| 1.3 Schedule of Activities | The immunogenicity sample collection was removed from the follow-up visit. | This assessment is not needed for the follow-up visit and thus was removed. | Non-substantial |

| Section # and Name | Description of Change | Brief Rationale | Substantial/Non-substantial |
|---|---|---|---|
| 5.2 Exclusion Criteria | Exclusion criterion 10 has been removed: "Doses administered daily or every other day for 5 or more consecutive days of systemic or topical corticosteroids, hydroxychloroquine, methotrexate, cyclosporine, cyclophosphamide, or (IV) immunoglobulin within 30 days before day -14." | Text amended to remove duplication of updated exclusion criterion 11 (now numbered 10). | Non-substantial |
| | Criterion 10 (previous criterion 11) was replaced with the following "Use of immunosuppressive medication, including, but not limited to: methotrexate, cyclosporine, azathioprine, topical and systemic corticosteroids within 4 weeks or 5 half-lives prior to the date informed consent is obtained, whichever is longer." | Text amended to align with the updated project specific safety requirements for the benralizumab development program | Non-substantial |
| | Criterion 18 was updated to clarify that planned elective major surgical procedures during the conduct of the study is reason to not enroll the patient. | Updated for improved clarity. | Non-substantial |
| 5.3 Lifestyle considerations | The inclusion criterion number referring to the definition of females of childbearing potential was updated from 10 to 9. | Updated to reflect the correct number in this protocol version. | Non-substantial |
| CCI [redacted] | | | |
| 6.5 Concomitant Medications | Clarified in the text that any prior biologic medication(s) are to be collected in the electronic case report form. | Updated to clarify that prior biologic medication(s) are to be collected. | Non-substantial |
| 6.5.4 Restrictions | The following bullet was added to the restrictions:<br>• Plasmapheresis is prohibited within 30 days prior to screening. | Omitted in error. | Non-substantial |
| | The following bullet was added to the restrictions:<br>• 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 | Exclusion of inactive vaccines was inadvertently not included in the previous versions and has been added so as to align with the current | Non-substantial |

| Section # and Name | Description of Change | Brief Rationale | Substantial/Non-substantial |
|---|---|---|---|
| | injection to a site distant from the vaccine site injection. | benralizumab safety information. | |
| 8<br>Study assessments and procedures | A note was added, stating that if not all laboratory kits are available at a given visit, the Investigator should contact the Study Physician to confirm whether the assessment is critical or may be postponed until supplies are available. | To allow for improved feasibility and to conduct study visits, in case specific laboratory kits are not available at a given time point. | Non-substantial |
| 8.2.1.1<br>Pregnancy tests | The inclusion criterion number referring to the definition of females not of childbearing potential was updated from 11 to 10. | Updated to reflect the correct number in this protocol version. | Non-substantial |
| 8.2.3<br>Vital signs | Wording was updated to clarify that pulse rate and blood pressure will be (instead of "should be") measured after the participant has been resting for at least 5 minutes, and that the pulse rate should be (instead of "will be") obtained before blood pressure. | Updated for improved clarity. | Non-substantial |
| 8.3<br>Adverse Events and Serious Adverse Events | The following text was removed:<br>"Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non leading verbal questioning of the subject is the preferred method to inquire about AE occurrences." | Text updated to clarify AE reporting procedures and to align with the current protocol template (Section 8.3.4 already provides the method for questioning for AE-related verbal questioning). | Non-substantial |
| 8.3.2<br>Follow-up of AEs and SAEs | The following text was removed:<br>"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, stabilisation, the event is otherwise explained, or the participant is lost to follow-up." | Text updated to clarify AE reporting procedures and to align with the current protocol template | Non-substantial |
| | "Description of AE" was included as one of the variables to be collected for SAEs. | Omitted previously from the protocol by error. | Non-substantial |
| 8.3.8.1<br>Maternal Exposure | The following text was added:<br>"The PREGREP module in the eCRF is used to report the pregnancy and the paper-based | Text updated to clarify pregnancy reporting procedures and to align | Non-substantial |

| Section # and Name | Description of Change | Brief Rationale | Substantial/Non-substantial |
|---|---|---|---|
| | PREGOUT module is used to report the outcome of the pregnancy." | with the current protocol template | |
| 8.3.8.2 Paternal Exposure | Section removed from the protocol. | Text amended to align with the updated project specific safety requirements for the benralizumab development program. | Non-substantial |
| 8.4 Overdose | It was reinforced that overdoses associated with an SAE will be reported to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days, consistent with the standard SAE reporting procedures. | Text updated to clarify overdose reporting procedures and to align with the current protocol template | Non-substantial |
| Appendix A 1 Regulatory and Ethical Considerations | The following text has been included:<br>"The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations." | To align with the updated protocol template. | Non-substantial |
| Appendix A 3 Informed Consent Process | The following text was removed:<br>"If the participant's partner becomes pregnant, despite prevention, state that the partner will be asked to sign an ICF for pregnant partners.<br>If a participant's partner becomes pregnant during or within 12 weeks after the last dose of study drug, the partner will be asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Participants" and provide information about the pregnancy accordingly." | Text amended to align with the updated project specific safety requirements for the benralizumab development program. | Non-substantial |
| Appendix A 6 Dissemination of Clinical Study Data | The link http://astrazenecaclinicaltrials.com was replaced with http://astrazenecagrouptrials.pharmacm.com. | To align with the updated protocol template. | Non-substantial |
| Appendix A 7 Data Quality Assurance | Text updated to clarify that the Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the electronic case report form. | To align with the updated protocol template and procedures. | Non-substantial |

AE, adverse event; CFR, Code of Federal Regulations; eCRF, electronic case report form; ICF, informed consent form; ICH, International Council for Harmonisation; IEC, Independent Ethics Committee; IP, investigational product; IRB, Institutional Review Board; IV, intravenous; SAE, serious adverse event.

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# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title: A Phase 2b Multinational, Randomised, Double-blind, Parallel Group, 24-week Placebo-controlled Study with 28-week Extension to Investigate the Use of Benralizumab in Patients with Chronic Spontaneous Urticaria Who Are Symptomatic Despite the Use of Antihistamines (ARROYO)**

**Short Title: A phase 2b study to investigate the use of benralizumab in patients with chronic spontaneous urticaria who are symptomatic despite the use of antihistamines (ARROYO)**

**Rationale:** The aim of this study is to investigate the use of benralizumab as treatment for patients with chronic spontaneous urticaria (CSU) who are symptomatic despite the use of antihistamines. It is proposed that benralizumab will deplete eosinophils and basophils from affected skin, improve symptoms of CSU, and improve CSU-related quality of life. This Phase 2b study is designed to evaluate 2 induction doses of benralizumab (60 mg and 30 mg) compared to placebo, and a comparison of maintenance dosing regimens (every 8 weeks [Q8W] versus every 4 weeks [Q4W]) in the 28-week extension period.

**Objectives and Endpoints:**

The primary and secondary objectives and associated endpoints are detailed in Table 1. For tertiary/exploratory objectives and endpoints, see Section 3 of this protocol.

## Table 1 Primary and Secondary Objectives

| **Primary Objective:** | **Estimand description / endpoints** |
|---|---|
| To determine the clinical efficacy of benralizumab compared to placebo in patients with CSU who are symptomatic despite the use of $H_1$ antihistamine treatment. | • Population: Full Analysis Set:<br>• Endpoint: Change from baseline in ISS7 at Week 12<br>• Intercurrent events: All data up to Week 12 will be included regardless of randomised treatment adherence or rescue medication received<br>• Summary measure: difference in least squares mean change from baseline in ISS7 at Week 12 between benralizumab and placebo |
| **Secondary Objectives:** | **Endpoint/variable:** |
| To evaluate the effect of benralizumab compared to placebo on supportive measures of clinical efficacy in patients with CSU who are symptomatic despite the use of $H_1$ antihistamine treatment. | • Key secondary endpoint: change from baseline in UAS7 at Week 12 [a]<br>• Change from baseline in UAS7 at Week 24<br>• Proportion of responders (UAS7 $\leq$ 6) at Week 12<br>• Change from baseline in HSS7 at Week 12<br>• Time to $\geq$ 5 point decrease (clinically relevant decrease) in ISS7<br>• Proportion of participants with complete UAS7 response (UAS7 = 0) at Week 12<br>• Measures of angioedema activity at Week 12 in participants with angioedema at baseline<br>• Change from baseline in UCT at Week 12 |
| To evaluate the effect of benralizumab on patient-reported health-related quality of life measures in patients with CSU who are symptomatic despite the use of $H_1$ antihistamine treatment. | • Change from baseline in CU-$Q_2$oL at Weeks 12 and 24<br>• Change from baseline in DLQI at Weeks 12 and 24 |
| To assess the PK and immunogenicity of benralizumab 30 mg and 60 mg in patients with CSU who are symptomatic despite the use of $H_1$ antihistamine treatment. | • Serum benralizumab concentration<br>• ADA |
| To evaluate the longer-term effect of benralizumab compared to placebo at Week 24 on measures of clinical efficacy in patients with CSU who are symptomatic despite the use of $H_1$ antihistamine treatment. | • Change from baseline in ISS7 at Week 24<br>• Change from baseline in UAS7 at Week 24<br>• Proportion of responders (UAS7 $\leq$ 6) at Week 24<br>• Change from baseline in HSS7 at Week 24<br>• Proportion of participants with complete UAS7 response (UAS7 = 0) at Week 24<br>• Measures of angioedema activity at Week 24 in participants with angioedema at baseline<br>• Change from baseline in UCT at Week 24 |

**Table 1 Primary and Secondary Objectives**

| | |
|---|---|
| To evaluate the efficacy of administration of benralizumab Q8W versus Q4W up to Week 52 in patients with CSU who are symptomatic despite the use of $H_1$ antihistamine treatment. | • Change from baseline in ISS7 at Week 52<br>• Other supportive efficacy assessments at Week 52 in participants on a Q8W dosing regimen compared to those on a Q4W dosing regimen. |
| **Safety Objective:** | **Endpoint/variable:** |
| To assess the safety and tolerability of benralizumab in patients with CSU who are symptomatic despite the use of $H_1$ antihistamine treatment. | Safety and tolerability will be evaluated in terms of AEs, vital signs, and clinical laboratory values.<br>Assessments related to AEs cover:<br>• Occurrence/frequency<br>• Relationship to IP as assessed by Investigator<br>• Intensity<br>• Seriousness<br>• Death<br>• AEs leading to discontinuation of IP<br><br>Vital signs parameters include systolic and diastolic blood pressure, and pulse, as well as respiration rate, body temperature, body weight, and height.<br>Assessments related to vital signs cover:<br>• Observed value<br>• Absolute and percent change from baseline values over time |

[a] The key secondary endpoint will use the same treatment policy strategy estimand as outlined for the primary endpoint. All other estimands will be detailed fully in the Statistical Analysis Plan (SAP).

ADA, anti-drug antibodies; AE, adverse event; CU-$Q_2$oL, Chronic Urticaria Quality of Life Questionnaire; CSU, chronic spontaneous urticaria; DLQI, Dermatology Life Quality Index; HSS7 hives severity score over 7 days; ISS7, itch severity score over 7 days; IP, investigational product; PK, pharmacokinetics; Q4W, every 4 weeks; Q8W, every 8 weeks; UAS7, urticaria activity score over 7 days; UCT, Urticaria Control Test.

## Overall Design

This is a Phase 2b, multinational, randomised, double-blind, parallel-group, 24-week placebo-controlled study with 28-week extension to evaluate the efficacy and safety of benralizumab in participants ≥ 18 years of age with CSU refractory to standard of care treatment, which may include second generation $H_1$ antihistamines (at approved or up to 4 times approved doses) as monotherapy, or in combination with leukotriene receptor antagonists and/or $H_2$ blockers. The study is designed to evaluate 2 induction doses of benralizumab (60 mg and 30 mg) compared to placebo, and a comparison of maintenance dosing regimens (Q8W versus Q4W) in the 28-week extension period.

The study comprises the following consecutive periods:

- A 10-day to 4-week run-in period
- A 24-week placebo-controlled, double-blind treatment period (comprising an initial 12-week 'induction dose' period followed by an additional 12-week dosing period)
- A 28-week blinded-to-dosing regimen extension period for maintenance treatment.

**Disclosure Statement:**

This is a Phase 2b parallel-group, placebo-controlled study with 5 treatment groups.

**Number of Participants:**

Approximately 240 participants will be enrolled/screened in order to achieve 160 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 randomised to the study will be considered "screen failures", unless otherwise specified by the protocol.

**Intervention Groups and Duration:**

Following a 10-day to 4-week run-in period, approximately 160 participants will be randomised in a ratio of 3:3:3:3:4, respectively, to one of the following 5 treatment sequences as illustrated in Figure 1 and Figure 2:

- **Benralizumab 60 mg Q4W** until Week 12, **30 mg Q4W** until Week 24, and **30 mg Q8W** during the extension period until Week 52 (n = 30)
- **Benralizumab 60 mg Q4W** until Week 12, **30 mg Q4W** until Week 24, and **30 mg Q4W** during the extension period until Week 52 (n = 30)
- **Benralizumab 30 mg Q4W** until Week 12, **30 mg Q4W** until Week 24, and **30 mg Q8W** during the extension period until Week 52 (n = 30)
- **Benralizumab 30 mg Q4W** until Week 12, **30 mg Q4W** until Week 24, and **30 mg Q4W** during the extension period until Week 52 (n = 30)
- **Placebo Q4W** until Week 24, **benralizumab 30 mg Q4W** until Week 36, and **30 mg Q8W** until Week 52 (n = 40).

Up to Week 24, ie, prior to start of the extension period evaluating Q4W and Q8W dosing regimens, participants in both benralizumab 60 mg initial dose treatment arms will be considered as a single treatment group (total n = 60), as will participants in both benralizumab 30 mg initial dose treatment arms (total n = 60).

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

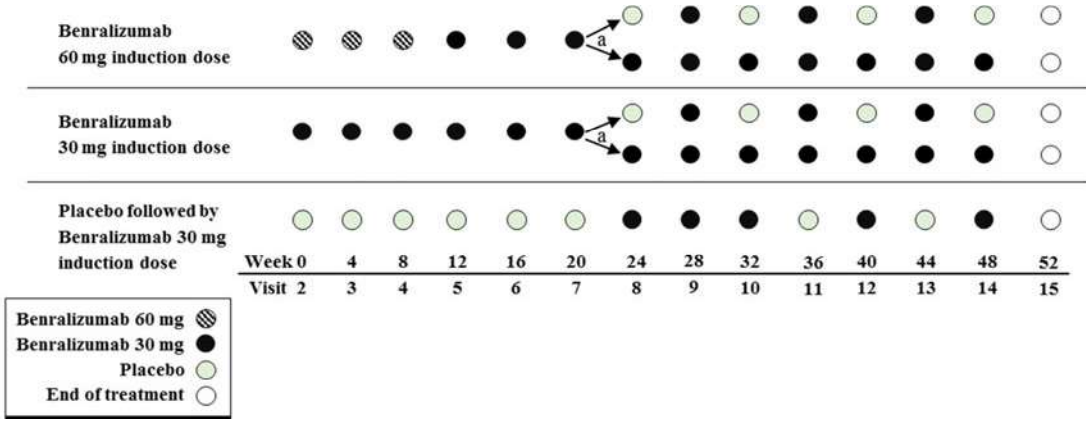
Benralizumab is available only as a 30 mg dose in a prefilled syringe. Since the 60 mg treatment requires 2 SC injections, all participants will receive 2 injections during the initial 12-week induction period to maintain the blind:

- Participants randomised to the benralizumab 30 mg group will receive one benralizumab 30 mg injection and one matching placebo injection
- Participants randomised to the benralizumab 60 mg group will receive 2 benralizumab 30 mg injections
- Participants randomised to the placebo group will receive 2 placebo injections.

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

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

**Figure 1 Investigational Product Administration**




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

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

**Data Monitoring Committee:** No

There is no data monitoring committee involved in the conduct of this study.

**Statistical Methods**

Approximately 160 participants will be randomised in a 3:3:3:3:4 ratio to different sequences of initial benralizumab dose or placebo, followed by Q4W or Q8W maintenance dosing with

benralizumab post Week 24 as described above. Randomisation will be stratified by region. Up to Week 24, ie, prior to start of the extension period evaluating Q4W and Q8W dosing regimens, participants in both benralizumab 60 mg initial dose treatment arms will be considered as a single treatment group (total n=60), as will participants in both benralizumab 30 mg initial dose treatment arms (total n=60).

By combining the treatment sequences with common initial benralizumab doses, the above randomisation will provide a 3:3:2 ratio across the benralizumab 60 mg and 30 mg initial dose groups and the placebo treatment arm (n=40), respectively, in order to assess the primary endpoint at Week 12. This provides 90% power for statistical significance at the 2-sided 2.5% level within each induction dose comparison versus placebo if the assumed effect is a 4.7 point mean difference in change in itch severity score over 7 days (ISS7) between benralizumab and placebo, assuming a standard deviation (SD) of 6 for the change in ISS7 and a 10% dropout rate.

The primary efficacy analyses will be based on the double-blind, 12-week placebo-controlled induction period. In this part of the study and the following 12 weeks (up to Week 24) all efficacy analyses will use the Full Analysis Set (FAS), defined as all randomised participants who received at least 1 dose of IP, irrespective of their protocol adherence and continued participation in the study, according to the Intent-to-Treat principle.

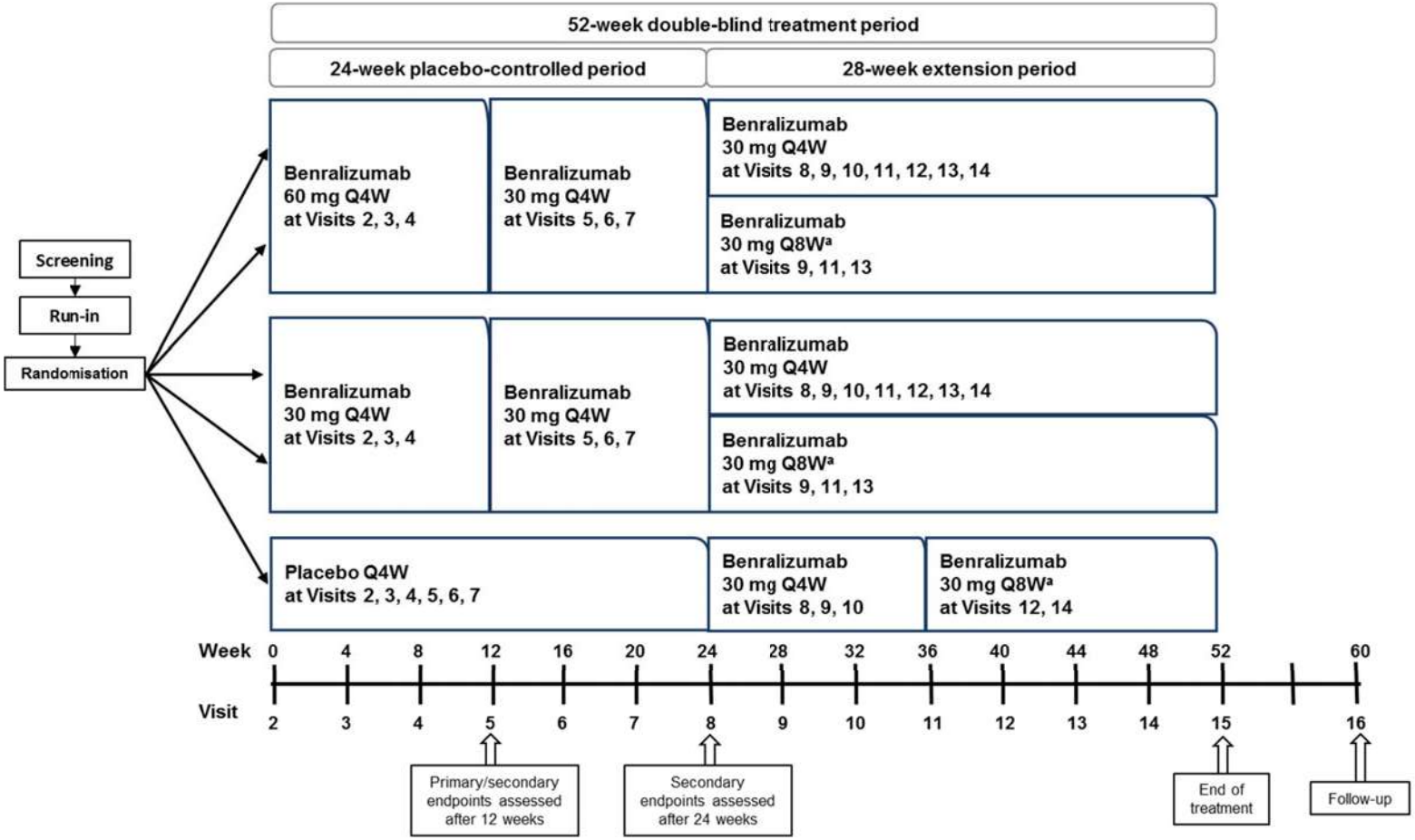
The primary endpoint, change from baseline in ISS7 at Week 12, will be compared between each benralizumab initial treatment group (60 mg and 30 mg) with placebo using a Mixed-effect Model for Repeated Measures (MMRM). The dependent variable in this model will be the change from baseline in ISS7 at post-baseline protocol-specified visits (up to the Week 24 visit). Treatment group will be included as an explanatory variable along with the baseline ISS7 score, region, visit and treatment-by-visit interaction as fixed effects. An unstructured covariance structure will be used to model the within-patient errors. If the model fails to converge, the following structures will be attempted in the specified order: Toeplitz, first-order autoregressive, compound symmetric, and variance components. Least squares mean estimates for change from baseline at Week 12 and differences in least squares mean estimates between the treatment groups and placebo will be obtained from this model.

To make a comparative assessment of the efficacy of the Q4W and Q8W dosing regimens between Weeks 24 and 52, the efficacy endpoints will be assessed out to Week 52 using the 5 treatment groupings described above. If appropriate, each of the Q4W and Q8W maintenance treatment arms will be pooled across initial benralizumab doses to allow a single comparison of Q8W versus Q4W dosing. The group of participants receiving placebo and then benralizumab will also be presented in these analyses but not formally compared to the other treatment groups.

## 1.2 Schema

The general study design is summarised in Figure 2.

**Figure 2 Study Design**




[a] To maintain the blind of the dosing regimen in the extension period, participants randomised to receive benralizumab Q8W will receive Q4W investigational product dosing including placebo administered Q8W, 4 weeks after their benralizumab administrations.

## 1.3 Schedule of Activities

The Schedule of Activities (SoA) at each site 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 Site Visit Activities**

| Procedure | Run-in | Double-blind placebo-controlled treatment period | | | | | | | Double-blind extension period | | | | | | | Follow-up | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | Unsch Visit [c] | IP Disc. [d] | CSP section or appendix with details |
| Week [a] | -4 wk to -10 days- [b] | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 60 | | | |
| 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 |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | Section 6.5 |
| Randomisation | - | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | Section 6.3.1 |
| Efficacy assessments | | | | | | | | | | | | | | | | | | | |
| Handheld device distribution | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | Section 8.1 |
| CCI | | | | | | | | | | | | | | | | | | | |
| Other assessments in-office | | | | | | | | | | | | | | | | | | | |
| Patient reported experience (free text entry) | X | - | X | - | X | - | - | X | - | - | - | - | - | X | - | - | - | | - Section 8.1.8 |
| Healthcare resource utilisation | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | - | X | Section 8.8 |
| Safety assessments[e] | | | | | | | | | | | | | | | | | | | |
| AEs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | Section 8.3 |
| Complete (Brief) physical exam | X | (X) | (X) | (X) | (X) | (X) | (X) | X | (X) | (X) | (X) | (X) | (X) | (X) | X | - | X | - | Section 8.2.2 |

**Table 2 Schedule of Site Visit Activities**

| Procedure | Run-in | Double-blind placebo-controlled treatment period | | | | | | | Double-blind extension period | | | | | | | Follow-up | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | Unsch Visit [c] | IP Disc. [d] | CSP section or appendix with details |
| Week [a] | -4 wk to -10 days- [b] | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 60 | | | |
| Vital signs[e] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | Section 8.2.3 |
| Weight (Height at baseline only) | - | X | - | - | - | - | - | X | - | - | - | - | - | - | X | - | - | - | Section 8.2.2 |
| ECG | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | Section 8.2.4 |
| Laboratory assessments | | | | | | | | | | | | | | | | | | | |
| Haematology | X | - | - | - | | - | - | X | - | - | | - | - | - | X | - | - | X | Section 8.2.1 |
| Clinical chemistry | X | - | - | - | | - | - | X | - | - | | - | - | - | X | - | - | X | Section 8.2.1 |
| Urinalysis | X | - | - | - | | - | - | X | - | - | | - | - | - | X | - | - | X | Section 8.2.1 |
| Serum pregnancy test | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | Section 8.2.1.1 |
| Urine dipstick pregnancy test | - | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | - | X | Section 8.2.1.1 |
| Post-menopause confirmation (FSH) | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | Section 8.2.1.1 |
| Hepatitis/HIV screening | X | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | Section 8.2.1.2 |
| Pharmacokinetics sample prior to IP administration | - | X | X | - | X | - | - | X | - | - | X | - | - | - | X | - | - | X | Section 8.5.1 |
| Immunogenicity sample (ADA) | - | X | - | - | X | - | - | X | - | - | X | - | - | - | X | - | - | X | Section 8.5.2 |
| CCI | | | | | | | | | | | | | | | | | | | |

**Table 2 Schedule of Site Visit Activities**

| Procedure | Run-in | Double-blind placebo-controlled treatment period | | | | | | | Double-blind extension period | | | | | | | Follow-up | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | Unsch Visit [c] | IP Disc. [d] | CSP section or appendix with details |
| Week [a] | -4 wk to -10 days- [b] | 0 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 | 40 | 44 | 48 | 52 | 60 | | | |
| CCI | | | | | | | | | | | | | | | | | | | |
| Skin biopsy | - | X | - | - | X | - | - | X | - | - | - | - | - | - | - | - | - | - | Section 8.6 |
| Investigational product administration | | | | | | | | | | | | | | | | | | | |
| IP administration [f] | - | X | X | X | X | X | X | X | X | X | X | X | X | X | - | - | - | - | Section 4.1.1 |

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

[b] The run-in period is a maximum of 4 weeks and minimum of 10 days.

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

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

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

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

ADA, Anti-drug antibodies; AE, Adverse Event; ECG, Electrocardiogram; EOT, End of treatment; FSH, Follicle-stimulating hormone; HIV, human immunodeficiency virus; IP, Investigational product; IPD, Investigational Product Discontinuation; PRO, Patient-reported outcomes.

All within-window PRO assessments (Table 3) that have not been completed prior to a site visit will be completed at the site before any other study procedures are conducted.

**Table 3 Schedule of PRO Assessments**

| Instruments | Schedule |
|---|---|
| Daily PRO: UPDD Question 1 | Every morning [a]. First assessment at home the day after Visit 1. |
| Daily PROs: UPDD Questions 2-7 | Every evening [b]. First assessment at home on the day of Visit 1. |
| Weekly PRO: PGI-S | At site at Visits 1 and 2. At home every 7 ± 3 days after Visit 2. |
| Monthly PROs: UCT, DLQI, CU-$Q_2$oL | At site at Visits 1 and 2.<br>At home every 28 ± 3 days after Visit 2. |
| EQ-5D-5L | At site at Visits 1, 2, 3, 4, 5, and 15. |
| CCI | [redacted] |

[a] Morning is defined as 05:00 to 12:00 on day *n*.

[b] Evening is defined as 17:00 on Day *n* to 04:00 on Day *n* + 1.

CU-$Q_2$oL, Chronic Urticaria Quality of Life Questionnaire; DLQI, Dermatology Life Quality Index; EQ-5D-5L, European Quality of Life-5 Dimensions; CCI [redacted] PGI-S, Patient Global Impression of Severity; PRO, patient-reported outcomes; UCT, Urticaria Control Test; UPDD, Urticaria Patient Daily Diary.

# 2 INTRODUCTION

## 2.1 Study Rationale

Chronic spontaneous urticaria (CSU), which affects between 0.5% and 1% of the global population, is difficult to treat and a substantial burden on patients (Maurer et al 2018); however, treatment options are limited for patients with symptoms not well controlled by standard of care with antihistamines (Maurer et al 2011, Zuberbier et al 2018).

Mast cells and basophils have been traditionally regarded as the main effector cells in CSU (Bracken et al 2019); however, the role of eosinophils in CSU pathology is emerging. Eosinophils are elevated in diseased tissue but remain within the normal range in blood, and the presence of elevated levels of eosinophils and basophils within diseased tissue has been correlated with CSU disease severity (Kay et al 2014, Marques et al 2016). Basopenia has been linked to severe antihistamine-resistant CSU, and type IIb autoimmunity and eosinopenia have been associated with high disease activity, as well as autoimmunity and poor response to treatment in patients with CSU (Kolkhir et al 2019). The role of eosinophils and basophils in the pathophysiology of CSU suggests that a direct eosinophil/basophil-depleting approach, as provided by benralizumab, may prove beneficial in the treatment of CSU.

Benralizumab 30 mg administered SC Q4W was shown in a Phase 2a pilot study to reduce signs and symptoms of CSU and improve health-related quality of life after 12 weeks of treatment (Bernstein and Singh 2019). Reduced disease activity and symptoms of chronic symptomatic dermographism (pruritus, itchy wheals upon skin exposure to friction), a form of chronic inducible urticaria, after 3 months of treatment with benralizumab was described in a recent case report of a patient who received benralizumab 30 mg Q4W for his severe allergic eosinophilic asthma (Bergmann et al 2019). Additionally, results from a pilot study of patients with hypereosinophilic syndrome showed improvements in skin-related symptoms, with eosinophil depletion seen in skin biopsies after 12 weeks of treatment with benralizumab (Kuang et al 2019). Based on these results, further investigation of the efficacy and safety of benralizumab in treating CSU is warranted.

## 2.2 Background

CSU is defined as the spontaneous appearance of wheals, angioedema, or both for a duration of at least 6 weeks or more due to known (eg, autoimmune) or unknown causes (Zuberbier et al 2018). Wheals are accompanied by pruritus, which can range from mild in intensity to sufficiently bothersome to interfere with normal daily activity or sleep. More than 30% of CSU patients with moderate to severe symptoms will continue to have CSU after 5 years (Maurer et al 2018, Nettis et al 2018, O'Donnell et al 1997). The impact of CSU on patients' quality of life is substantial; health status scores and subjective satisfaction in patients with CSU are lower than in healthy subjects as well as in patients with respiratory allergy (Maurer et al 2018, Zuberbier et al 2018). Productivity, sleep, and daily activities are

negatively affected by CSU. (Note: CSU was formerly known as chronic idiopathic urticaria; however, with the understanding that some of cases are caused by autoimmune disorders, this subtype is now referred to as CSU.)

The current first-line standard of care for CSU is second generation non-sedating antihistamines (Zuberbier et al 2018), but treatment options are limited for patients with CSU that is unresponsive to antihistamines. The guideline-recommended second-line treatment is increasing the antihistamine dose to up to 4 times the approved dose. Leukotriene receptor antagonists (LTRA) and H2 blockers may be used in combination with H1 antihistamines although evidence of their efficacy is limited. Third-line treatment is omalizumab as add-on to antihistamine; however, it requires monthly injections, and many patients do not respond or have incomplete response to treatment. Fourth line-treatment is cyclosporine as add-on to antihistamine; however, cyclosporine is associated with significant side effects, including nephrotoxicity and hypertension, and with long-term use, malignancies. Thus, there is an unmet medical need for treatments for CSU unresponsive to antihistamines that are more efficacious, including an earlier onset of effect, have a favourable safety profile, and that are more convenient for patients to administer.

Significantly increased numbers of eosinophils and basophils, as well as neutrophils, macrophages, T cells, endothelial cells, and blood vessels, have been seen in the wheals of patients with CSU (Kay et al 2014). Benralizumab is a humanised, recombinant IgG1k monoclonal antibody that binds to the alpha chain of the human interleukin-5 (IL-5) receptor (IL-5Rα), which is selectively expressed by mature eosinophils, eosinophil progenitor cells, and basophils. Benralizumab is afucosylated, (ie, without a fucose sugar residue in the Fc domain) which also facilitates binding to FcγRIII receptors on immune effector cells, such as natural killer cells, leading to apoptosis of eosinophils and basophils through enhanced antibody-dependent cell-mediated cytotoxicity (ADCC). In patients with asthma, the enhanced ADCC activity of benralizumab results in the rapid and nearly complete depletion of eosinophils in the blood as well as depletion of eosinophils in the lung tissue, sputum, and bone marrow (Busse et al 2013, Kolbeck et al 2010, Laviolette et al 2013. The enhanced ADCC activity of benralizumab also results in depletion of circulating basophils (Finlay and Khan 1994, Ito et al 2011, Kolbeck et al 2010, Laviolette et al 2013). Since infiltration of eosinophils and basophils has been shown in urticaria lesions in CSU patients (Kay et al 2014), benralizumab may be an effective treatment for CSU.

This study is designed to evaluate the efficacy and safety of benralizumab in treating participants with CSU who remain symptomatic despite treatment with at least approved doses of second generation $H_1$ antihistamines.

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

## 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 CSU showed that benralizumab was well-tolerated, with no AEs attributable to treatment with benralizumab (Bernstein and Singh 2019).

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

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

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

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

Based on the results of previous studies, expected benefits of benralizumab over placebo include clinically significant improvements in symptoms of CSU disease activity and health-related quality of life of patients with CSU despite treatment with $H_1$ antihistamines.

The benefit/risk assessment for benralizumab in patients with CSU based on results from the previous clinical experience in other eosinophil-driven diseases (asthma and hypereosinophilic syndrome) and the Phase 2a study is expected to continue to be favourable. Based on the extensive safety data already available, the benefit risk profile in patients with CSU is

expected to be commensurate with that observed in the benralizumab asthma pivotal trials. Risk minimisation 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 minimisation 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.

**Table 4 Study Objectives**

| **Primary Objective:** | **Estimand description / Endpoints** |
|---|---|
| To determine the clinical efficacy of benralizumab compared to placebo in patients with CSU who are symptomatic despite the use of $H_1$ antihistamine treatment. | • Population: Full Analysis Set:<br>• Endpoint: Change from baseline in ISS7 at Week 12<br>• Intercurrent events: All data up to Week 12 will be included regardless of randomised treatment adherence or rescue medication received<br>• Summary measure: difference in least squares mean change from baseline in ISS7 at Week 12 between benralizumab and placebo |
| **Secondary Objectives:** | **Endpoint/variable:** |
| To evaluate the effect of benralizumab compared to placebo on supportive measures of clinical efficacy in patients with CSU who are symptomatic despite the use of $H_1$ antihistamine treatment. | • Key secondary endpoint: change from baseline in UAS7 at Week 12[a]<br>• Change from baseline in UAS7 at Week 24<br>• Proportion of responders (UAS7 $\leq$ 6) at Week 12<br>• Change from baseline in HSS7 at Week 12<br>• Time to $\geq$ 5 point decrease (clinically relevant decrease) in ISS7<br>• Proportion of participants with complete UAS7 response (UAS7 = 0) at Week 12<br>• Measures of angioedema activity at Week 12 in participants with angioedema at baseline<br>• Change from baseline in UCT at Week 12 |
| To evaluate the effect of benralizumab on patient-reported health-related quality of life measures in patients with CSU who are symptomatic despite the use of $H_1$ antihistamine treatment. | • Change from baseline in CU-$Q_2$oL at Weeks 12 and 24<br>• Change from baseline in DLQI at Weeks 12 and 24 |

**Table 4 Study Objectives**

| | |
|---|---|
| To assess the PK and immunogenicity of benralizumab 30 mg and 60 mg in patients with CSU who are symptomatic despite the use of $H_1$ antihistamine treatment. | • Serum benralizumab concentration<br>• ADA |
| To evaluate the longer-term effect of benralizumab compared to placebo at Week 24 on measures of clinical efficacy in patients with CSU who are symptomatic despite the use of $H_1$ antihistamine treatment. | • Change from baseline in ISS7 at Week 24<br>• Change from baseline in UAS7 at Week 24<br>• Proportion of responders (UAS7 $\leq$ 6) at Week 24<br>• Change from baseline in HSS7 at Week 24<br>• Proportion of participants with complete UAS7 response (UAS7 = 0) at Week 24<br>• Measures of angioedema activity at Week 24 in participants with angioedema at baseline<br>• Change from baseline in UCT at Week 24 |
| To evaluate the efficacy of administration of benralizumab Q8W versus Q4W up to Week 52 in patients with CSU who are symptomatic despite the use of $H_1$ antihistamine treatment. | Change from baseline in ISS7 at Week 52<br>Other supportive efficacy assessments at Week 52 in participants on a Q8W dosing regimen compared to those on a Q4W dosing regimen. |
| **Safety Objective:** | **Endpoint/variable:** |
| To assess the safety and tolerability of benralizumab in patients with CSU who are symptomatic despite the use of $H_1$ antihistamine treatment. | Safety and tolerability will be evaluated in terms of AEs, vital signs, and clinical laboratory values.<br>Assessments related to AEs cover:<br>• Occurrence/frequency<br>• Relationship to IP as assessed by Investigator<br>• Intensity<br>• Seriousness<br>• Death<br>• AEs leading to discontinuation of IP<br><br>Vital signs parameters include systolic and diastolic blood pressure, and pulse, as well as respiration rate, body temperature, body weight, and height.<br>Assessments related to vital signs cover:<br>• Observed value<br>• Absolute and percent change from baseline values over time |
| **Tertiary/exploratory** | **Endpoint/variable:** |
| To evaluate the effect of benralizumab compared to placebo on healthcare resource utilisation due to CSU in patients with CSU who are symptomatic despite the use of $H_1$ antihistamine treatment. | Rate of CSU-related healthcare resource utilisation during the study |
| To evaluate the effect of benralizumab compared to placebo on overall severity of disease patients with CSU who are symptomatic despite the use of $H_1$ antihistamine treatment. | Change from baseline in PGI-S score at Week 12 and at Week 24 |

**Table 4 Study Objectives**

| | |
|---|---|
| To evaluate the mechanism of action of benralizumab in patients with CSU who are symptomatic despite the use of $H_1$ antihistamine treatment. | CCI [redacted] |
| CCI [redacted] | [redacted] |
| To evaluate the effect of benralizumab compared to placebo on general health status in patients with CSU who are symptomatic despite the use of $H_1$ antihistamine treatment. | Change from baseline in EQ-5D-5L domain and VAS scores |

[a] The key secondary endpoint will use the same treatment policy strategy estimand as outlined for the primary endpoint. All other estimands will be detailed fully in the SAP.

ADA, anti-drug antibodies; AE, adverse event; CU-$Q_2$oL, Chronic Urticaria Quality of Life Questionnaire; CSU, chronic spontaneous urticaria; DLQI, Dermatology Life Quality Index; EQ-5D-5L, European Quality of Life-5 Dimensions; HSS7, hives severity score over 7 days; ISS7, itch severity score over 7 days; IP, investigational product; PGI-S, Patient Global Impression of Severity; PK, pharmacokinetics; Q4W, every 4 weeks; Q8W, every 8 weeks; RNA, ribonucleic acid; SAP, Statistical Analysis Plan; UAS7, Urticaria Activity Score over 7 days; UCT, Urticaria Control Test; VAS, visual analogue scale.

# 4 STUDY DESIGN

## 4.1 Overall Design

This is a Phase 2b multinational, randomised, double-blind, parallel-group, 24-week placebo-controlled study with 28-week extension to evaluate the efficacy and safety of benralizumab in male and female participants ≥ 18 years of age with CSU refractory to standard of care treatment which may include second generation $H_1$ antihistamines (at approved or up to 4 times approved doses) as monotherapy or in combination with leukotriene receptor antagonists and/or $H_2$ blockers. The study is designed to evaluate 2 induction doses of benralizumab (60 mg and 30 mg) compared to placebo, and a comparison of maintenance dosing regimens (Q8W versus Q4W) in the 28-week extension period.

This study consists of the following consecutive periods:

- A 10-day to 4-week run-in period
- A 24-week placebo-controlled, double-blind treatment period (comprising an initial 12-week 'induction dose' period followed by an additional 12-week dosing period)
- A 28-week blinded-to-dosing regimen extension period for maintenance treatment.

Following informed consent, all eligible participants will enter a run-in period of 10 days to 4 weeks during which inclusion/exclusion criteria will be assessed, medical history taken, and complete physical exam will be conducted (Visit 1; Table 2). Potentially eligible participants will remain on a stable, locally-approved dose of their $H_1$ antihistamine treatment throughout the run-in period. Participants will be provided with a handheld device to respond to PRO questionnaires during the study.

Following the 10 days to 4-week run-in period, approximately 160 participants will be randomised at Visit 2 stratified by region, in a ratio of 3:3:3:3:4 (n=30:30:30:30:40), respectively, to one of the following 5 treatment sequences (refer also to Figure 1 and Figure 2):

- **Benralizumab 60 mg Q4W** until Week 12, **30 mg Q4W** until Week 24, and **30 mg Q8W** during the extension period until Week 52 (n = 30)
- **Benralizumab 60 mg Q4W** until Week 12, **30 mg Q4W** until Week 24, and **30 mg Q4W** during the extension period until Week 52 (n = 30)
- **Benralizumab 30 mg Q4W** until Week 12, **30 mg Q4W** until Week 24, and **30 mg Q8W** during the extension period until Week 52 (n = 30)
- **Benralizumab 30 mg Q4W** until Week 12, **30 mg Q4W** until Week 24, and **30 mg Q4W** during the extension period until Week 52 (n = 30)
- **Placebo Q4W** until Week 24, **benralizumab 30 mg Q4W** until Week 36, and **30 mg Q8W** until Week 52 (n = 40).

Up to Week 24, ie, prior to start of the extension period evaluating Q4W and Q8W dosing regimens, participants in both benralizumab 60 mg initial dose treatment arms will be considered as a single treatment group (total n = 60), as will participants in both benralizumab 30 mg initial dose treatment arms (total n = 60).

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

Throughout the study, participants will be required to maintain stable doses of their pre-randomisation $H_1$ antihistamine treatment (refer to Section 6.5.1). Participants will be permitted to use additional doses (up to 4 x recommended dose per day) of the pre-randomization $H_1$ antihistamine on an as-needed basis when symptoms are more severe, and use should be documented in the electronic patient-reported outcome (ePRO) device. A switch of the rescue medication for an individual participant is not permitted; refer to Section 6.5.3.

The primary database lock (DBL) is targeted to occur when all participants have completed the double-blind 24-week treatment period (Figure 2). The final DBL will occur when all participants have completed the 52-week treatment period and the Week 60 follow-up visit and/or the IPD/EOT visit (Table 2). An additional analysis between the primary and final

analyses may be performed to report data accumulated during the extension part of the study if needed to support end of Phase 2 decision making. Participants and investigators will remain blinded to the treatment and regimen (refer to Section 4.1.2) until the final DBL.

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

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

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

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

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

- Obtaining [consent/reconsent] for the mitigation procedures (note, in the case of verbal [consent/reconsent], the Informed Consent Form (ICF) should be signed at the participant's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated study physician.
- Home or Remote visit: Performed by a site qualified Health Care Professional (HCP) or HCP provided by a third-party vendor (TPV).
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home Investigational Product (IP) administration: Performed by a site qualified HCP, 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 patient testing is performed due to the public health crisis the results may be documented for this study.

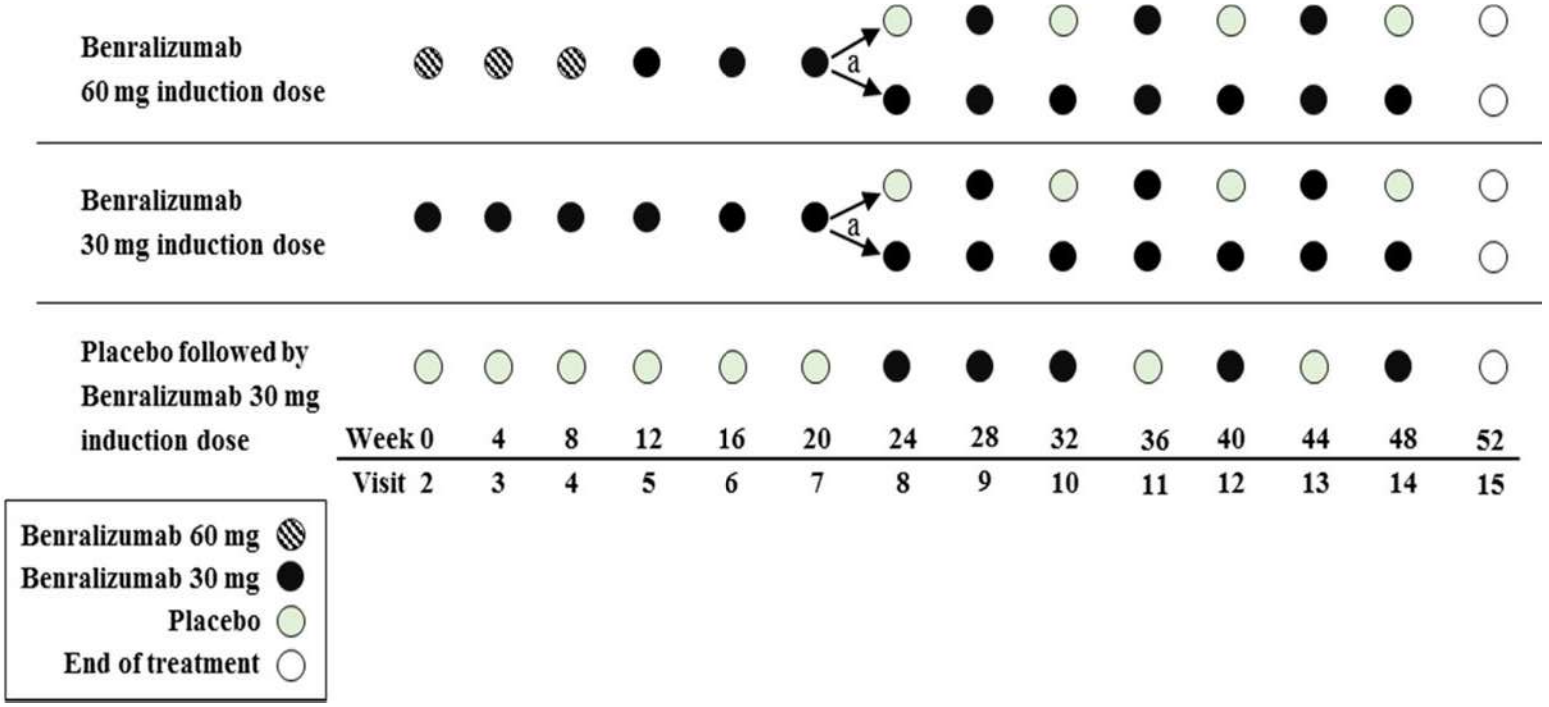
For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix F.

### 4.1.2 Investigational Product Dosing Regimen

Participants who meet entry criteria will be randomised 3:3:3:3:4 by the interactive voice/web response system (Interactive Voice Response System [IVRS]/Interactive Web Response System [IWRS]) to one of the 5 treatment sequences described in Section 4.1.

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

**Figure 3 Investigational Product Administration**




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

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

**Dosing Regimen at Visits 2, 3, and 4 (Initial Double-blind 12-week Treatment Period)**

All participants will receive randomised double-blind study medication Q4W at Visits 2 ,3 and 4 (ie, Weeks 0, 4, and 8; Figure 3).

**Dosing Regimen at Visits 5, 6, and 7**

Participants randomised to receive either 60 mg or 30 mg benralizumab during the initial 12-week period will receive 30 mg benralizumab Q4W at Visits 5, 6 and 7 (ie, Weeks 12, 16 and 20; Figure 3).

Participants receiving placebo will continue to receive placebo (Figure 3).

**Dosing Regimen at Visits 8 Through 14**

At Week 24 (Visit 8), participants initially randomised to benralizumab 60 mg or benralizumab 30 mg will receive benralizumab 30 mg Q4W or Q8W according to their original randomisation at Week 2. Participants randomised to the Q8W regimen will receive placebo at Week 24 and benralizumab 30 mg at Week 28 (Figure 3).

At Weeks 24, 28, and 32 (ie, Visits 8, 9 and 10), participants initially randomised to placebo will receive benralizumab 30 mg Q4W. At Week 36 (ie, Visit 11), participants randomised initially to placebo will receive benralizumab 30 mg Q8W; these participants will receive placebo at Week 36 and benralizumab 30 mg at Week 40 (Visit 12) (Figure 3).

Participants transitioned to the benralizumab 30 mg Q8W dosing regimen will remain on the Q8W dosing regimen. Participants will continue to receive SC injections Q4W at the study site visits; thus, participants receiving benralizumab 30 mg Q8W will receive placebo at every other site visit (Figure 3).

The final dose of benralizumab or placebo will be administered at Week 48 (Visit 14).

## 4.2 Scientific Rationale for Study Design

This is a Phase 2b study designed to evaluate the efficacy and safety of benralizumab in the treatment of participants with CSU.

This study's inclusion/exclusion criteria and run-in period are designed to capture a population appropriate for treatment with benralizumab, that is participants with chronic spontaneous urticaria that are symptomatic despite treatment with $H_1$ antihistamine. Both patient-reported symptoms and prior diagnosis of disease will be captured to ensure the participant population is appropriate for the study and to establish baseline measurements for determining clinical effect.

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

considered the gold standard for demonstrating efficacy and safety without bias in a clinical trial. The duration of the placebo-controlled period is limited to 24 weeks as it is considered the maximum duration of treatment with placebo that is ethically appropriate in this disease.

The primary endpoint chosen is change in (itch severity score) ISS7 score from baseline to Week 12. The ISS7 is the itch subscore of UAS7. UAS7 is the commonly used diary-based patient-reported outcome measure that assesses the severity of the key sign (wheals) and symptom (pruritus) of CSU. UAS7 is recommended by international guidelines to be used in clinical practice to determine disease activity and response to treatment. The ISS7 is considered to be more clinically relevant than the UAS7 because improvements in UAS7 could potentially be driven by decreasing number of hives without corresponding improvement in symptoms of itch. Therefore, ISS7 is considered to directly assess a benefit to participants and has been used in clinical trials for the registration of other products for the treatment of CSU. Onset of effect is important for patients, and the assessment at 12 weeks has been chosen as primary analysis based on results of a Phase 2a study that showed improvements in skin-related symptoms and eosinophil depletion in skin biopsies after 12 weeks of treatment with benralizumab (Kuang et al 2019). Additional secondary endpoints are included to provide a complete picture of the efficacy achieved with benralizumab treatment. Assessments of the benefits of benralizumab at 24 weeks is included to determine if efficacy observed in the initial 12-week period is sustained through Week 24.

The 28-week extension period will provide an opportunity to evaluate the effect of a Q8W maintenance dosing regimen versus that of the Q4W dosing regimen for comparison over the longer-term treatment period. To provide a preliminary evaluation of the efficacy and safety of the approved severe asthma dosing regimen when administered to patients with CSU, participants in the placebo group during the previous 24-week treatment period will switch to benralizumab 30 mg treatment and will receive 3 doses Q4W followed by Q8W dosing for the duration of the extension period.

## 4.3 Justification for Dose

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

The approved dosing regimen of benralizumab in severe asthma is 30 mg Q4W for the first 3 doses, followed by 30 mg Q8W thereafter. In adult and adolescent patients with severe asthma

(SIROCCO [Bleecker et al 2016] and CALIMA [FitzGerald et al 2016]), treatment with benralizumab 30 mg Q8W and Q4W, resulted in near complete blood eosinophil 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 skin and GI tissue of patients with varied clinical subtypes of hypereosinophilic syndrome where patients have higher blood eosinophils and significant organ manifestations of eosinophilic inflammation (Kuang et al 2019).

Given that it is a goal of this phase 2 study to evaluate the appropriate induction dose of benralizumab based on time of onset and robustness of effectiveness in treatment of CSU, two different induction doses have been selected. Although efficacy of benralizumab 30 mg in the treatment of CSU has been observed in a study where patients received a total of 3 doses only (Bernstein and Singh 2019), it is recognised that the majority of benralizumab data in tissues relates to blood and lung. Therefore, for this current study involving effects in this skin disease, it is considered necessary and appropriate to evaluate a higher initial dose of 60 mg in addition to the 30 mg dose as currently approved for treatment of severe asthma. Thus, this Phase 2b study will compare 2 induction doses of benralizumab, 30 mg (administered as one SC injection plus one SC injection of matching placebo) and 60 mg (administered as 2 SC injections) versus placebo (administered as 2 SC injections) during the initial 12-week double-blind treatment period to evaluate time to onset of symptom relief. From Week 12 until Week 24, participants randomised to benralizumab will continue to receive double-blind study medication 30 mg Q4W to observe for any differential effects beyond the initial 60 mg and 30 mg induction doses. These participants will subsequently either transition to 30 mg Q8W dosing regimen or remain on a 30 mg Q4W regimen during the blinded extension period to evaluate the effect of a Q8W maintenance dosing regimen relative to Q4W over the longer-term treatment period.

### 4.4 End of Study Definition

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

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

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

## 5 STUDY POPULATION

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

Each participant should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be randomised 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. "Randomised" participants are defined as those who undergo randomisation and receive a randomisation 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/Gender**

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

2 Adult participants ≥ 18 years of age at the time of signing the Informed Consent Form (ICF).

**Type of Participants and Disease**

3 Physician-confirmed diagnosis of CSU (also known as chronic idiopathic urticaria) for at least 6 months prior to screening (Visit 1).

4 Presence of pruritus and wheals for at least 6 consecutive weeks prior to screening (Visit 1), despite receiving standard of care, which may include second generation $H_1$ antihistamines (at approved or up to 4-times approved doses) as monotherapy or in combination with LTRAs and/or $H_2$ blockers.

5 Symptomatic during run-in, defined by the following:

(a) UAS7 total score of ≥ 16 with an ISS7 of ≥ 8, during the 7 days prior to randomisation (Visit 2)

(b) In-clinic UAS total score of ≥ 4 on at least one of the screening days.

6 Willing to use a second-generation $H_1$ antihistamine at the approved dose and as monotherapy (Section 6.5.1) from the screening visit (Visit 1) until the end of the study.

7 Participants must complete daily PRO assessments and meet the following compliance criteria:

(a) Complete at least 80% of daily PRO assessments between Visit 1 and Visit 2 and

(b) Complete at least 6 of 7 daily PRO assessments in the 7 days prior to Visit 2.

8 Compliance with the locally-approved dose of antihistamine (see Section 6.5.1), maintained at randomisation.

**Reproduction**

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

Highly effective methods of birth control include:

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

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

(c) Intrauterine device.

(d) Intrauterine hormone-releasing system.

(e) Bilateral tubal occlusion or ligation.

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

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

10 Females not of childbearing potential are defined as females who are either permanently sterilised (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 randomisation without an alternative medical cause. The following age-specific requirements apply:

(a) 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, the participant should be treated as a FOCBP.

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

## 5.2 Exclusion Criteria

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

**Medical Conditions**

1 Participants with predominant inducible urticaria, ie, urticaria that is predominantly due to a clearly defined stimulus (eg, pressure [dermographism], delayed pressure, cold, heat, sunlight, vibration, water, physical exercise, or increased body temperature [cholinergic]).

2 Participants with diseases, other than chronic urticaria, with urticaria or angioedema symptoms such as urticaria vasculitis, erythema multiforme, cutaneous mastocytosis (urticaria pigmentosa) and hereditary or acquired angioedema (eg, due to C1-inhibitor deficiency). Additionally, any other skin disease associated with chronic itching and/or skin lesions that, in the investigators opinion, might influence the study evaluations and results (eg, atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus, etc.).

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

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

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

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

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

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

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

5 History of anaphylaxis to any biologic therapy or vaccine.

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

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

8 Current active liver disease:

   (a) Chronic stable hepatitis B and C (including positive testing for hepatitis B surface antigen [HBsAg] 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, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice, or cirrhosis.

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

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

**Prior/concomitant Therapy**

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

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

**Other**

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

13 Receipt of any marketed (eg, omalizumab) or investigational biologic within 4 months or 5 half-lives prior to the date informed consent is obtained, whichever is longer.

14 Receipt of live attenuated vaccines 30 days prior to the date of randomisation

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

16 Previously received benralizumab (MEDI-563, FASENRA)

17 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

18 Planned elective major surgical procedures during the conduct of the study

19 Previous randomisation in the present study

20 Concurrent enrollment in another clinical trial

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

22 For females only: Currently pregnant, breastfeeding, or lactating females

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

## 5.3 Lifestyle Considerations

Females 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 9, 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 eCRF. This reason for study withdrawal is only valid for screen failures and not randomised participants.

### 5.4.1 Re-screening

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

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

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

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

# 6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to 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 Interventions 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 30 mg/mL solution (20 mM L-histidine/L-histidine hydrochloride monohydrate, 0.25 M trehalose dihydrate and 0.006% [w/v] polysorbate 20, pH 6.0) for injection in APFS, 1 mL fill volume | Matching placebo solution (20 mM L-histidine/L-histidine hydrochloride monohydrate, 0.25 M trehalose dihydrate and 0.006% (w/v) polysorbate 20, pH 6.0) for injection in an APFS, 1 mL fill volume |
| **Route of Administration** | Subcutaneous injection | Subcutaneous injection |
| **Dosing Instructions** | Benralizumab active solution will be administered subcutaneously to participants by health care 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 Labelling** | Study intervention will be provided in an APFS.<br>Each syringe will be labelled in accordance with GMP Annex 13 and per country regulatory requirement. | Study intervention will be provided in an APFS.<br>Each syringe will be labelled in accordance with GMP Annex 13 and per country regulatory requirement. |

APFS, accessorised pre-filled 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 [redacted], PK, and ADA samples and on-site PRO assessments, should be completed prior to IP administration.

Prior to each IP administration:

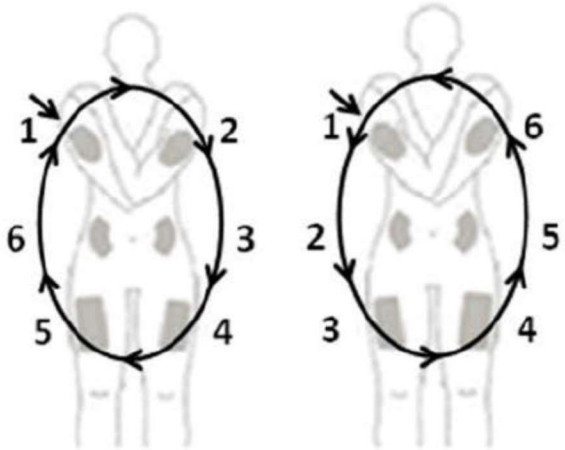
- For FOCBP, the urine pregnancy test must be performed; IP will be administered only when the result of the test is negative (see Section 8.2.1.1).
- Investigator, or designee, will evaluate the participant's condition for potential contraindications for dosing (see Section 6.5.4).
- Investigator, or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

**IP Administration**

The IP will be administered SC as 2 single injections via the accessorised prefilled syringe (APFS) by the Investigator, or designee during the initial 12-week treatment period; a single SC injection will be administered thereafter (Section 4.1.2).

During the initial 12-week treatment period, the 2 injections 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. Suggested injection site rotation sequence is presented below (see Figure 4). The injection site must be documented in the source at each treatment visit and recorded in the electronic case report form (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 4 Injection Sites and Examples of Rotation Scheme**




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

At Visits 2 and 3, appropriate participants and/or their caregiver may be trained in IP administration by the investigator or designee. If not possible at Visits 2 and 3 this may occur at later visits. This training will be provided to have participants prepared in case telemedicine visits may be required secondary to study disruptions as described in Section 4.1.1. Participants may still participate in the study if they do not consent to this training.

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

**After IP Administration**

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

### 6.1.2 Investigational Product Administration Re-scheduling

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

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

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

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

It is recommended that the AstraZeneca 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.

Re-scheduled 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 re-scheduled along with IP dose.

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

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

## 6.2 Preparation/handling/storage/accountability

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

Only participants enrolled in the study may receive study treatment and only authorised 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 labelled storage conditions with access limited to the Investigator and authorised 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 randomised to the study may receive IP and only authorised 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 the IVRS/IWRS (please refer to IVRS/IWRS 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 authorised 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).

A 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 study monitor to initiate a product complaint process according to applicable guidelines.

## 6.3 Measures to Minimise Bias: Randomisation and Blinding

### 6.3.1 Randomisation

All participants will be centrally assigned to randomised IP using an IVRS/IWRS. Randomisation codes will be assigned strictly sequentially in each stratum as participants become eligible for randomisation. Randomisation will be stratified by region. Participants who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be randomised or receive IP. There can be no exceptions to this rule. Participants may be rescreened under certain conditions (Section 5.4.1).

If a participant withdraws from the study, then his/her enrollment/randomisation code cannot be reused unless the participant is rescreened. Withdrawn participants will not be replaced.

### 6.3.2 Blinding

Benralizumab and placebo will not be visually distinct from each other. All packaging and labelling 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, AstraZeneca or the 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. Since the 60 mg treatment requires 2 SC injections, all participants will receive 2 injections during the initial 12-week treatment period (ie, at Visits 2, 3, and 4) to maintain the blind:

- Participants randomised to the benralizumab 30 mg group will receive one benralizumab 30 mg injection and one placebo injection
- Participants randomised to the benralizumab 60 mg group will receive 2 benralizumab 30 mg injections
- Participants randomised to the placebo group will receive 2 placebo injections

All participants will receive one SC injection at Visit 5 through Visit 16 (End of Treatment [EOT]). During the extension period, participants receiving benralizumab 30 mg Q8W will receive a placebo injection at every other site visit; thus, the investigational staff, participants, and AstraZeneca will remain blinded to the participant's dosing regimen (refer to Section 4.1.2 for details on dosing regimens).

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

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

- Those generating the randomisation list
- Personnel at the IWRS/IVRS company
- The AstraZeneca supply chain department
- Participant safety department at AstraZeneca
- Bioanalytical laboratory performing the PK and ADA sample analysis

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

**Maintaining the Blind to the Participant's Blood Eosinophil and Basophil Counts and Blood eosinophil-derived neurotoxin (EDN) Level**

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

- Haematology assessments will be conducted by a central laboratory. Post-randomisation (beginning at Visit 2, Week 0), AstraZeneca, study site personnel, and participants will be blinded to the eosinophil and basophil counts. The absolute eosinophil, basophil, and monocyte counts, and percentages will be redacted from the haematology 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 haemoglobin is desired, the Investigator should avoid ordering a complete blood cell count with a differential count.
- In cases where the Investigator requires an eosinophil, basophil, or monocyte count for managing safety issues, he/she may order these tests as per regular site practice. AstraZeneca should be notified of all such cases without being revealed absolute eosinophil counts, absolute basophil counts, or absolute monocyte counts.
- Site staff who are directly involved in the participant's management should remain blinded to any eosinophil, basophil, and monocyte results included as part of an outside laboratory report or electronic medical record. To help ensure this, each investigational site will designate an individual (eg, administrator or another ancillary person) not directly involved in participant management, to receive and redact any eosinophil, basophil, and monocyte results prior to the report being handed over to the site staff involved in the participant's management and prior to filing the laboratory report as a source document. Similarly, eosinophil, basophil, and monocyte results must be redacted from all communications with AstraZeneca.
- CCI [redacted]

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

### 6.3.3 Methods for Unblinding

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

The randomisation code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomisation. The Investigator will document and report the action to AstraZeneca, without revealing the participant's treatment randomisation to the AstraZeneca representative 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 Study Physician to discuss the medical emergency and the reason for revealing the actual treatment received by that participant;

however, this may not be mandatory and should not cause any delay in unblinding in case of emergencies. The treatment assignment will be unblinded by the Investigator through IVRS/IWRS.

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. Randomisation 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 Clinical Study Protocol (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

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 long-acting $H_1$ antihistamines
  - All other medications taken for any reason in the 3 months prior to Visit 1 (except for prior biologic medication[s], which will be collected regardless of the time of administration)
  - Concomitant treatments given during the study (at each study visit).

### 6.5.1 Background Medication

From Visit 1 and throughout the study, participants will be required to maintain stable, locally approved second generation $H_1$ antihistamine treatment for CSU. The permitted doses allowed during the study are:

- Cetirizine hydrochloride tablets, 5 or 10 mg once daily (QD)
- Levocetirizine dihydrochloride 2.5 or 5 mg QD
- Fexofenadine 60 mg twice per day or 180 mg QD,
- Loratadine 10 mg QD
- Desloratadine 5 mg QD.

### 6.5.2 Other Concomitant Treatment

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

### 6.5.3 Rescue Medication

Throughout the study (ie, from the screening visit to end of treatment visit), participants are permitted to take additional doses of pre-randomization background medication on days on which symptoms are intolerable. Increase in background antihistamine will be allowed up to four times the labelled dose as permitted by local regulations and as directed by the investigator. A switch of the rescue medication for an individual participant is not permitted.

The participants will be instructed on the use of rescue medication for CSU symptoms that are severe enough to impact normal daily activities and how rescue use should be recorded in the ePRO device.

The number of tablets of the rescue medication taken is recorded in the handheld ePRO device as part of the UPDD.

### 6.5.4 Restrictions

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

- Immunosuppressive medication including corticosteroids (other than for treatment for AEs where no alternative treatment is available); see 'angioedema' below.
  - Topical immunosuppressive medications for non-CSU related dermatological conditions (eg, poison ivy) may be permitted for short term use (7 days).
- Topical antihistamines.

- Intravenous and/or oral first generation antihistamines (eg, cetirizine hydrochloride IV injection and diphenhydramine); see 'angioedema' below.
- Leukotriene inhibitors or $H_2$ blockers as treatments for CSU are prohibited within 7 days prior to Day -14.
- Regular (daily/every other day) doxepin (oral) use is prohibited within *14 days* prior to Day -14.
- Plasmapheresis is prohibited within *30 days* prior to screening.
- Receipt of live attenuated vaccines is not allowed within 30 days prior to randomisation, during the treatment period, 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 within 4 months or 5 half-lives (whichever is longer) prior to randomisation, during the treatment period, and is not ideally recommended within 4 months or 5 half-lives (whichever is longer) after the last dose of the IP.
- Other IPs for 30 days prior to randomisation and during the study period.

Oral first-generation antihistamines may also be necessary as treatment for clinically significant CSU-related angioedema. Treatment for life threatening CSU-related angioedema, posing a risk to the airways may include systemic glucocorticoids and/or IV antihistamines. These participants may require discontinuation of IP and should be discussed with study physician/sponsor.

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

## 6.6 Dose Modification

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

## 6.7 Intervention After the End of the Study

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

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 Discontinuation of Study Intervention

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

Discontinuation from IP does NOT automatically lead to a complete withdrawal from the study. Participants discontinuing from IP are strongly encouraged to continue in the study up to the study completion (Visit 17, Week 60) as described in Section 7.1.1.

Participants will be discontinued from IP in the following situations:

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

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 Early Discontinuation of Study Intervention and at End of Study

A participant who decides to discontinue IP should always be asked about the reason(s) and the presence of any AEs. The reason for discontinuing treatment and the date of last IP administration should be recorded in the eCRF. Participants permanently discontinuing IP administration should be given locally available standard of care therapy, at the discretion of the Investigator. Participants who discontinue IP at any time will be allowed to modify their antihistamine background therapy and still be followed at study visits. Discontinuation of IP will be captured in the eCRF.

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 Early Discontinuation of Study Intervention

All participants who prematurely discontinue IP should return to the study site for 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.

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

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

#### 7.1.1.2 Discontinuation of Study Intervention Upon Notification of Closure of Study

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

### 7.1.2 Procedures for Handling Incorrectly Enrolled or Randomised Participants

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

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

If the agreed decision is to discontinue IP, participants should be encouraged to remain in the study and continue to be followed-up until the end of the treatment period.

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

## 7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, the IPD visit should be conducted. See the SoA (Table 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.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- 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 AstraZeneca or their representative.

Participants who withdraw from the study will return the handheld ePRO device.

### 7.2.1 Discontinuation or Suspension of the Whole Study Program

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

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

## 7.3 Lost to Follow-up

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

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

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

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

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

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

The participant will be classified as lost to follow-up only if he/she has failed to return for the required study visits and his/her vital status remains unknown at the end of the study, 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 summarised in the SoA (Table 2).

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

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

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

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

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

Procedures conducted as part of the participant's routine clinical management (eg, blood test, echocardiography, biopsy, etc.) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

## 8.1 Efficacy Assessments

Participants will complete all PRO assessments using a handheld device. The handheld device will be the only accepted source of PRO data.

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

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

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

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

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

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

### 8.1.1 Urticaria Patient Daily Diary (UPDD)

The Urticaria Patient Daily Diary (UPDD) will be completed twice daily (morning and evening; Table 3) to capture key measures of urticaria disease activity. Compliance with twice-daily completion of the UPDD will be reviewed at every visit (Table 2).

Participants will be asked to document twice a day (morning and evening) the intensity of itch and number of hives they experienced over the previous 12 hours. The criteria used to define itch severity score (ISS) and hives severity score (HSS), respectively, on a 0- to 3-point scale are shown in Table 6.

**Table 6 Assessment of CSU disease activity in study participants**

| Score | Itch intensity | Intensity (number) of hives |
|---|---|---|
| 0 | None | None |
| 1 | Mild | Mild (1 - 6 hives/12 hour) |
| 2 | Moderate | Moderate (7 - 12 hives/12 hour) |
| 3 | Severe | Intense (> 12 hives/12 hour) |

Scoring criteria are as defined in omalizumab Study Q4882g (EUDRACT: 2010-022785-27).

The mean of the morning and evening itch scores is taken as the ISS for the day. The mean of the morning and evening hive scores is taken as the HSS for the day. The sum of the HSS and the ISS for the day is the urticaria activity score (UAS) for the day.

ISS7 is the sum of ISS scores for the previous 7 days. UAS7 is the sum of UAS for the previous 7 days, ie, the sum of HSS7 and ISS7. HSS7 is the sum of HSS scores for the previous 7 days.

The minimum UAS7 is 0 and the maximum is 42. The baseline UAS7 will be the sum of the UAS during the 7 days prior to randomisation. The UAS7 at Week 12 will be the sum of the daily UAS during the previous 7 days.

In addition to the itch and hives questions, the UPDD also includes a daily yes/no question asking whether the participant experienced angioedema. If yes, the participant is asked a follow-up question about how they treated the swelling.

### 8.1.2 Urticaria Control Test (UCT)

Urticaria disease control will be assessed by the Urticaria Control Test (UCT). The UCT is the first valid and reliable tool to assess disease control in participants with chronic urticaria. It has a retrospective approach using a recall period of 4 weeks and responses on 4-point Likert scales.

### 8.1.3 Chronic Urticaria Quality of Life Questionnaire (CU-Q$_2$oL)

The Chronic Urticaria Quality of Life Questionnaire (CU-Q$_2$oL) is a 23-item assessment of CSU-specific health-related quality of life (Baiardini et al 2005). Participants are asked to rate their CSU symptoms and the impact of their symptoms on several domains: Pruritus, Swelling, Impact on Life Activities, Sleep Problems, Limits, and Looks. Both the overall score and domain scores will be calculated.

### 8.1.4 Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (DLQI) is a 10-item assessment of dermatology-specific health-related quality of life (Finlay and Khan 1994). Participants are asked to rate their symptoms and the impact of their symptoms on several domains: Symptoms and Feelings, Daily Activities, Leisure, Work and School, Personal Relationships, and Treatment. Both the overall score and domain scores will be calculated.

### 8.1.5 Patient Global Impression of Severity (PGI-S)

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

### 8.1.6 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 analogue scale (VAS), where the participant will be asked to rate current health status on a scale of 0 to 100, with 0 being the worst imaginable health state.

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### 8.1.8 Patient-Reported Experience

Participants will be asked to respond in writing (free text) to 3 open-ended questions about their experience with CSU and their study intervention. The assessment will be conducted

during the site visits specified in Table 2, using a provisioned tablet to access the secure web form.

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

## 8.2 Safety Assessments

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

### 8.2.1 Clinical Safety Laboratory Assessments

Table 7 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, haematology and urinalysis will be performed at a central laboratory.

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

**Table 7 Laboratory Safety Variables**

| Clinical chemistry | | Haematology | Urinalysis |
|---|---|---|---|
| Alkaline phosphatase | Gamma-GT (gamma-glutamyl transpeptidase) | Haematocrit | Appearance |
| ALT (alanine aminotransferase) | Glucose | Haemoglobin | Blood |
| AST (aspartate aminotransferase) | Phosphorus | Mean corpuscular volume (MCV) | Color |
| BUN (blood urea nitrogen) | Potassium | Platelet count | Ketones |

**Table 7 Laboratory Safety Variables**

| Clinical chemistry | | Haematology | Urinalysis |
|---|---|---|---|
| Calcium | Sodium | Red blood cell (RBC) count | Microscopy including White blood cell (WBC)/high power field (HPF), RBC/HPF |
| Chloride | Total bilirubin | WBC count (absolute and differential) [a] | pH |
| $CO_2$ (carbon dioxide) [b] | Uric acid | | Specific gravity |
| Creatinine | Creatine kinase | | |
| TSH (Thyroid Stimulating Hormone) | | | |

[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.

#### 8.2.1.1 Pregnancy Tests

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

- Serum beta-human chorionic gonadotropin (HCG): To be performed for all female participants at Visit 1 except for those who are NOT of childbearing potential as defined in inclusion criterion 10. This test is to be sent to and analysed at the central laboratory.
- FSH: To be performed at Visit 1 only for female participants < 50 years who have been amenorrhoeic for ≥ 12 months prior to the planned date of randomisation to confirm postmenopausal status. This test is to be sent to and analysed at the central laboratory; all females should be treated as pre-menopausal until results are received from the central laboratory.
- Urine HCG (dipstick): To be performed locally at the study site before each IP administration (starting at Visit 2 through the EOT), and at IPD visits for all female participants except for those who are NOT of childbearing potential as defined in inclusion criterion 10. A positive urine test result must be confirmed with serum beta-HCG.

#### 8.2.1.2 Serology

Hepatitis B surface antigen and hepatitis C antibody tests will be assessed in accordance with the SoA (Table 2); test to be performed at the central laboratory.

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

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

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

### 8.2.2 Physical Examinations

Physical examinations (complete or brief), including height (only at baseline) and weight, will be conducted in accordance with the schedule provided in Table 2. Baseline data will be collected at the randomisation 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: 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 general appearance, abdomen, cardiovascular, and respiratory system. For the brief physical examination, only information on whether the assessment was performed or not is to be recorded.

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

### 8.2.3 Vital Signs

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

### 8.2.4 Electrocardiograms

Single 12-lead electrocardiogram (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 authorised delegate will be responsible for the overall interpretation and determination of clinical significance of any potential ECG findings. The ECG printouts will be signed and dated by the Investigator and stored at the study site. Any findings will be recorded in the eCRF.

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

## 8.3 Adverse Events and Serious Adverse Events

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

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

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

### 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 AstraZeneca 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

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 hospitalisation
- 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 summarised 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, 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, anaemia versus low haemoglobin 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 CSU (eg, pruritis, wheals, and angioedema). Events which are unequivocally due to CSU

should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the IP.

CSU-related angioedema is episodic and can last for hours or days with recurrence. It is characterized by several features (Zuberbier et al 2018):

- a sudden, pronounced erythematous or skin coloured swelling of the lower dermis and subcutis or mucous membranes,
- sometimes pain, rather than itch.
- a resolution slower than that of wheals (can take up to 72 hours).

Angioedema related to CSU may be treated with rescue antihistamines (Section 6.5.3). Participants with angioedema with airway compromise may be treated with IV antihistamines and/or systemic steroids as indicated at the discretion of the investigator. The investigator will also need to evaluate whether the angioedema was related to CSU or an anaphylactic reaction (refer to Appendix E). Actions and/or treatments related to angioedema occurrences will be documented. In cases of life-threatening CSU-related angioedema, participants may require discontinuation of IP and this should be discussed with study physician/sponsor.

### 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, then investigators or other site personnel 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 works 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 is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but no later than 24 hours of when he or she becomes aware of it).

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

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

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

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

### 8.3.8 Pregnancy

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

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

Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, 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 one day (ie, immediately but no later than 24 hours of when he or she becomes aware of it).

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

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

### 8.3.9 Device Constituent Deficiencies

- In a combination drug-device IP (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.

### 8.3.10 Serious Adverse Device Effect Reporting

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

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

### 8.3.11 Medication Error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the 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 (see Section 8.3.1) and within 30 days for all other medication errors.

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

### 8.3.12 Management of Investigational Product-related Drug Reactions

Appropriate drugs, such as epinephrine, $H_1$ antihistamines and $H_2$ blockers, 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 recognise and treat anaphylaxis (Lieberman et al 2010). Details on anaphylaxis management are provided in Appendix E.

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

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

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

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

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

## 8.4 Overdose

For this study, any 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 appropriate AstraZeneca representatives immediately, or 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 overdoses associated with an SAE (see Section 8.3.7) and within 30 days for all other overdoses.

## 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 finalisation 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 anonymised by pooling. Additional analyses may be conducted on the anonymised, 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 characterisation of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

### 8.5.1 Pharmacokinetics

All PK samples will be collected before administration of study medication according to the SoA (Table 2).

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 report. Only samples from the benralizumab treatment arm will be analyzed.

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

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

### 8.5.2 Immunogenicity Assessments

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

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

Samples will be collected, labelled, 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 will be assessed as part of the haematology safety testing (Section 8.2.1). Tissue eosinophil and basophil levels will be assessed as part of the CCI [redacted]

CCI [redacted]

#### 8.6.1.1 Serum and Plasma

Serum and plasma samples will be collected according to the SoA (Table 2) to evaluate the pharmacodynamics of benralizumab including CCI [redacted]. Additional markers of cellular inflammation and/or activation may be assessed including, but not limited to, those associated with T cell subsets (eg, IL-13, IFN-γ, 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.

CCI

[redacted]

#### 8.6.1.4 Transcriptomic (RNA) Assessments in Blood and Skin Biopsies

Transcriptome studies will be conducted using microarray, RNA-sequencing, and/or alternative equivalent technologies which facilitate the simultaneous measurement of the relative abundances of thousands of RNA species resulting in a transcriptomic profile for each blood or tissue sample. This will enable the evaluation of baseline transcript levels and disease activity in CSU and/or response to benralizumab as well as changes in transcriptomic profiles that may correlate with mechanism and therapeutic response with benralizumab.

CCI [redacted]

CCI

## 8.8 Healthcare Resource Utilisation

Broad-based CSU-related healthcare resource utilisation 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 randomisation, retrospective CSU-related healthcare resource utilisation information will be collected with a one-year recall period. At all subsequent visits, CSU-related healthcare resource utilisation 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
- Duration of hospitalisation (total days or length of stay, including duration by wards [eg, intensive care unit])
- Number and type of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and interventions (including physician or emergency room visits, tests and procedures, and medications).

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

# 9 STATISTICAL CONSIDERATIONS

The primary DBL is targeted to occur when all participants have completed the 24-week double-blind treatment period. The final DBL will occur when all participants have completed the 52-week treatment period and the Week 60 follow-up visit and/or the IPD/EOT visit.

An additional analysis may be performed between the primary and final DBLs, to report data accumulating during the extension part of the study if needed to support end of phase 2 decision making.

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

## 9.1 Statistical Hypotheses

For the primary endpoint, change from baseline in ISS7 score to Week 12, for each dose of benralizumab the null hypothesis (H0) is that the change in ISS7 at Week 12 on benralizumab is equal to the change in ISS7 at Week 12 on placebo. The alternative hypothesis is that the change in ISS7 with benralizumab treatment is not equal to the change in ISS7 for placebo:

- $H_0$: Change from baseline ISS7 at Week 12 (benralizumab 60 mg – Placebo) $=$ 0
- $H_1$: Change from baseline ISS7 at Week 12 (benralizumab 60 mg – Placebo) $\neq$ 0
- $H_0$: Change from baseline ISS7 at Week 12 (benralizumab 30 mg – Placebo) $=$ 0
- $H_1$: Change from baseline ISS7 at Week 12 (benralizumab 30 mg – Placebo) $\neq$ 0

Hypothesis testing for the primary analyses will be performed according to the multiple testing procedure described in Section 9.4.6. If the p-value is less than 0.025 (or 0.05 if alpha can be recycled from the other dose group), the null hypothesis ($H_0$) will be rejected and the alternative hypothesis ($H_1$) will be accepted.

A multiple testing procedure will be applied to the primary endpoint and the key secondary endpoints at Week 12 and Week 24; details are provided in Section 9.4.6.

## 9.2 Sample Size Determination

Approximately 160 participants will be randomised in a ratio of 3:3:3:3:4, respectively, to receive one of the 5 treatment sequences as follows:

- **Benralizumab 60 mg Q4W** until Week 12, **30 mg Q4W** until Week 24, and **30 mg Q8W** during the extension period until Week 52 (n = 30)

- **Benralizumab 60 mg Q4W** until Week 12, **30 mg Q4W** until Week 24, and **30 mg Q4W** during the extension period until Week 52 (n = 30)
- **Benralizumab 30 mg Q4W** until Week 12, **30 mg Q4W** until Week 24, and **30 mg Q8W** during the extension period until Week 52 (n = 30)
- **Benralizumab 30 mg Q4W** until Week 12, **30 mg Q4W** until Week 24, and **30 mg Q4W** during the extension period until Week 52 (n = 30)
- **Placebo Q4W** until Week 24, **benralizumab 30 mg Q4W** until Week 36, and **30 mg Q8W** until Week 52 (n = 40).

Up to Week 24, ie, prior to start of the extension period evaluating Q4W and Q8W dosing regimens, participants in both benralizumab 60 mg initial dose treatment arms will be considered as a single treatment group (total n=60), as will participants in both benralizumab 30 mg initial dose treatment arms (total n=60). Together with the 40 participants in the placebo treatment arm the above randomisation will provide a 3:3:2 ratio across the treatment group to assess the primary endpoint at Week 12.

This provides 90% power for statistical significance at the 2-sided 2.5% level within each induction dose comparison versus placebo if the assumed effect is a 4.7 point mean difference in change in ISS7 between benralizumab and placebo, assuming a SD of 6 for the change in ISS7 and a 10% dropout rate. These assumptions are in line with those for previous CSU trials (Saini et al 2015). The proposed sample size also provides a robust dataset to assess the key secondary endpoints, assess potential responders in sub-populations, and make a comparative assessment of the Q4W and Q8W dosing regimens in the maintenance period.

## 9.3 Populations for Analyses

The populations for purposes of analyses are defined in Table 8:

**Table 8 Populations for Analyses**

| Population | Description |
|---|---|
| All participants analysis set | All participants who sign the ICF |
| Full analysis set | The full analysis set will comprise all randomised participants who receive at least one dose of IP, irrespective of their protocol adherence and continued participation in the study. Participants will be analysed according to their randomised treatment irrespective of whether or not they were prematurely discontinued, according to the ITT principle. Data for participants who withdraw consent to participate in the study will be included up to the date of permanent discontinuation. |

**Table 8 Populations for Analyses**

| Population | Description |
|---|---|
| Safety analysis set | The safety analysis set will comprise all participants who receive at least one dose of IP. Erroneously-treated participants (eg, those randomised to treatment A but actually given treatment B) will be included in the group of the treatment they received. A participant who receives at least one dose of active IP will be classified as active and included in the active IP treatment group. A participant who receives both active dose regimens will be classified as the higher active dose regimen (ie, 60 mg). |
| Pharmacokinetic analysis set | All participants who received benralizumab and from whom PK blood samples are assumed not to be affected by factors such as protocol violations (eg, received wrong dose) and who had at least one quantifiable serum PK observation post first dose. All PK summaries will be based on this analysis set. |
| Placebo-to-benralizumab extension analysis set | All participants who received benralizumab at the start of the extension period who were previously on placebo. |

ICF, Informed consent form; IP, Investigational product; ITT, Intent-to treat; PK, Pharmacokinetic.

## 9.4 Statistical Analyses

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

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

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

Analyses will be performed by AstraZeneca or its representatives.

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

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

All point estimates will be presented together with 95% confidence intervals (CIs) as measures of precision, and nominal 2-sided p-values.

### 9.4.1 General Considerations

All analyses across the 24-week double-blind period will include 3 treatment groups comprising, respectively, all participants randomised to benralizumab 60 mg initial dose (n=60), all participants randomised to benralizumab 30 mg initial dose (n=60) and all participants randomised to placebo initial dose (n=40).

The primary efficacy analyses will be based on the double-blind, 12 week placebo-controlled induction period. In this part of the study and the following 12 weeks (up to Week 24) all efficacy analyses will use the full analysis set as defined above.

The primary estimand, analysed using the treatment-policy strategy, is the difference in mean change from baseline at Week 12 in ISS7 between each benralizumab dose and placebo, using the full analysis set, including all data up to week 12 regardless of discontinuation of IP or whether use of rescue medication has or has not occurred. As all participants who prematurely discontinue from IP in the study are asked to come in for all visits and study assessments up to Week 52, the amount of missing data expected in the analysis is assumed to be low and this estimand strategy is considered appropriate. However, sensitivity analyses may be performed to assess the robustness of the efficacy results to the missing data assumptions as described in individual endpoint analysis methods and Section 9.4.7.

As described above, in general, analyses will follow an Intention-to-Treat principle, and while changes to background medications for CSU and related treatments are discouraged, if any do occur, data following any changes to background therapies, or post missed doses or discontinuation of IP will still be included in the analyses. However, sensitivity analyses may be performed to assess any impact of changes in study and background medications if deemed appropriate.

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

### 9.4.2 Efficacy

#### 9.4.2.1 Primary Endpoint

Change from Baseline in (ISS7)

The primary endpoint, change from baseline in ISS7 score at Week 12, will be compared between each benralizumab initial treatment group (60 mg and 30 mg) with placebo using MMRM) analyses. The dependent variable in this model will be the change from baseline in ISS7 at post-baseline protocol-specified visits (up to the Week 24 visit). Treatment group will be included as an explanatory variable along with the baseline ISS7 score, region, visit and treatment-by-visit interaction as fixed effects. An unstructured covariance structure will be used to model the within-participant errors. If the model fails to converge, the following

structures will be attempted in the specified order: Toeplitz, first-order autoregressive, compound symmetric, and variance components. Least squares mean estimates for change from baseline at Week 12 and differences in least squares mean estimates between the treatment groups and placebo will be obtained from this model.

The missing at random assumption for the analysis is considered appropriate and justified as the primary estimand includes all data collected up to Week 24 in the analysis regardless of discontinuation of randomised treatment, as described in Section 9.4.1, and so the amount of missing data is expected to be low and is considered not likely to impact the primary results. Sensitivity analyses to alternative missing data assumptions may be performed as described in Section 9.4.7.

#### 9.4.2.2 Secondary Endpoints

The key secondary endpoint of change from baseline UAS7 at Week 12 for both benralizumab 60 mg and benralizumab 30 mg treatment groups will be analysed using MMRM models in a similar way to that described for the primary endpoint analyses. For these analyses, the dependent variable will be the change from baseline in the respective continuous endpoint at post-baseline protocol-specified visits up to Week 24, and each analysis will include the relevant baseline score as a covariate as well as the other covariates listed for the primary endpoint analysis.

The secondary endpoints of proportion of responders (UAS7 $\leq$ 6) at Weeks 12 and 24 will be compared between the benralizumab 60 mg and placebo treatment groups, and the benralizumab 30 mg and placebo treatment groups, respectively, using logistic regression. The model will include terms for treatment group and region. The results of the analyses will be presented as an odds ratio, together with its associated 95% confidence intervals (CIs) and 2-sided p-value. Results will also be transformed into a difference in proportions for ease of interpretation. The number and percentage of responders will also be summarised by randomised treatment with CIs around the proportions.

Continuous secondary endpoints collected by visit, including changes from baseline in ISS7 and UAS7 at Week 24 for both benralizumab 60 mg and benralizumab 30 mg treatment groups, will be analysed using MMRM models in a similar way to that described for the primary endpoint analyses. For these analyses, the dependent variable will be the change from baseline in the respective continuous endpoint at post-baseline protocol-specified visits up to Week 24, and each analysis will include the relevant baseline score as a covariate as well as the other covariates listed for the primary endpoint analysis.

Other continuous secondary endpoints collected by visit up to Week 12 and 24 including changes from baseline in HHS7, UCT, CU-$Q_2$oL, and DLQI will be analysed using MMRM models in a similar way to that described for the primary endpoint. For these analyses the dependent variable will be the change from baseline in the respective continuous endpoint at

post-baseline protocol-specified visits up to Week 12 and 24, respectively, and each will include the relevant baseline score as a covariate as well as the other covariates listed for the primary endpoint analysis. Additional responder analyses and descriptive summaries of the PRO assessments may be produced to further characterise participant symptomatology and health status. Summaries of number of angioedema free days will be produced for participants with angioedema at baseline.

The secondary endpoints of proportion of participants achieving UAS7 = 0 at Week 12 and 24 will be analysed using logarithmic regression in a similar way to the key secondary endpoint of responders (UAS7 ≤ 6). Results will be displayed as difference in proportions with 95% CI and 2-sided p-value.

The secondary endpoints of time to ≥ 5 point decrease (clinically relevant decrease) for ISS7 will be summarised using descriptive statistics. Details will be provided in the SAP.

To make an assessment of the efficacy of Q8W dosing relative to Q4W as a benchmark between Weeks 24 and 52, the efficacy endpoints outlined above will be assessed out to week 52 using the 5 treatment sequences described in the randomisation of the study. The focus will be to compare effects on the Q4W and Q8W maintenance regimens. The group of participants receiving placebo and then benralizumab will also be presented in these analyses but not formally compared to the other treatment groups. As an example, for the change from baseline in ISS7 score endpoint an MMRM model will be fit over the entire 52-week treatment period as described for the primary analysis, but with the 5 individual treatment groups to initial dose and maintenance regimen. If it is suitable to pool the data across the initial dose groups to enable one comparison of Q4W vs Q8W with 60 participants per arm, then this will be performed by fitting an MMRM model over the entire 52-week treatment period then including 3 treatment groups (those randomised to benralizumab then Q4W maintenance, those randomised to benralizumab then Q8W maintenance and those randomised to placebo followed by benralizumab treatment). Similar analyses may be performed for other efficacy endpoints as appropriate.

Full details will be provided in the SAP.

#### 9.4.2.3 Tertiary/exploratory Endpoints

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

### 9.4.3 Safety Analyses

Safety analyses will be performed using the safety analysis set.

Analyses will be presented for the overall study period split by the 5 treatment sequences and presented separately for the first 24 weeks split by the 3 induction dose treatment groups as noted in Section 9.2.

Participants will be analysed according to the treatment they received.

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

**Adverse Events**

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

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

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

An overview of AEs will be presented for each treatment 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.

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

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

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

**Treatment Emergent**

The following events are considered treatment emergent:

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

**Clinical Laboratory Safety Assessments**

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

**Vital Signs and Physical Examination**

Vital sign parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, Minimum, Q1, median, Q3, and Maximum. Frequency tables cover number and percentage of participants in the respective category.

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

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

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

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

### 9.4.4 Immunogenicity Analyses

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

### 9.4.5 Other Analyses

Pharmacokinetic and pharmacodynamic exploratory analyses will be described in the SAP which will be finalised before primary DBL.

### 9.4.6 Methods for Multiplicity Control

To control the overall type I error rate to be $\leq 0.05$ for the multiple comparisons in the primary and the key secondary endpoints, a Multiple Testing Procedure (MTP) with Bonferroni-Holm over groups, and Fixed-Sequence within groups will be applied. Specifically, there will be 2 groups defined by the doses of 30 and 60 mg, and within each group there will be a pre-defined fixed-sequence MTP of comparisons of the primary and key secondary endpoints vs placebo (ie, change from baseline in ISS7 at W12, then change from baseline in UAS7 at

W12) at level of α/2. If the null hypotheses for 1 dose group can be rejected entirely (ie, significant difference between active vs placebo for both endpoints at α=0.025), one will increase the level to α (ie, 0.05) for the other group. This amounts to using Bonferroni-Holm over groups, and fixed-sequence within groups. This multiplicity adjustment method follows the general results described by Bretz (Bretz et al 2009) and by Burman (Burman et al 2009).

### 9.4.7 Sensitivity Analyses

Sensitivity analyses for the primary and key secondary endpoints based on different missing data mechanism assumptions including those expected to be more conservative, such as missing not at random, may be used to explore the robustness of any treatment effect including multiple imputation approaches. Full details of sensitivity analyses will be pre-specified in the SAP and documented prior to primary DBL of the studies.

Sensitivity analyses may also be considered to explore the effect of extreme outliers on individual endpoints, such as rank-based methods. Full details of these will be pre-specified in the SAP.

### 9.4.8 Subgroup Analysis

To explore the uniformity of the detected overall treatment effect on the primary efficacy variable, subgroup analyses will be provided. Details of these analyses will be provided in the SAP.

## 9.5 Interim Analyses

No formal interim analysis is planned for the study.

Analyses will begin with the primary DBL which is targeted to occur when all participants have completed the 24-week double-blind treatment period. The final DBL will occur when all participants have completed the 52-week treatment period and the Week 60 follow-up visit and/or the IPD/EOT visit. An additional analysis may be performed between the primary and final DBLs, to report data accumulating during the extension period if needed to support end of phase 2 decision making.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

# SIGNATURE PAGE

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