Clinical Study Protocol	
Study Intervention	Benralizumab
Study Code	D3258C00001
Version	5
Date	29 March 2023

A Multi-center, Randomized, Double-blind, Parallel-group, Placebo-controlled 3-Part Phase 3 Study to Demonstrate the Efficacy and Safety of Benralizumab in Patients with Eosinophilic Gastritis and/or Gastroenteritis (The HUDSON GI Study)

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Regulatory Agency Identifier Number
EudraCT number: 2021-000085-14
ClinicalTrials.gov number: NCT05251909

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 Version Number: 5
Study Intervention: Benralizumab
Study Phase: 3

Short Title: Efficacy and Safety of Benralizumab in Patients with Eosinophilic Gastritis and/or Gastroenteritis (HUDSON GI)

Study Physician Name and Contact Information will be provided separately.

International coordinating investigator:

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History	
Document	**Date of Issue**
Amendment 4 (CSP version 5.0)	28-Mar-2023
Amendment 3 (CSP version 4.0)	15-Sept-2021
Amendment 2 (CSP version 3.0)	04-Mar-2021
Amendment 1 (CSP version 2.0)	23-Feb-2021
Original protocol (Initial creation 1.0)	26-Jan-2021

Amendment 4 (CSP version 5.0): 28-Mar-2023
This amendment is considered to be 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.
Following the decision to close recruitment to this study early, the primary rationale for this amendment is to fulfill a commitment to participants as they enrolled in the trial, of open-label access to benralizumab following double-blind treatment. This amendment will make available a streamlined 24-week open-label trial of benralizumab with the addition of a Part D, contingent on the Investigator's clinical judgement and the potential for benefit.

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial/ Non-substantial**
1.1 Synopsis, Rationale	Emerging evidence added to Rationale	Provide justification for Amendment 4	Substantial
1.1 Synopsis, Objectives and Endpoints	Note that original Part A objectives will not be assessed due to enrollment stop and small number of patients added. Part B objectives removed.	Updates synopsis to be consistent with changes made to protocol body due to Amendment 4	Substantial
1.1 Synopsis, Design	Part B removed. New design with Part A and Part C patients moving to Part D added		Substantial
1.1 Synopsis, Participants	Part B removed. New design with Part A and Part C patients moving to Part D added		Substantial
1.1 Synopsis, Intervention	Part B removed. New design with Part A and Part C patients eligible for 24 weeks of open-label benralizumab in Part D added.		Substantial
1.1 Synopsis, IDMC	Statement that IDMC will not be used during Part D added		Substantial
1.1 Synopsis, Statistical Methods	Part B analysis removed. Note that population is only 12 patients added. Analysis methods deleted and replaced with descriptive summaries and patient listings.		Substantial
1.2 Schema	New study schema, with deletion of Part B and addition of Part D, added (Figure 2).	To reflect the new design.	Substantial
1.3 Schedule of activities	Note added to Table 1 and 2 that all Part A and Part C patients will advance to Part D (V20) at next visit. Part B removed from Table 1. Part C after Week 76 SoA (Table 3) deleted. Part D SoA with reduced assessments added as new Table 3. Follow-up visit reduced from 12 to 8 weeks post last dose. Table 4 PRO SoA revised with last PRO at V20 and no IP discontinuation assessments.	Part B cancelled as not recruited. Part C will not extend into after Week 76 New Part D requires an SoA.	Substantial
2.1 Rationale	2.1.1 added with rationale for Amendment 4 and information on Part D as an extended closure segment.	To update the study rationale	Substantial
2.2 Background	2.2.1 added with emerging scientific evidence, closure of study recruiting, and addition of Part D	To update background with emerging scientific information supporting the change in study design	Substantial

2.3 Benefit/Risk Assessment	Note that following the approval of Amendment 4, there are no protocol-mandated endoscopy procedures added to 2.3.1. Text on expected benefits deleted from 2.3.2 Amendment specific text for overall benefit:risk conclusion added to 2.3.3	New Part D requires a statement on its benefit:risk	Substantial
3 Objectives and Endpoints	Note that original Part A objectives will not be assessed due to enrollment stop and small number of patients added. Part B objectives removed. Part D objective added.	Part B cancelled as not recruited. New Part D requires an objective	Substantial
4.1 Overall Design	Part B and the post-52-week extension in Part C deleted. Part D added.	Due to closure of enrollment and addition of extended study closure.	Substantial
4.2 Scientific Rationale for Study Design	Note that medication and dietary restrictions will not apply to Part D added.	Reduce patient burden and allowing real world clinical management	Substantial
4.4 End of Study Definition	Text for open-label extension deleted.	Open-label extension cancelled with closure of enrollment	Substantial
5.3 Lifestyle Considerations	Note that medication and dietary restrictions will not apply to Part D added.	Reduce patient burden and allowing real world clinical management.	Substantial
6.1 Investigational Products	Text on termination of open-label extension deleted from 6.1.2. Dosing for Part D added to 6.1.2. Requirement for urine pregnancy test prior to every IP administration deleted from 6.1.3.1	Due to closure of enrollment and addition of extended study closure. Align with current product safety requirements.	Substantial Substantial Non-substantial
6.3 Measures to Minimize Bias	Note on open-label treatment in Part D and unblinding added to 6.3.2. Text on breaking the blind allowed after Amendment 4 added to 6.3.3	Due to closure of enrollment, blinding restrictions relaxed.	Substantial
6.5 Concomitant Therapy	Text on relaxing background medication restriction in Part D added to 6.5.1 and Table 8 in 6.5.3. Text on relaxing dietary restriction in Part D added to 6.5.2.	Due to closure of enrollment, blinding restrictions relaxed. Reduce patient burden.	Substantial
7.1 Discontinuation of Study Intervention	Text encouraging IP discontinued patients to continue trial participation deleted in 7.1.1. End of study text deleted from 7.1.2.	Due to closure of enrollment, text is no longer needed.	Substantial Substantial
7.2 Participant Withdrawal from the Study	Text referring to Part A or Part B withdrawals should be informed about modified follow-up options (7.1.2) has been deleted. Request for discontinued patients to return for biopsy has been deleted.	Due to closure of enrollment, text is no longer needed (ie, no modified follow-up options and no need for post-withdrawal endoscopies).	Substantial Substantial

8.1 Efficacy Assessment	Note stating biopsies and endoscopies not required at any clinic visit after implementation of Amendment 4 added to 8.1.1 and 8.1.2 respectively. Note stating PROs will not be collected after implementation of Amendment 4 added to 8.1.3. CGIS assessments in Part D added to 8.1.4 Note that CGIC assessments will not be collected after implementation of Amendment 4 added to 8.1.5. Note that Qualitative Patient Interview Sub-study has been discontinued added to 8.1.7. Note that handheld devices will be returned at next visit added to 8.1.8.	Clarification that due to closure of enrollment, these efficacy assessments will not be done.	Substantial
8.2 Safety Assessments	Note that patients should be strongly encouraged to monitor for pregnancy during the study and report a pregnancy to the site as soon as possible added to 8.2.5 and 8.3.9.	Align with current product safety requirements.	Substantial
8.3 Adverse Events and Serious Adverse Events	8.3.9.2 text on paternal exposure has been deleted.	Align with current product safety requirements.	Substantial
8.3.10 Medication Error, Drug Abuse, and Drug Misuse	Section amended with addition of Drug Abuse and Drug Misuse and Reporting of Overdose	Update required due to CT-3^ Regulation and corporate safety CAPA	Non-substantial
8.5 Human Biological Samples	Note stating no further biological samples will be collected after implementation of Amendment 4 added.	Due to closure of enrollment.	Substantial
8.6 Human Biological Sample Biomarkers	Note stating no further biological samples will be collected after implementation of Amendment 4 added.	Due to closure of enrollment.	Substantial
9 Statistical Considerations	All text on planned statistical analysis has been deleted.	Due to closure of enrolment meaning original objectives will not be assessed and so analysis plans have been modified accordingly.	Substantial

9.1 Statistical Hypotheses	Text on hypotheses has been deleted and replaced with statement "No hypothesis testing will be performed given the decision to terminate recruitment to the study, resulting in the intended sample sizes required not being recruited". PK analysis set deleted from Text in 9.4.1 General Considerations and 9.4.2 Efficacy have been deleted and replaced with text appropriate for the revised design and low number of patients. Text specifying output for related events and most common events in 9.4.3.1 Adverse Events has been deleted.	Due to closure of enrolment meaning original objectives will not be assessed and so analysis plans have been modified accordingly.	Substantial
9.2 Sample Size Determination	Text concerning missing data and Part B sample size have been deleted. A statement that the sample size will be limited to 12 patients has been added.	Due to closure of enrollment.	Substantial
9.3 Populations for Analyses	PK analysis set deleted.	Due to closure of enrolment meaning original objectives will not be assessed and so analysis plans have been modified accordingly.	Substantial
9.4 Statistical Analysis	Statement that personnel will remain blinded until DBL has been deleted Text in 9.4.1 General Considerations and 9.4.2 Efficacy have been deleted and replaced with text appropriate for the revised design and low number of patients. Text specifying output for related adverse events and most common adverse events in 9.4.3.1 has been deleted. Other analyses (9.4.4) have been deleted. 9.4.5 Methods for multiplicity control has been deleted.	Due to closure of enrolment meaning original objectives will not be assessed and so analysis plans have been modified accordingly.	Substantial
9.6 Data Monitoring Committed	Note stating with the approval of Amendment 4, the open-label dosing in Part D will not require the use of an IDMC has been added.	Communicating decision by AstraZeneca, endorsed by IDMC, that the open-label dosing in a small cohort of adults does not require the IDMC.	Substantial
Appendix A1	Added sub-heading "Regulatory Reporting Requirements for Serious Breaches"	Update required to comply with regulatory requirement (e.g. EU CTR) and global company requirement	Non-substantial
Appendix A3	Note that patients who participate in Part D will be required to sign a supplemental ICF specific for Part D added.	As Part D was not part of the original study to which patients consented, supplemental consent will be required for patient participation in Part D.	Substantial

Appendix A5	Note that with the approval of Amendment 4, the open-label dosing in Part D will not require the use of an IDMC added.	Communicating decision by AstraZeneca, endorsed by IDMC, that the open-label dosing in a small cohort of adults does not require the IDMC.	Substantial
Appendix A7	Updated information about retention timelines of records and documents to [25 years after study archiving or as required by local regulations]	Update required to comply with EU CTR and global company requirement	Non-substantial
Appendix B4	Added detailed Drug Abuse and Drug Misuse definition and examples	Update required due to CT-3^ Regulation and corporate safety CAPA	Non-substantial
10 References	Added: Allakos Press Release 2021 Kliewer et al 2023 Kuang et al 2022	Updated	Non-substantial

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Multi-center, Randomized, Double-blind, Parallel-group, Placebo-controlled 3-Part Phase 3 Study to Demonstrate the Efficacy and Safety of Benralizumab in Patients with Eosinophilic Gastritis and/or Gastroenteritis (HUDSON GI)

Short Title: Efficacy and Safety Benralizumab in Patients with Eosinophilic Gastritis and/or Gastroenteritis (HUDSON GI)

Regulatory Agency Identifier Number:

EudraCT number: 2021-000085-14
ClinicalTrials.gov number: NCT05251909

Rationale: Eosinophilic gastritis and gastroenteritis (EG/EGE) are inflammatory disorders characterized by eosinophilic infiltration of the stomach (EG) and/or duodenum (EGE) with a resultant significant burden of gastrointestinal symptoms (eg, abdominal pain, nausea, and bloating). Benralizumab is a humanized, afucosylated, monoclonal antibody that binds specifically to the IL-5Rα on target cells, resulting in the depletion of eosinophils through antibody-dependent cell-mediated cytotoxicity. This mechanism of action makes benralizumab a potential treatment for patients with symptomatic and histologically active EG/EGE. This 3-part Phase 3 study was designed to 1) validate a patient-reported outcome (PRO) instrument for EG/EGE symptoms while providing preliminary efficacy and safety data (24-week Part A), 2) provide pivotal efficacy and safety data for EG/EGE for the registration of this indication (24-week Part B), and 3) provide long-term efficacy and safety data of benralizumab (Part C) during an open-label extension.

Based on emerging evidence of eosinophil-independent mechanisms in the pathology of eosinophilic upper gastrointestinal disease, including EG/EGE (eg, Kuang et al 2022, Allakos Press Release 2021 of the ENIGMA 2 study topline results, and results from the Benralizumab for Eosinophilic Gastritis study [NCT03473977, Kliewer et al 2023), recruitment was terminated early during the recruitment of Part A. Subsequently, a decision was made to amend the protocol (Amendment 4) with the deletion of the unrecruited Part B and the addition of a Part D, which will serve as an extended closure segment of the study. Following approval of Amendment 4, all active participants will advance to Part D at their next clinic visit, at which time, investigators may give participants the option of receiving 6 months (ie, 6 doses) of open-label benralizumab treatment.

Objectives and Endpoints

The original objectives of Part A are presented below. Given the decision to stop recruitment to the study, it will not be possible to assess these objectives with the data collected during Part A. A revised analysis plan is presented in Section 9.

Objectives for Part A	Estimands descriptions / endpoints
Primary	
• Part A: To compare the effect of benralizumab 30 mg every 4 weeks (Q4W) with placebo on histologic signs and gastrointestinal symptoms in patients with eosinophilic gastritis and/or gastroenteritis	Dual primary endpoints including histology-based and symptom-based endpoints: Histology-based dual primary endpoint • Population: Full analysis set • Histologic Endpoint: Proportion of patients achieving a histological response (defined as ≤6 eosinophils/high power field (hpf) in the stomach and/or, ≤15 eosinophils/hpf in the duodenum) at Week 24 • Intercurrent events: A composite approach whereby participants who receive restricted[a] or rescue medications, or discontinue randomized therapy prior to Week 24 will be considered as histologic non-responders at Week 24 • Summary measure: Odds ratio and difference in response rates between benralizumab and placebo
	Symptom-based dual primary endpoint • Population: Full analysis set • Symptom Endpoint: Absolute change from baseline in SAGED score at Week 24 • Intercurrent events: A composite approach whereby participants who receive restricted[a] or rescue medications or discontinue randomized therapy prior to Week 24 will be considered as treatment failures at Week 24. Such patients will have their worst observation prior to or at the intercurrent event carried forward to week 24. • Summary measure: Difference in least squares mean change from baseline in SAGED score at Week 24 between benralizumab and placebo

Secondary	
• Part A: To compare the effect of benralizumab 30 mg Q4W with placebo on clinical features of eosinophilic gastritis/ gastroenteritis and disease activity	• Key[b]: Percentage change from baseline in tissue eosinophils (stomach and/or duodenum) at Week 24 • Key[b]: Proportion of patients who achieve treatment response: tissue remission (≤ 6 eosinophils/hpf in the stomach and/or ≤ 15 eosinophils/hpf in the duodenum) and an improvement in symptoms at Week 24 • Change from baseline in proportion of vomiting-free days and change from baseline in frequency of vomiting episodes at week 24 • Change from baseline in proportion of diarrhea-free days and change from baseline in frequency of diarrhea episodes at week 24 • Change from baseline in proportion of days both diarrhea- and constipation-free • Time to clinically meaningful improvement in SAGED score • Change from baseline in PROMIS Fatigue 7a score and PAGI-SYM score at Week 24
• Part A: To compare the effect of benralizumab 30mg Q4W with placebo on rescue corticosteroid use	• Key[b]: Proportion of patients with no rescue corticosteroid use up to Week 24
• Part A: To compare the effect of benralizumab 30 mg Q4W with placebo on health-related quality of life in patients with eosinophilic gastritis and/or gastroenteritis	• Change from baseline in SF-36v2 PCS and MCS at Week 24 • Change from baseline in PAGI-QOL at Week 24
• To assess the pharmacokinetics and immunogenicity of benralizumab in patients with EG/EGE	• Serum benralizumab concentration over time • Anti-drug antibodies over time
Safety	
• To assess the safety and tolerability of benralizumab in patients with eosinophilic gastritis and/or gastroenteritis	• Safety and tolerability will be evaluated in terms of adverse events, vital signs, physical exam, and clinical laboratory parameters.

[a] Only restricted medications given that are considered to have a potentially meaningful impact on EG/EGE outcomes will be considered intercurrent events.

For Exploratory objectives, see Section 3 of the protocol.

Overall Design

This is a 3-part study. Part A is a parallel-group, randomized, double-blinded, placebo-controlled with up to 24-weeks of treatment. Part A was planned to include approximately 70 participants in total with eosinophilic gastritis (with or without eosinophilic duodenitis) or duodenal-only disease, including a minimum of at least 50 with EG (with or without duodenal involvement), respectively. After a 4-week to 8-week run-in period, symptomatic participants with EG with or without duodenitis and patients with eosinophilic duodenitis only, on stable background medications and diet, with histologically-confirmed disease were to be randomized 1:1 to benralizumab or placebo treatments.

Patients that completed Part A prior to the approval of Amendment 4 could choose to continue to Part C, an extended open-label benralizumab treatment period. Participants were to remain on stable background medication and diet throughout the first 52 weeks of the study (including Part A and the first 28 weeks of Part C).

Following approval of protocol Amendment 4, patients in Part A and Part C will advance to Part D at their next clinic visit and may be given the option of discontinuing or receiving 6 months of open-label benralizumab treatment, contingent on the Investigator's clinical judgement and the potential for benefit.

Disclosure Statement: This is a parallel-group efficacy and safety study with 2 arms that are participant and investigator blinded, with an open-label extension.

Number of Participants:

The study planned to randomize a minimum of approximately 210 and a maximum of approximately 230 participants. (Note: enrollment was terminated after the enrollment of 34 participants, of which 12 were randomized.)

Intervention Groups and Duration:

After a 4-week to 8-week run-in period, eligible patients were randomized 1:1 to 24 weeks of subcutaneous treatment with benralizumab 30 mg Q4W or matching placebo Q4W, in Part A. Subsequently, all participants were to receive benralizumab 30 mg Q4W subcutaneously in an open-label period, Part C, which was intended to allow patients at least 1 year of treatment with open-label benralizumab treatment. Patients were to maintain stable background medication and diet regimen for EG/EGE treatment through Week 52.

With the approval of Amendment 4, patients currently in Part A and Part C will advance to Part D at their next clinic visit. These patients may then be given the option of continuing with 24 weeks of open-label benralizumab Q4W dosing in Part D. Investigators may consider clinically appropriate adjustments to background medications and dietary restrictions in those

patients that continue in Part D.

Independent Data Monitoring Committee: Yes

Note: With the approval of Amendment 4, it has been agreed with the IDMC chair that the open-label dosing in Part D will not require the use of an IDMC.

Statistical Methods

Part A of the study was intended to provide a preliminary assessment of efficacy and safety and data to assess the measurement properties and responsiveness of the de novo Symptom Assessment for Gastrointestinal Eosinophilic Diseases (SAGED) instrument.

Sample Size Justification

The sample size calculations for the original study were based on the change from baseline in SAGED score at Week 24 dual primary endpoint. Changes in the other dual primary histological response rate endpoint required smaller sample sizes as larger relative differences are assumed (10% placebo response versus 80% benralizumab response).

Part A was intended to enroll approximately 50 patients with EG. Eligible patients with duodenal only disease were also included whilst enrolling the required 50 EG patients, with no minimum requirement on the number of duodenal only patients. A minimum of 60 and maximum of 80 patients in the overall population (i.e. with either EG or duodenal only disease) were to be enrolled in Part A. Thirty patients per arm in the overall population and 25 patients per arm with EG will provide >85% / >80% power for statistical significance at the 10% 2-sided level in each population respectively, if the true treatment effect for the change from baseline in SAGED score is a standardized effect size (difference in means/ standard deviation) of 0.75. A standardized effect size is used as the variability of the SAGED Score is not yet known. An effect size of 0.75 is a similar relative effect size as that observed in the lirentelimab (formerly antolimab) Phase 2 trial. Approximately 20 adolescent patients (12 to 17 years of age) with either EG or duodenal only disease were targeted for inclusion in Part A.

Note: Only 12 patients were randomized due to closure of enrollment.

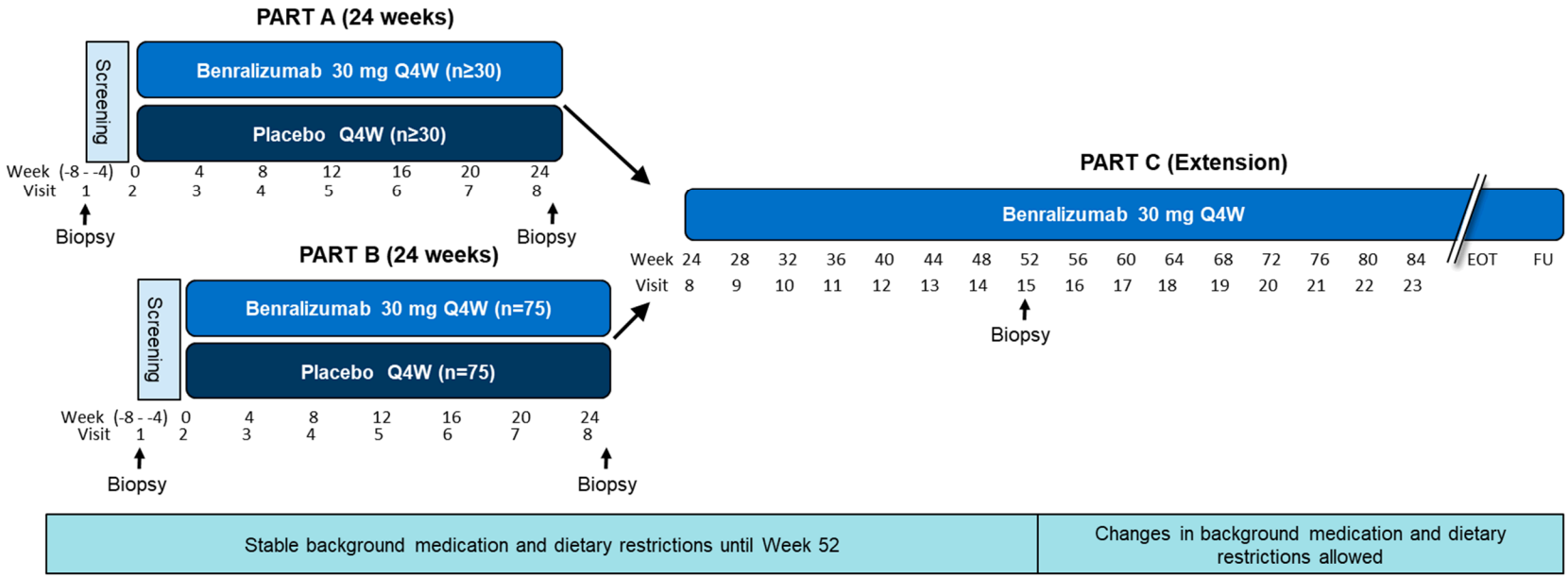
Analysis Methods

Analyses will consist of descriptive summaries of safety data for the double-blind placebo-controlled period (Part A) and the open-label period (Parts C and D) and select patient listings of baseline characteristics, safety data, and key efficacy data. Safety data presentations will use the safety analysis set which includes all randomized patients who receive at least one dose of investigational product. No hypothesis testing will be performed due to the small sample size.

1.2 Schema

1.2.1 Previous Schema (Protocol versions 1-4)

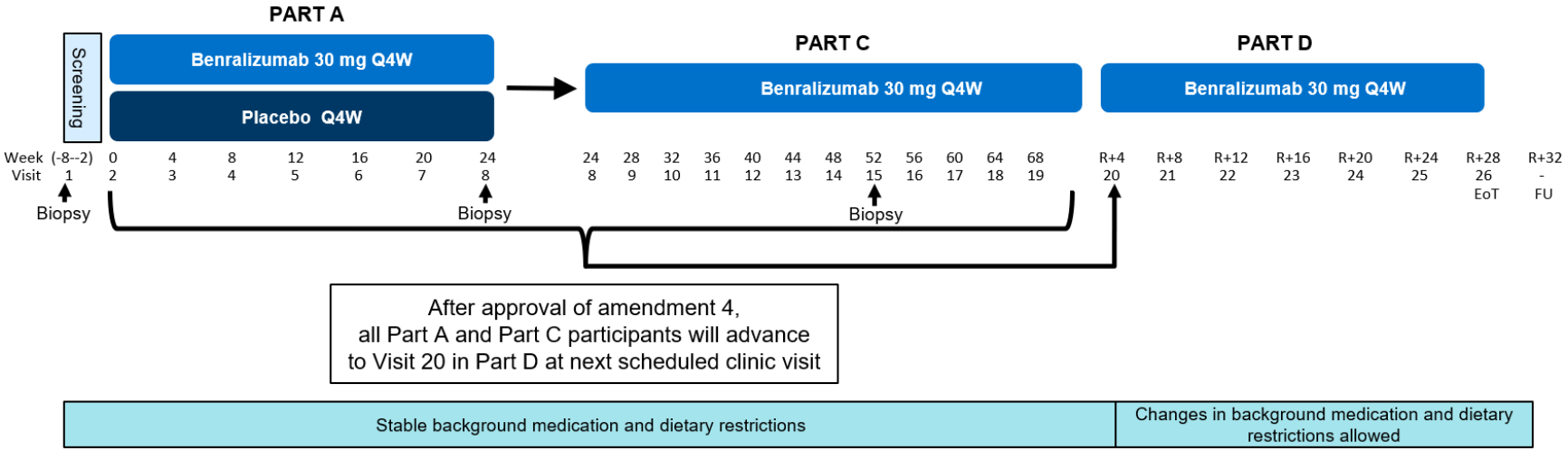
Figure 1 Previous Study Design



Q4W: every fourth week; EoT: end of treatment; FU: follow-up.

1.2.2 Current schema (Amendment 4, Protocol version 5)

Figure 2 Current Study Design



Q4W: every fourth week; R: reference visit number of weeks (ie, visit prior to approval of Amendment 4); EoT: end of treatment; FU: follow-up.

1.3 Schedule of Activities

Table 1 presents the schedule of activities for Part A prior to approval of Amendment 4. Following approval of Amendment 4, all participants in Part A will directly proceed to Visit 20 of Part D (Table 3) at their next clinic visit.

Table 1 Schedule of Activities – Part A

	Run-in	Double-blinded treatment period								In case of discontinuation[a]		CSP Section
Visit (V)	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8 /EOT[b]**	**Unscheduled[c]**	**IP Discontinuation**	**Follow-up**	
Week	**-8 to -4**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**-**	**4 weeks post-dose**	**8 weeks post-dose**	
Visit Window (Days)			**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**± 3**	**± 7**	
General procedures												
Informed consent/assent	X	-	-	-	-	-	-	-	-	-	-	Appendix A 3
Demography/medical history	X	-	-	-	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	X	-	-	-	-	-	-	-	-	-	5.1, 5.2
Height, Weight	X	-	-	-	-	-	-	X	-	X	-	8.2.1
Efficacy assessments												
Provide PRO device and instructions	X	-	-	-	-	-	-	-	-	-	-	8.1.3
Site visit PRO assessments (see Table 4)	X	X	-	-	-	-	-	X	-	X	-	8.1.3
Review PRO assessment compliance	-	X	X	X	X	X	X	X	-	X	-	8.1.3
Clinical Global Impression of Severity		X	-	-	-	-	-	X	-	X	X	8.1.4
Clinical Global Impression of Change	-		X	X	X	X	X	X	-	X	X	8.1.5
Diet questionnaire	X	X	X	X	X	X	X	X	X	X	X	8.1.6

Qualitative interview reminde	-	X	-	-	-	-	-	-	-	-	-	8.1.7
Healthcare resource utilization	-	X	X	X	X	X	X	X	-	X	X	8.8
Endoscopy: biopsy, EG-REFS, and EREFS	X[e]	-	-	-	-	-	-	X	-	X[f]	-	8.1.1, 8.1.2
Safety assessments												
Adverse events	X	X	X	X	X	X	X	X	X	X	X	8.3
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	6.5
Complete/(brief) physical exam	X	(X)	(X)	(X)	(X)	(X)	(X)	X	(X)	X	(X)	8.2.1
Vital signs	X	X	X	X	X	X	X	X	X	X	-	8.2.2
Electrocardiograms	-	X	-	-	-	-	-	-	-	-	-	8.2.3
Laboratory assessments												
Hematology/clinical chem	X	-	-	X	-	X	-	X	-	X	X	8.2.4
Serology (hepatitis/HIV)	X	-	-	-	-	-	-	-	-	-	-	8.2.6
Urinalysis	X	-	-	-	-	X	-	X	-	X	-	8.2.4
Post-menopause confirmation[i]	X	-	-	-	-	-	-	-	-	-	-	8.2.5
Serum/(urine) pregnancy	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	-	(X)	(X)	8.2.5
Pharmacokinetics	-	X	-	X	-	X	-	X	-	X	X[h]	8.5.1
Immunogenicity	-	X	-	X	-	X	-	X	-	X	X[h]	8.5.2
Biological sampling												
Serum for total IgE	X	-	-	-	-	-	-	-	-	-	-	8.6.1.1
Serum for tryptase	X	-	-	-	-	--		X				
Blood, serum, plasma for biomarkers	X	-	-	X	-	X	-	X	-	-	-	8.6.1.1
Tissue for histopathology/biomarkers	X	-	-	-	-	-	-	X	-	X[f]	-	8.6.1.2

Blood for genetic analysis	-	X[k]	-	-	-	-	-	-	-	-	-	8.7
Investigational product administration												
Randomization	-	X	-	-	-	-	-	-	-	-	-	6.3.1
Administration	-	X	X	X	X	X	X	X[j]	-	-	-	6.1.3

EG-REFS: Eosinophilic Gastritis Endoscopic Reference System; EOT: End of treatment; IP: investigational product; PRO: patient-reported outcomes.

[a] For participants who discontinue treatment but remain in study see Section 7.1, for participants who discontinue from study see Section 7.2, and for participants lost to follow up see Section 7.3.

[b] For patients continuing in PART C, Visit 8 is the first treatment of the PART C period. If a patient chooses not to continue in PART C, then the patient will be considered to have completed the study; the site will perform an EOT visit at Week 24, and the patient will return for a FU visit 12 weeks (±7days) after the last dose of IP, after which the patient exits the study.

[c] Other assessments may be performed at discretion of the Investigator.

[d] At sites in select countries, in adult patients who have consented to the sub-study.

[e] H.pylori testing to be performed at first endoscopy (at Screening)

[f] To be performed at the discretion of the Sponsor and in accordance with guidance in Section 7.2.

[g] To confirm postmenopausal status in women < 50 years of age who have been amenorrhoeic for ≥12 months.

[h] Assessments/procedures only performed on discontinued patients who attend the follow-up visit at the study site.

[i] Optional. Collected any time from Week 0 (Visit 2) after consent for genetic sample is obtained

[j] IP will be administered at Visit 8 (Week 24) only for patients entering the OLE period

Table 2 presents the schedule of activities for Part C prior to approval of Amendment 4. Following approval of Amendment 4, all participants in Part C will directly proceed to Visit 20 in Part D (Table 4) at their next clinic visit.

Table 2 Schedule of Activities – Part C

Open-label treatment period														**In case of discontinuation[a]**	**CSP Section**
Visit (V)	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**Unscheduled[b]**	**IP discon-tinuation**	**Follow-up**	
Week	**28**	**32[c]**	**36[c]**	**40**	**44[c]**	**48[c]**	**52**	**56[c]**	**60[c]**	**64**	**68[c]**	**-**	**4 weeks post-dose**	**8 weeks post-dose**	
Visit Window (Days)	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**± 3**	**± 7**	
General procedures															
Height, Weight	-	-	-	-	-	-	-	-	-	-	-	-	X	-	8.2.1

Table 2 Schedule of Activities – Part C

	Open-label treatment period													In case of discontinuation[a]	CSP Section
Visit (V)	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**Unscheduled[b]**	**IP discon-tinuation**	**Follow-up**	
Week	**28**	**32[c]**	**36[c]**	**40**	**44[c]**	**48[c]**	**52**	**56[c]**	**60[c]**	**64**	**68[c]**	**-**	**4 weeks post-dose**	**8 weeks post-dose**	
Visit Window (Days)	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**± 3**	**± 7**	
Efficacy assessments															
Site visit PRO assessment (See Table 4)							X						X		8.1.3
Review compliance with PRO assessments	X	X	X	X	X	X	X	X	X	X	X	-	X	-	8.1.3
Clinical Global Impression of Change	X	X	X	X	X	X	X	X	X	X	X	-	X	-	8.1.5
Diet questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X	-	8.1.6
Healthcare resource utilization	X	X	X	X	X	X	X	X	X	X	X	-	X	-	8.8
Qualitative interview reminder[d]	X		-	-	-	-	-	-	-	-	-	-	-	-	8.1.7
Endoscopy: biopsy, EG-REFS, and EREFS	-	-	-	-	-	-	X	-	-	-	-	-	-	-	8.1.1, 8.1.2
Safety assessments															
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	6.5
Complete/(brief) physical exam	(X)	(X)	(X)	(X)	(X)	(X)	X	-	-	(X)	-	(X)	X	(X)	8.2.1

Table 2 Schedule of Activities – Part C

	Open-label treatment period													In case of discontinuation[a]	CSP Section
Visit (V)	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**Unscheduled[b]**	**IP discon-tinuation**	**Follow-up**	
Week	**28**	**32[c]**	**36[c]**	**40**	**44[c]**	**48[c]**	**52**	**56[c]**	**60[c]**	**64**	**68[c]**	**-**	**4 weeks post-dose**	**8 weeks post-dose**	
Visit Window (Days)	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**± 3**	**± 7**	
Vital signs	X	X	X	X	X	X	X	-	-	X	-	X	X	-	8.2.2
Laboratory assessments															
Hematology/clinical chem	-	-	-	X	-	-	X	-	-	-	-	-	X	X	8.2.4
Urinalysis	-	-	-	X	-	-	X	-	-	-	-	-	X	-	8.2.4
Urine pregnancy test	X	-	-	X	-	-	X	-	-	X	-	-	X	X	8.2.5
Pharmacokinetics	-	-	-	X	-	-	X	-	-	-	-	-	X[e]	X	8.5.1
Immunogenicity	-	-	-	X	-	-	X	-	-	-	-	-	X[e]	X	8.5.2
Biomarkers sampling															
Blood, serum, and plasm for biomarker analyses	-	-	-	-	-	-	X	-	-	-	-	-	-	-	8.6.1.1
Tissue for histopathology and biomarkers	-	-	-	-	-	-	X	-	-	-	-	-	-	-	8.6.1.2
Investigational product administration															
Administration	X	X	X	X	X	X	X	X	X	X	X	-	-	-	6.1.3

EG-REFS: Eosinophilic Gastritis Endoscopic Reference System; IP: investigational product; PRO: patient-reported outcomes.

[a] For participants who discontinue treatment but remain in the study, see Section 7.1; for patients who discontinue from the study, see Section 7.2.

[b] Other assessments may be performed at discretion of the Investigator.

[c] For patients who are self-administering IP, these visits can optionally be conducted remotely by telephone contact.

[d] In adult participants at select sites.

[e] To be completed at the discretion of the Sponsor and in accordance with guidance in Section 7.2.

Table 3 Schedule of Activities – Part D

											CSP Section
Visit (V)	**V20**	**V21[a]**	**V22[a]**	**V23**	**V24[a]**	**V25[a]**	**V26 EOT**	**Unscheduled**	**IP discontinuation (Section 7)**	**Follow-up[b]**	
Week	**R+4**	**R+8**	**R+12**	**R+16**	**R+20**	**R+24**	**R+28**	**-**	**4 weeks post-dose**	**8 weeks post-dose**	
Visit Window (Days)	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**		**± 3**	**± 7**	
General procedures											
Informed consent/assent	X	-	-	-	-	-	-	-	-	-	Appendix A 3
Return PRO device	X	-	-	-	-	-	-	-	-	-	8.2.1
Efficacy assessments											
Clinical Global Impression of Severity	X	X	X	X	X	X	X	-	X	-	8.1.5
Diet questionnaire	X	-	-	-	-	-	X	X	X	-	8.1.6
Healthcare resource utilization	X	-	-	-	-	-	X	-	X	-	8.8
Safety assessments											
Adverse events	X	X	X	X	X	X	X	X	X	X	8.3
Concomitant medication	X	X	X	X	X	X	X	X	X	X	6.5
Complete (brief) physical exam	-	-	-	-	-	-	X	(X)	X	-	8.2.1
Vital signs	-	-	-	-	-	-	X	X	X	-	8.2.2
Laboratory assessments											
Hematology/clinical chemistry	-	-	-	-	-	-	X	-	X	X	8.2.4
Urine pregnancy test[c]	-	-	-	-	-	-	X	-	X	X	8.2.5
Investigational product administration											
Administration	X	X[d]	X[d]	X	X[d]	X[d]	-	-	-	-	6.1.3

EOT: end of treatment; IP: investigational product. R: reference visit number of weeks (ie, number of weeks for the visit prior to approval of Amendment 4).

[a] For patients who are self-administering IP, these visits can be conducted remotely by telephone contact.

[b] Can be conducted remotely by telephone contact

[c] Patients should be strongly encouraged to monitor for pregnancy during the study and report a pregnancy to the site as soon as possible.

[d] Optional at-home or remote location self-administration (Section 6.1.3.5).

Table 4 presents the schedule of activities for patient-reported outcomes prior to approval of Amendment 4. There will be no further collection of patient-reported outcome data following Visit 20 of Part D.

Table 4 Schedule of Activities – Patient-Reported Outcomes

	During scheduled clinic visits				At home			CSP Section
	Run-in	Treatment period			Run-in, double-blinded and open-label			
Visit (V) (if applicable)	**V1**	**V2**	**V8**	**V15**				
Week[a]/Frequency	**-8 to -4**	**0**	**24**	**52**	**Every evening from V1 until V20[b]**	**Every 2 weeks from V1 until V20[c]**	**Every 4 weeks after V2 until V20[c]**	
Symptom Assessment for Gastrointestinal Eosinophilic Diseases (SAGED)	-	-	-	-	X	-	-	8.1.3.1
Bristol Stool Form Scale	-	-	-	-	X	-	-	8.1.3.2
Dysphagia Symptom Questionnaire (DSQ)	-	-	-	-	X	-	-	8.1.3.3
Patient Assessment of Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM)	X	X	-	-	-	-	X	8.1.3.4
Patient-Reported Outcome Measurement Information System (PROMIS) Short Form – Fatigue 7a	X	X	-	-	-	-	X	8.1.3.5
Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life	X	X	-		-	-	X	8.1.3.6
Short Form Health Survey Version 2, Acute Recall (SF-36v2)	X	X	-	-	-	-	X	8.1.3.7
Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: SHP, Version 2 (WPAI+CIQ)	X	X	-	-	-	-	X	8.1.3.8
Patient Global Impression of Severity (PGI-S)	X	X	-	-	-	X	-	8.1.3.9
Patient Global Impression of Change (PGI-C)	-	-	-	-	-	X	-	8.1.3.10
Patient Global Impression of Benefit-Risk (PGI-BR)	-	-	X	X	-	-	-	8.1.3.11

[a] Scheduled Visit 8 at Week 24 and Visit 14 at Week 52 should occur within a window of ±3 days; discontinuation visit may occur within a window of ±7 days.

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

[c] 2 weeks defined as 14 ± 3 days. 4 weeks defined as 28 ± 3 days.

2 INTRODUCTION

Benralizumab is a humanized, afucosylated, monoclonal antibody that binds specifically to the IL-5Rα on the target cell and thus directly depletes eosinophils through antibody-dependent cell-mediated cytotoxicity. Benralizumab has been widely approved for treatment of asthma and also has been or is being investigated in patients with asthma, chronic obstructive pulmonary disease, hypereosinophilic syndrome, nasal polyposis, eosinophilic granulomatosis with polyangiitis, eosinophilic chronic rhinosinusitis, and eosinophilic esophagitis. This AstraZeneca-sponsored clinical trial investigates the use of benralizumab in patients with eosinophilic gastritis and/or gastroenteritis.

2.1 Study Rationale

In patients with asthma, the enhanced antibody-dependent cell-mediated cytotoxicity 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 direct eosinophil-depleting ability of benralizumab has been shown to be effective in eosinophilic asthma (Bleecker et al 2016, FitzGerald et al 2016) and steroid-dependent asthma (Nair et al 2017), and preliminary results suggest that benralizumab is effective in treating hypereosinophilic syndrome (Kuang et al 2018, Kuang et al 2019), which shares clinical and histologic features with EG/EGE. Based upon the above, benralizumab is a potentially safe and effective treatment for EG/EGE.

The central role of eosinophil inflammation in the pathophysiology of EG/EGE strongly suggests that a direct eosinophil depleting approach, as provided by benralizumab, may prove beneficial in reducing/eliminating eosinophils from gastrointestinal tissues and improve gastrointestinal symptoms and outcomes. This Phase 3 study originally had 3 overall aims: 1) Part A will validate an EG/EGE symptom PRO instrument, as no fit-for-purpose instrument is available, and provide a preliminary assessment of efficacy and safety, 2) Part B will provide pivotal efficacy and safety data to support registration of benralizumab for this indication, and 3) Part C will provide longer term efficacy and safety data.

2.1.1 Protocol Amendment 4 (Version 5)

Based upon an emergent body of evidence (see Section 2.2.1), AstraZeneca has elected to close recruitment of the HUDSON study, with Part A only partially enrolled.

Subsequently, the protocol has been amended to allow investigators to offer participants who elect to continue in the study at least 6 months of open-label benralizumab in a Part D, which serves as an extended closure segment of the study.

2.2 Background

Eosinophilic gastritis and eosinophilic gastroenteritis (EG/EGE) are rare chronic allergic inflammatory disorders of the gastrointestinal tract characterized by increased infiltration of eosinophils in the stomach and duodenum tissues and accompanying gastrointestinal symptoms, such as nausea, vomiting, abdominal pain, and diarrhea. Although these disorders have been increasingly recognized and diagnosed in both adults and adolescents, there are currently neither established diagnostic criteria nor treatment guidelines and no approved treatments.

The etiology of EG/EGE has not been fully characterized, but there is some evidence to support an allergic cause of eosinophilic gastrointestinal diseases (Rothenberg 2004). Food allergy, immune-dysregulation in response to an allergic reaction, and intestinal dysbiosis have been suggested or implicated in the pathogenesis (Sunkara et al 2019). A strong type 2 immune response has been shown to occur systemically and locally, with marked overproduction of eosinophil chemoattractant and activating factors including eotaxins and IL-5 (Caldwell 2014, Shoda et al 2020). Murine models of EG/EGE have demonstrated a role for eosinophils in eliciting gastrointestinal pathology, including motility problems and neurotoxicity (Hogan et al. 2001). A history of atopic conditions is common in patients, including rhinitis, asthma, food allergies, eczema and atopic dermatitis (Jensen et al 2016). Histopathology of affected tissue demonstrates high numbers of eosinophils and evidence of eosinophilic degranulation. This increase, especially when associated with aggregation, degranulation and infiltration of squamous epithelium along with architectural changes in the mucosa, indicates a pathologic process, and the histopathology of affected tissue demonstrates high numbers of eosinophils and evidence of eosinophilic degranulation (Egan and Furuta 2018).

Currently there are no established treatment guidelines and no approved treatments for EG/EGE. Dietary elimination therapy and corticosteroids (systemic and topical) are the most common treatments but are suboptimal and have limitations.

Food elimination diets may be considered as an initial therapy. Diets used in EG/EGE include elemental diets, a 6- or 7-food empiric elimination diet, and empiric avoidance of specific foods (eg, milk). However, determination of the type of food to eliminate can be challenging, and elimination diets have variable results, and data evaluating this strategy is limited for EG/EGE compared to eosinophilic esophagitis. Empirical dietary elimination can be burdensome on patients, as it may require numerous attempts of trial and error, including follow-up endoscopies, and each error can cause significant relapse of symptoms. Elemental/amino acid-based diets may be more effective but have not been proven for long-term efficacy; cost and compliance can also be problematic, and these are not feasible for long-term use in adults as the sole-source of nutrition.

Corticosteroids, which suppress eosinophilic growth factors IL-3, IL-5, and GM-CSF, and various other chemokines, are currently the most effective pharmacological treatment for EG/EGE. Systemic corticosteroids are typically used for severe disease or when dietary changes have failed to achieve adequate response or were impractical. A low-dose maintenance corticosteroid treatment may be necessary in some patients. Swallowed budesonide, a corticosteroid formulation that has limited systemic exposure due to high first-pass metabolism, is a treatment option, including an enteric-coated formulation of budesonide developed for inflammatory bowel disease (ie, Entocort); this is considered a relatively local or topical treatment compared with systemic prednisone.

There is an unmet medical need for new therapies for patients with EG/EGE.

Nomenclature of eosinophilic gastrointestinal diseases (EGIDs) is evolving, especially in the area of the GI tract distal to the esophagus. Although Eosinophilic Gastroenteritis suggests involvement of the stomach and the small intestine, there are literature references that utilize Eosinophilic Enteritis (Gurkan et al 2021) and Eosinophilic Duodenitis (Dellon et al 2020) to specify small intestine involvement. Where necessary in this protocol, precise segment of the gastrointestinal tract will be identified for clarity.

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

2.2.1 Emerging scientific evidence and closure of study recruitment

There is a growing body of emergent evidence of eosinophil independent mechanisms in the pathology of eosinophilic upper gastrointestinal (GI) disease, including eosinophilic esophagitis and EG/EGE. The results of the ENIGMA II trial of lirentelimab, first communicated in a press release (Allakos Press Release 2021), showed that while the histologic endpoint of eosinophil depletion was met, the symptom co-primary endpoint was not. In addition, an in-depth open-label analysis of a 7-patient eosinophil GI subgroup among the 20 patient hypereosinophilic syndrome Phase 2 trial of benralizumab showed that despite durable eosinophil depletion in the GI tract, prolonged clinical response was heterogeneous and that residual symptoms may reflect persistent epithelial inflammation (Kuang et al 2022). AstraZeneca has recently announced high-level results from the Phase 3 MESSINA study in eosinophilic esophagitis, in which the histologic endpoint was met, but not the symptomatic endpoint. Most recently, new clinical data generated in the investigator-sponsored Benralizumab for Eosinophilic Gastritis study (NCT03473977, in press) raises further questions regarding the role of eosinophils in disease of the upper GI tract.

Given the scientific evidence referenced above that has accrued since HUDSON was initiated, AstraZeneca elected to close recruitment of the HUDSON study. There is no new data to warrant any changes to the benralizumab safety profile in this patient population, more that

eosinophil independent mechanisms may work to maintain previously considered eosinophilic gastrointestinal diseases, even when eosinophils are robustly depleted.

Participants may be given the option of receiving 6 months (ie, 6 doses) of open-label benralizumab treatment in Part D, which will serve as an extended closure segment of the study.

2.3 Benefit/Risk Assessment

In order to assess the benefit/risk for participation in this benralizumab study, preclinical and clinical data for the investigational product have been taken into consideration as well as the risks associated with the study procedures.

More detailed information about the known and expected benefits and potential risks associated with benralizumab may be found in the Investigator's Brochure.

2.3.1 Risk Assessment

Benralizumab is approved for severe asthma with an eosinophilic phenotype and has a well-established safety profile. Benralizumab has been well tolerated with the most frequently observed adverse events (AEs) from the asthma and chronic obstructive pulmonary disease Phase 3 controlled studies being generally reflective of each study's respective patient population. Additionally, benralizumab is approved for use in asthma with an eosinophilic phenotype in many areas of the world. Potential risks that may be associated with the use of benralizumab are presented in Table 5. **Note: following the approval of Amendment 4, there are no protocol-mandated endoscopy/biopsy procedures.**

Table 5 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention (benralizumab or matching placebo)		
Serious infections	Serious infections have been reported for benralizumab. A relationship between eosinophil depletion and serious infection has not been established.	In addition to routine pharmacovigilance activities and an Independent Data Monitoring Committee, benralizumab will not be administered to a patient with a clinically significant active infection until the infection has resolved (see Section 6.1.3.3).
Malignancies	Malignancies have been reported at a low incidence in the completed and ongoing studies of benralizumab. Eosinophils have been circumstantially	In addition to routine pharmacovigilance activities and an Independent Data Monitoring Committee, risk minimization

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	associated with a positive prognosis in certain solid tumors, especially tumors of epithelial origin (breast and colon) and may play an active role in tumor defense by modulating host defenses or may be a bystander effect. However, the cause and consequences (ie, pro-tumorigenic versus anti-tumorigenic) of eosinophil recruitment and accumulation into tumors are unclear.	measures include exclusion of patients with active or recent malignancy (see exclusion criteria 14).
Serious hypersensitivity reactions (including anaphylaxis)	Serious hypersensitivity reactions (including anaphylaxis) are an identified risk of biologic therapy, including benralizumab. Anaphylaxis may be life-threatening.	Risk minimization includes exclusion of patients with known hypersensitivity to investigational product (exclusion criteria 17) and observation following administration for the appearance of any acute drug reactions, in line with clinical practice.
Development of anti-drug antibodies	Development of anti-drug antibodies to benralizumab has been documented. Theoretical risks of developing anti-drug antibodies may include decreased effective drug concentrations and hypersensitivity reactions (eg, anaphylaxis or immune complex disease). There was no impact of anti-drug antibodies on overall benralizumab safety or efficacy in the previous Phase 3 studies in asthma.	
Helminth infection	Eosinophils are a prominent feature of the inflammatory response to helminthic parasitic infections. Therefore, there is a theoretical risk that prolonged eosinophil depletion may diminish the ability to defend against helminthic parasites.	In addition to routine pharmacovigilance activities, risk minimization measures include exclusion of patients with untreated parasitic infection (see exclusion criteria 17).
Study procedures		
Esophagogastroduodenoscopy with biopsy	Beside risks associated with routine clinical practice (eg, blood draw), study procedures include endoscopies with biopsies. Potential AEs associated with this procedure include bleeding complications, infection, and tears of the gastrointestinal tract.	Procedures will be performed by specialist physicians at centers where this procedure is routinely performed.

2.3.2 Benefit Assessment

The goals of treatment for EG/EGE are to decrease its gastrointestinal signs and symptoms, with histologic improvement in gastrointestinal eosinophilia, and improve patient quality of life. By depleting eosinophils, benralizumab might still improve clinical outcomes in patients with EG/EGE.

This amendment adds an open label extended closure for patients who feel, along with their investigator, that they are receiving or may receive benefit from treatment with benralizumab.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the purpose and design of this trial, the well-established safety profile of benralizumab, and the measures taken to minimize potential risks to participants participating in this study, the benefit: risk for participation in this trial is deemed to be acceptable.

Protocol V5 (Amendment 4): Given the well-established safety profile of benralizumab, the perceived benefit of benralizumab treatment by patients along with their physician, and the measures taken to minimize potential risks to participants participating in the extended closure, the benefit: risk for continued participation is deemed to be acceptable.

3 OBJECTIVES AND ENDPOINTS

Note: Given the small number of patients randomized at the time of decision to stop recruitment to the study, it will not be possible to assess of these objectives with the data collected during Part A. A revised analysis plan is presented in Section 9.

Table 6 Objectives and Endpoints

Objectives	Estimand description/Endpoint
Primary	
• Part A: To compare the effect of benralizumab 30 mg every 4 weeks (Q4W) with placebo on histologic signs and gastrointestinal symptoms in patients with eosinophilic gastritis and/or gastroenteritis	Dual primary endpoints including histology-based and symptom-based endpoints: Histology-based dual primary endpoint • Population: Full analysis set • Histologic Endpoint: Proportion of patients achieving a histological response (defined as ≤6 eosinophils/hpf in the stomach and/or, ≤15 eosinophils/hpf in the duodenum) at Week 24 • Intercurrent events: A composite approach whereby participants who receive restricted[a] or rescue medications, or discontinue randomized therapy prior to Week 24 will be considered as histological non-responders at Week 24 • Summary measure: Odds ratio and difference in response rates between benralizumab and placebo
	Symptom-based dual primary endpoint • Population: Full analysis set • Symptom Endpoint: Absolute change from baseline in SAGED Score at Week 24 • Intercurrent events: A composite approach whereby participants who receive restricted[a] or rescue medications or discontinue randomized therapy prior to Week 24 will be considered as treatment failures at Week 24. Such patients will have their worst observation prior to or at the intercurrent event carried forwards to Week 24. • Summary measure: Difference in least squares mean change from baseline in SAGED score at Week 24 between benralizumab and placebo

Table 6 Objectives and Endpoints

Objectives	Estimand description/Endpoint
Secondary	
• Part A: To compare the effect of benralizumab 30 mg Q4W with placebo on clinical features of eosinophilic gastritis/ gastroenteritis and disease activity	• Key[b]: Percentage change from baseline in tissue eosinophils (stomach and/or duodenum if applicable) at Week 24 • Key[b]: Proportion of patients who achieve treatment response: tissue remission (≤6 eosinophils/hpf in the stomach and ≤15 eosinophils/hpf in the duodenum, if applicable) and improvement in symptoms at Week 24 • Change from baseline in proportion of vomiting-free days, and change from baseline in frequency of vomiting episodes at Week 24 • Change from baseline in proportion of diarrhea-free days, and change from baseline in frequency of diarrhea episodes at Week 24 • Change from baseline in proportion of days both diarrhea and constipation free at Week 24 • Time to clinically meaningful improvement in SAGED score • Change from baseline in PROMIS Fatigue 7a score and PAGI-SYM score at Week 24
• Part A: To compare the effect of benralizumab 30mg Q4W with placebo on rescue corticosteroid use	• Key[b]: Proportion of patients with no rescue corticosteroid use up to Week 24
• Part A: To compare the effect of benralizumab 30 mg Q4W with placebo on health-related quality of life in patients with EG/EGE	• Change from baseline in SF-36v2 PCS and MCS at Week 24 • Change from baseline in PAGI-QoL at Week 24
• To assess the pharmacokinetics and immunogenicity of benralizumab in patients with EG/EGE	• Serum benralizumab concentration over time • Anti-drug antibodies over time
Safety	
• To assess the safety of benralizumab in patients with eosinophilic gastritis and/or gastroenteritis	• Adverse Events, vital signs, physical exam, and laboratory parameters

Table 6 Objectives and Endpoints

Objectives	Estimand description/Endpoint
Exploratory	
• Part A: To describe the effect of benralizumab on clinical features of EG/EGE and disease activity	• Change from baseline in vomiting severity at Week 24 • Change from baseline in diarrhea severity at Week 24 • Change from baseline in endoscopic measures of inflammation and remodeling, EG-REFS, by central reader at Week 24 • Change from baseline in PAGI-SYM, DSQ, PGIS, PGI-C, CGI-S, and CGI-C
• Part D: To collect more information on the safety and clinical response of benralizumab in EG/EGE.	• Adverse Events, vital signs, physical exam, and laboratory parameters • Change from baseline in CGI-S

[a] Only restricted medications given that are considered to have a potentially meaningful impact on EG/EGE outcomes will be considered intercurrent events.

4 STUDY DESIGN

4.1 Overall Design

•

- The study will be performed in patients ages 12 and above with EG/EGE that are symptomatic and histologically active on stable background medication and diet.
- Following screening to confirm eligibility, an initial double-blinded, randomized placebo-controlled, parallel-group 24-week treatment period aimed to validate a PRO instrument for EG/EGE symptoms and provide preliminary efficacy and safety data (Part A).
- Participants completing Part A may continue to a subsequent exploratory open-label Part C which will provide further efficacy and safety data.
- Following approval of Amendment 4, patients in both Part A and Part C may proceed to Part D in which they may be offered 24 weeks of open-label benralizumab treatment. contingent on the Investigator's clinical judgement and the potential for benefit.

4.1.1 Study Conduct Mitigation During Study Disruption

The guidance given below supersedes instructions provided elsewhere in this clinical study protocol 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 or a Health Care Professional provided by a third-party vendor.
- 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 administration: Performed by a site qualified Health Care Professional, Health Care Professional provided by a third-party vendor, or by the participant or the participant's caregiver, if possible. Additional information related to the visit can be obtained via telemedicine.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, see Appendix G.

4.2 Scientific Rationale for Study Design

As a registration trial, this study was designed to evaluate benralizumab's effect on both the signs and symptoms of EG/EGE and the underlying eosinophilic inflammation, with dual primary outcome variables, in a double-blinded, randomized, placebo-controlled fashion. With regard to the symptoms, as no suitable clinical outcome assessment was available, AstraZeneca has performed initial activities to develop such a tool to be used in this study, the SAGED PRO instrument, including identifying the symptoms that are most important to this patient population. The first part of this study, Part A, will evaluate the measurement properties of this PRO instrument and demonstrate whether the SAGED score is fit for purpose as one of the dual primary endpoints for this indication and patient population. This was to be done in a population separate from the population in which pivotal efficacy data was to subsequently generated, Part B.

This symptom-based endpoint will be supported by a histology endpoint, the number of eosinophils present in the stomach and duodenal biopsy samples, to document whether or not a histological response to treatment, ie, eosinophil depletion, underlies improvement in symptoms. The histological cut-off to be used for patient entry into the study (≥30 eosinophils/hpf in 5hpf) (Collins MH 2014) is higher than established clinical guidelines recommend for eosinophilic esophagitis diagnosis, which is ≥15 eosinophils/hpf (with 2 to 4 biopsies obtained) (Dellon et al 2013a). Normally, eosinophils do not occur in the esophagus, whereas they are normally present in the remainder of the gastrointestinal tract tissue, including the stomach and small intestine. As such, a higher threshold will be used for diagnosing EG/EGE in this study compared with eosinophilic esophagitis guidelines.

Patients will be eligible for this study if they have been diagnosed by a clinician with EG/EGE at least 3 months prior to screening. This duration serves several purposes. Firstly, it works to support the persistence of the disease, and with it decreases the likelihood for spontaneous remission and similarly decreases the potential for a higher than expected placebo response in patients spontaneously remitting. In addition, this time period enables assessment for diet modification and medication strategies to be considered prior to enrollment in the study.

While the conditions of EG/EGE are rare, the gastric and duodenal pathophysiology, symptomatology and diagnostic evaluation of EG/EGE are sufficiently consistent between adolescents and adult patients, supporting the study of both populations in the same study and utilizing the same measures. The available data and safety profile from studies with benralizumab in adolescents in addition to robust PK modelling support the inclusion of adolescent patients (12 to 17 years of age) in this EG/EGE study. Modelling also supports the use of the 30mg dose in these adolescent patients in order for exposure to be commensurate to that of adult patients.

Variability in background medications and diet could have confounding effects on the outcomes being measured for EG/EGE; stable medications and dietary restrictions are thus required to show the benefit of benralizumab. Prior to screening, patients' background medication must be stable for at least 4 weeks and diet restrictions must be stable for at least 6 weeks, and patients were to agree that there will be no changes during Part A and until Week 52 of the study (unless medically indicated). These medication and dietary restrictions will not apply to Part D of the study.

4.2.1 Participant Input into Design

4.2.1.1 Participant Input into Study Design

The study team sought input from patients on the proposed study design and discussed patient experiences with key experts in the field and their clinical staff. Input on aspects of the study design such as the use of endoscopy, the use of injectable medications, the presence of a placebo treatment arm, and the potential for self-administration was provided.

4.2.1.2 Participant Input into Patient-Reported Outcomes

The primary data source for the development of the SAGED instrument was semi-structured concept elicitation interviews with EG/EGE patients, in which concepts (ie, symptoms and their impacts) that are important to patients emerge spontaneously through open-ended questions. Patients' responses were the basis of the conceptual framework. The wording of the questions in the instrument was directly adapted from language patients used in the interviews. Drafts of the SAGED instrument were cognitively debriefed with patients to ensure the instrument captured all concepts of interest and used language and response options that were meaningful to patients.

4.3 Justification for Dose

The pharmacokinetics of benralizumab are well-characterized (Wang et al 2017), and it is expected to demonstrate consistent pharmacokinetics across different disease populations. In adult and adolescent patients with severe asthma (CALIMA [Bleecker et al 2016] and SIROCCO [FitzGerald et al 2016]) treated with benralizumab 30 mg every 8 weeks (Q8W) or Q4W, near complete blood eosinophil depletions were observed for both dosing regimens. In a study of benralizumab in hypereosinophilic syndrome, where patients have high blood eosinophils and significant organ manifestations of eosinophilic inflammation, a dosing regimen of 30 mg Q4W was effective in reducing blood and tissue eosinophilia (including gastrointestinal tissue) in patients, with an associated improvement in gastrointestinal symptoms (Kuang et al 2019). For the planned clinical study of patients with eosinophilic esophagitis, which is similar to hypereosinophilic syndrome in that the disease is characterized by significant eosinophilic inflammation of tissues that are thicker and less vascular than lung tissue, the Sponsor is proposing a dosing regimen of 30 mg Q4W as it is believed that a higher concentration is necessary to generate meaningful eosinophil reduction in the tissues of the esophagus and resolution of associated clinical symptoms.

In the CALIMA/SIROCCO studies, the pharmacological profiles of benralizumab in blood (30 mg Q4W and 30 mg Q8W) were consistent between adolescents and adults, and the safety profile of benralizumab was similar to that of placebo in both adolescents and adults. Among adolescent participants who received benralizumab 30 mg Q4W, the incidence of treatment-emergent AEs and the most commonly reported preferred terms were similar to the Q8W group.

4.4 End of Study Definition

The end of study is defined as the last expected visit/contact of the last patient undergoing the study.

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

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waiver or exemption, is not permitted.

5.1 Inclusion Criteria

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

Age

1 Participant must be at least 12 years of age at the time of signing the ICF or informed assent form.

Type of Participant and Disease Characteristics

2 Clinician confirmed diagnosis of EG/EGE for at least 3 months prior to screening.

3 Participants who have documented previous diagnosis of eosinophilic gastritis, with or without duodenitis, or eosinophilic duodenitis alone. This will be confirmed by biopsy for the purpose of this study, defined as a gastric count of ≥30 eosinophils/hpf in 5 hpfs and/or duodenal eosinophil count ≥30 eosinophils/hpf in at least 3 hpfs without any other cause for the gastrointestinal eosinophilia (eg, parasitic or other infection or malignancy). Participants can have duodenal only disease and be enrolled in the duodenal only subject population. See Section 8.1.1 for details regarding endoscopy and biopsy.

4 At Visit 1 (screening), participants who in the investigator's judgement have a history of symptoms of abdominal pain, nausea, bloating, early satiety, and/or loss of appetite to an extent that they would meet criteria 5 at Visit 2.

5 At Visit 2 (randomisation), participants who are symptomatic, defined as having a mean SAGED score ≥12 (on a 0 to 50 point scale) over the last 14 days of the run-in period.

6 Must be adherent to daily PRO assessments:

(a) Must complete 70% SAGED, DSQ, and Bristol Stool Form Scale assessments between Visit 1 and Visit 2 AND

(b) Must have completed at least 8 of 14 SAGED assessments in the 14 days prior to randomization

7 If on background medications for EG/EGE during the study, background medications have been stable for at least 4 weeks prior to the run-in period.

(a) Patient must agree not to change type of background medication or dosage during the study unless medically indicated or allowed by protocol during Part C OL after Week 52 as clinically indicated. If a medication for EG/EGE (including swallowed steroids, systemic steroids and PPI) is discontinued prior to screening, there should be a washout period of at least 8 weeks prior to screening. See Section 6.5 for details regarding background medications.

Reproduction

8 Negative serum pregnancy test for women of childbearing potential (WOCBP) at Visit 1 (enrollment).

9 Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female participants:

- Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women 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:
  - Women <50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and have follicle stimulating hormone levels in the postmenopausal range. Until FSH is documented to be within menopausal range, she should be treated as a WOCBP
  - Women ≥50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Female participants that are WOCBP must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. WOCBP who are sexually active with a non-sterilized male partner must agree to use one highly effective method of birth control, as defined below, from enrollment throughout the study and until at least 12 weeks after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together. All women of childbearing potential must have a negative serum pregnancy test result at Visit 1.
- Highly effective birth control methods include:
  - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation- oral, intravaginal, or transdermal
  - Progestogen-only hormonal contraception associated with inhibition of ovulation- oral, injectable, or implantable
  - Intrauterine device
  - Intrauterine hormone-releasing system
  - Bilateral tubal occlusion
  - 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 patient)
  - Vasectomized sexual partner provided that partner is the sole sexual partner of the WOCBP study patient and that the vasectomized partner has received medical assessment of the surgical success

Informed Consent

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

5.2 Exclusion Criteria

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

Medical Conditions

1 Any disorder, including, but not limited to, cardiovascular, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, hematological, psychiatric, or major physical impairment that is not stable in the opinion of the investigator and could:
   - Affect the safety of the patient throughout the study
   - Influence the findings of the studies or their interpretations
   - Impede the patient's ability to complete the entire duration of study.

2 Other gastrointestinal disorders such as active *Helicobacter pylori* infection, history of achalasia, esophageal varices, Crohn's disease, ulcerative colitis, inflammatory bowel disease, or celiac disease.

3 Hypereosinophilic syndrome or eosinophilic granulomatosis with polyangiitis.

4 Current malignancy, or history of malignancy, except for patients who have had basal cell, localized squamous cell carcinoma of the skin, or in situ carcinoma of the cervix are eligible provided that the patient is in remission and curative therapy was completed at least 12 months prior to the date of informed consent, and assent when applicable was obtained. Patients who have had other malignancies are eligible provided that the patient is in remission and curative therapy was completed at least 5 years prior to the date informed consent, and assent when applicable, was obtained.

5 History of anaphylaxis to any biologic therapy or vaccine.

6 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 patient otherwise meets eligibility criteria. Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice, or cirrhosis.
   (b) Alanine aminotransferase or aspartate aminotransferase level > 3 times the upper limit of normal, confirmed by repeated testing during the run-in period. Transient increase of aspartate aminotransferase/alanine aminotransferase level that resolves by

the time of randomization is acceptable if in the Investigator's opinion the patient does not have an active liver disease and meets other eligibility criteria.

7 Helminth parasitic infection diagnosed within 24 weeks prior to the date informed consent or assent (if applicable) is obtained that has not been treated with or has failed to respond to standard of care therapy.

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

9 Known immunodeficiency disorder including testing positive for HIV.

Prior/Concomitant Therapy

10 Concomitant use of immunosuppressive medication (including but not limited to: methotrexate, cyclosporine, and azathioprine (see Table 8).

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

12 Receipt of live attenuated vaccines 30 days prior to date of informed consent or assent.

13 Receipt of inactive vaccines within 7 days of informed consent or assent.

14 Receipt of any marketed or investigational biologic (monoclonal or polyclonal antibody) within 4 months or 5 half-lives prior to the date informed consent or assent (if applicable), is obtained, whichever is longer, and during the study period.

Prior/Concurrent Clinical Study Experience

15 Previous participation in a benralizumab clinical study.

16 Participation in another clinical study with an investigational product administered in the last 30 days or 5 half-lives prior to randomization, whichever is longer.

17 Participants with a known hypersensitivity to benralizumab or any of the excipients of the product.

Other Exclusions

18 Initiation or change of a food-elimination diet regimen or re-introduction of a previously eliminated food group from 6 weeks prior to start of the run-in period and unable or unwilling to remain on a stable diet until the completion of Week 52.

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

20 Judgment by the investigator that the participant is unlikely to comply with study procedures, restrictions, and requirements.

21 For women: currently pregnant confirmed with positive pregnancy test or breast-feeding.

5.3 Lifestyle Considerations

Patients must abstain from donating blood, plasma, or platelets from the time of informed consent or assent (if applicable) and for 12 weeks after last dose of investigational product.

WOCBP must use highly effective contraceptive methods throughout the study and 12 weeks after last dose of the investigational product (see also inclusion criterion 8 in Section 5.1).

Prior to Amendment 4, patients were to remain on stabilized diet for treatment of their EG/EGE during the first 52 weeks of the study (stable diet is defined as no initiation of single or multiple elimination diets or reintroduction of previously eliminated food groups). For participants in Part D, there will be no such restrictions.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to treatment. 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, and any serious adverse event (SAE).

Individuals who do not meet criteria for participation in this study (screen failure) may be re-screened after careful consideration by the Investigator and in agreement with the AstraZeneca study physician (eg, if a patient needs a long-term follow up to rule out an exclusory condition). Patients cannot be re-screened more than one time. Re-screened patients should sign new ICF form. In case of re-screening, all medical events that have occurred since the first enrollment will be recorded as part of medical history. All study procedures scheduled for Visit 1 (Table 1) should be repeated at the re-screening visit, with the exception of the endoscopy and biopsy, which may be performed again at the discretion of the Investigator. Re-screened patients should be assigned the same patient number as for the initial screening. Re-screening will be documented so that its effect on study results, if any, can be assessed. Re-screening a patient after failing the following inclusion/exclusion criteria is not allowed:

- Biopsy in order to confirm diagnosis of EG/EGE (inclusion criterion #3)
- Establishing the patient is symptomatic prior to randomization (inclusion criterion #5)
- Non-adherence to daily PRO assessments (inclusion criterion #6)

Patients may be considered for re-screening in order to meet all other inclusion/exclusion criteria.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention, marketed product, or placebo intended to be administered to or medical devices utilized by a study participant according to the Clinical Study Protocol.

Only patients randomized in the study may receive study intervention and only authorized site staff may supply or administer study intervention, except when self-administration or administration by the patient's caregiver is an option (Section 6.1.3.4).

6.1 Study Interventions Administered

6.1.1 Investigational Products

Descriptions of the investigational products are provided in Table 7..

Table 7 Investigational Products

Arm name	Benralizumab	Placebo
Intervention name	Benralizumab	Placebo
Type	Combination Product	Combination Product
Dose formulation	Solution for injection	Solution for injection
Unit dose strengths	30 mg/ml	-
Dosage level	30 mg every 4 weeks	-
Administration route	Subcutaneous injection	Subcutaneous injection
Use	Experimental	Placebo comparator
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	
Packaging and labelling	Investigational product will be supplied to the site in a kit with an accessorized pre-filed syringe of either benralizumab or placebo. Each kit will have a unique ID number that is printed on all labels within the kit (ie, the outer carton label and the label of each container within the carton). Each syringe will be labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirement. The labels will be translated into local languages where applicable and required by local regulations.	
Former/current names	CCI [redacted] in earlier clinical development. Marketed under the brand name Fasenra.	-

6.1.2 Duration and Frequency of Treatment with Investigational Products

Patients will receive investigational product (ie, benralizumab or matching placebo) Q4W. The investigational product will be administered on-site or, optionally, at home (see Sections 6.1.3.4 and 6.1.3.5). The acceptable visit windows are specified in the schedule in Section 1.3, and reasons and procedures for rescheduling investigational product administration are detailed in Section 6.1.3.3.

Prior to the approval of Amendment 4, patients who complete the 24-week double-blind treatment period are eligible to continue receiving benralizumab 30 mg Q4W in the open-label extension starting at Visit 8. The open-label extension treatment period was intended to allow patients at least 1-year treatment with open-label benralizumab 30 mg Q4W.

Following the approval of the protocol Amendment 4, patients in both Part A and Part C that are offered and choose to continue in Part D will be offered 24 weeks of open-label benralizumab Q4W treatment (ie, patients will not complete their current treatment period).

6.1.3 Administration of Investigational Products

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention, except when self-administration or administration by the patient's caregiver is an option (see Sections 6.1.3.4 and 6.1.3.5).

6.1.3.1 Before Investigational Product Administration

All applicable visit procedures, including biological sample collection, should be completed prior to investigational product administration. If the participant does not undergo a particular visit procedure during the visit, investigational product can be administered, and the procedure should be re-scheduled for a different date, preferably within the visit window. No procedures should be performed after the dosing on the day of investigational product administration. Pharmacokinetic and anti-drug antibody samples must always be collected before investigational product administration.

Prior to each investigational product administration:

- Investigator/authorized delegate will evaluate the participant's condition for potential contraindications for dosing (see investigational product administration rescheduling, below).
- Investigator/authorized delegate will assess the injection site as per standards of medical care.

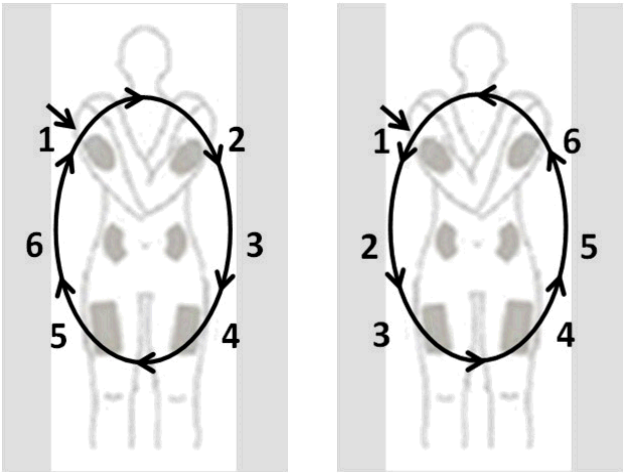
6.1.3.2 In-Clinic Investigational Product Administration

The investigational product will be administered subcutaneously as a single injection via the accessorized pre-filled syringe by the Investigator/authorized delegate. It is advised that the site of injection of investigational product is rotated such that the participant receives

investigational product at a different anatomical site at each treatment visit. Suggested injection site rotation sequence is presented below. Investigational product should not be administered into areas where the skin is tender, bruised, erythematous, or hardened.

The injection site must be documented in the source at each treatment visit and recorded in the electronic Case Report Form (eCRF).

Figure 3 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.

Further details on investigational product administration are provided in the Pharmacy Manual. Investigational product administration must be carried out in line with these instructions and clinical practice.

After investigational product administration

Participants should be observed after investigational product administration for the appearance of any acute drug reactions, in line with clinical practice (Section 8.3.12). If the patient reports an injection site reaction or other AEs, the Investigator or qualified designee will complete the AE eCRF page and additional eCRF questions about the injection site reaction or other AEs.

6.1.3.3 Investigational Product Administration Re-scheduling

Every effort should be taken to keep investigational product administration within the visit window.

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

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

- An intercurrent illness that, in the opinion of the Investigator, may compromise the safety of the participant.
- Signs of a clinically significant infection. Benralizumab should not be administered to a participant with a clinically significant active infection treated with oral or intravenous antimicrobials, antivirals, or antifungals until it is confirmed by the Investigator that the infection has resolved.
- An acute or emerging condition requiring systemic steroids. Benralizumab should not be administered until it is confirmed by the Investigator that the condition has clinically resolved.
- Fever (≥38°C; ≥100.4°F) within 72 hours prior to investigational product administration.
- Any event or laboratory abnormality that, in the opinion of the Investigator or the Sponsor, contraindicates dosing or could result in complications.

It is recommended that the AstraZeneca study physician/delegate be contacted in case of any questions.

If investigational product cannot be administered at a scheduled treatment visit (eg, due to conditions listed above), it can be postponed as necessary and administered as soon as possible.

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

Re-scheduled investigational product dose can be then administered at an unscheduled visit along with the pregnancy test. Brief physical exam and vital signs assessment 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 investigational product dose.

If a dose is significantly delayed it is recommended to keep at least 2 weeks 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 investigational product given at the regularly scheduled visit. The visit schedule will be always calculated from randomization visit date.

A 'missed' dose is a dose not administered until the next treatment visit window. If 2 or more doses (consecutive or non-consecutive) of investigational product are missed within a 1-year period, a conversation between the Investigator and the AstraZeneca study physician should take place to review the participant's adherence to treatment and decide on the participant's further disposition. During the double-blinded and open-label treatment periods, all participants, regardless of whether they remain on investigational product or not, will be encouraged to remain in the study through the end of the double-blinded and open-label treatment periods. Discontinuation procedures are described in Section 7.1.

6.1.3.4 Self-administration of Investigational Product as Mitigation to Disruption

At Visits 2 and 3, appropriate patients and/or their caregiver may be trained in self-administration of investigational product 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 so that patients are prepared in case remote visits may be required secondary to study disruptions as described in Section 4.1.1. Patients may still participate in the study if they do not consent/assent to this training.

6.1.3.5 Optional At-home or Remote Location Self-administration

To reduce participant burden and to allow flexibility during open-label treatments in Part C and Part D, patients will have the option for at-home or remote location participant/caregiver administration of investigational product. The investigator will first assess the participant and/or caregiver to ensure they are appropriate for administration of investigational product and ensure they have received appropriate training. Both will be captured in the source documentation.

All necessary supplies and instructions for administration and documentation of investigational product administration will be provided. See the 'Pharmacy Manual' or the 'Study Instructions for At-home or Remote Location Administration of Benralizumab by the [Participant/Patient] and/or His/Her Caregiver' for step-by-step guidance including drug accountability and reconciliation requirements.

If the investigational product is administered at the participant's home/remotely, the participant should administer the investigational product on the same day as the Visit after the visit assessments. It is strongly encouraged that the patient is contacted by the Investigator or qualified designee after the dose is administered in line with clinical practice. If the patient reports an injection site reaction or other AEs, the Investigator or qualified designee will complete the AE eCRF page and additional eCRF questions about the injection site reaction or other AEs

6.1.3.6 Optional Remote Visits for Patients Doing At-Home or Remote-Location Investigational Product Administration

In case of self-administration, some clinic visits (see Table 1 - Table 3) can be done as remote visits by telephone contact to reduce participant burden. WOCBP should be asked if they are pregnant during the telephone visit. Between on-site pregnancy testing, the patient is encouraged to monitor for pregnancy, and, if pregnant, should contact the site and should not administer IP.

6.2 Preparation/Handling/Storage/Accountability

The investigator or designee must confirm via the shipment data logger that appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area, in the original outer container, in accordance with the labelled storage conditions (between 2 to 8°C [36 to 46°F], protected from light) with access limited to the investigator and authorized site staff. The temperature should be monitored on a daily basis and documented in the temperature monitoring log. Further details are provided in the separate Pharmacy Manual.

In the following cases the center staff should not use affected investigational product and should immediately contact AstraZeneca representative for further guidance:

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

Damaged investigational product should be documented using the RTSM (please see the RTSM manual for further details).

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

An AstraZeneca site monitor will account for all investigational product received at the site, for unused investigational product, and for appropriate destruction of unused investigational products.

Any unused kits will be destroyed locally (for further details, see the Pharmacy Manual). Documentation of investigational product delivery and destruction should be maintained according to applicable AstraZeneca and institution procedures.

Devices sent to a patient's home must be returned to a site for traceability.

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

In the case of a malfunctioning benralizumab/matching placebo accessorized pre-filled syringe, the site should contact the study monitor to initiate a product complaint process according to applicable guidelines.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Methods for Assigning Treatment Groups

In Part A, all eligible participants were centrally assigned to randomized study intervention using the Randomisation and Trial Supply Management (RTSM) system. Before the study is initiated, the log-in information & directions for the RTSM will be provided to each site.

The RTSM will provide to the investigators or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. Routines for this will be described in the RTSM user manual that will be provided to each center.

Randomization codes will be assigned strictly sequentially in each stratum as patients become eligible for randomization. Randomization will be stratified by location of disease (EG with or without duodenal involvement vs duodenal disease alone) and baseline steroid use (eg, patients on a background of systemic or swallowed steroids/enteric-coated corticosteroids vs no use of these steroids at baseline). Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be randomized or receive investigational product. There can be no exceptions to this rule.

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

6.3.2 Maintaining Blind to the Investigational Product

Note: following the approval of Amendment 4 (CSP version 5), only open-label treatment is provided in Part D, and in addition, all parties may be unblinded to patient's treatment. The text below concerns maintaining the blind prior to implementation of Amendment 4.

Benralizumab and placebo will not be visually distinct from each other. All packaging and labelling of the investigational product will be done in such a way as to ensure blinding for all Sponsor and investigational site staff during the first 24 weeks of the study. Neither the participant nor any of the Investigators or Sponsor staff who are involved in the treatment, clinical evaluation and monitoring of the participants will be aware of the treatment received

during the double-blinded 24-week treatment period. Since benralizumab and placebo are not visually distinct, investigational product will be handled by an appropriately qualified member of the study team (eg, pharmacist, Investigator, or qualified designee) at the site.

An AstraZeneca site monitor will perform investigational product accountability. In the event that 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 Sponsor must be notified immediately by the Investigator and, if possible, before unblinding.

The following personnel will have access to the randomization list during the study, prior to database lock:

- Those carrying out the packaging and labelling of investigational product
- Those generating the randomization list
- The AstraZeneca Supply Chain department
- Bioanalytical lab personnel analyzing pharmacokinetic samples.

The information in the randomization list will be kept from other personnel involved in the conduct of the study in a secure location until the end of the study. No other member of the extended study team at AstraZeneca, or any Contract Research Organization handling data, will have access to the randomization scheme during the conduct of the study.

6.3.3 Maintaining Blind to the Participant's Eosinophil Counts

While not entirely assured, participants on active benralizumab treatment are expected to have lower eosinophil and basophil counts than participants on placebo. Procedures to mitigate unblinding on this basis will be in place from randomization (Visit 2/Week 0) and up to Visit 12/Week 40.

- Hematology will be run by the central laboratory. Post-randomization (starting from Visit 2), eosinophil and basophil counts will be redacted from the full hematology reports sent back to the investigative sites. Because complete knowledge of the remaining cell types could permit deduction of the eosinophil + basophil compartment, monocyte counts will also be redacted from the full hematology reports sent back to the investigative sites.
- If the Investigator orders any local safety laboratory assessments, the requested tests should be restricted to the question at hand. For example, if hemoglobin is desired, the Investigator should avoid ordering a complete blood cell count with a differential count.
- In cases where the Investigator requires an eosinophil, basophil, or monocyte count for managing safety issues, he/she may order these tests as per regular site practice. AstraZeneca should be notified of all such cases without absolute eosinophil counts, absolute basophil counts or absolute monocyte counts being revealed.

- Site staff who are directly involved in the participant's management and participant 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 blind 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 the Sponsor.
- Biopsy results will be reported to the investigative sites for the purposes of confirming eligibility criteria following Visit 1. Blinded biopsy results through Week 24 will not be reported to the investigator sites until the completion and reporting of Part A, as appropriate. In addition, biopsy results from after Week 24 may be provided to the investigator upon request.

Prior to the approval of Amendment 4, the randomisation code should not have been broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff. After the approval of Amendment 4, the randomisation code may be broken without a need to conceal the unblinding from AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product 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

The investigational product will be administered within visit windows as specified in Table 1 through Table 3.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic, as well as any missed doses, will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When study interventions are administered at home, compliance with study intervention will be assessed at subsequent visit. Compliance will be assessed by direct questioning and returned investigational product during the site visits and documented in the source documents

and eCRF. A record of the number of investigational product kits dispensed to and used by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays will also be recorded in the eCRF.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency.

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Background Medication

Background medications for EG/EGE (eg, systemic and topical ingested or swallowed corticosteroids, PPIs) and steroid treatments used for asthma or allergies that are inhaled or administered intranasally should be maintained at the same dose and schedule for at least 4 weeks prior to the run-in period.

If a medication for EG/EGE (eg. systemic and topical ingested or swallowed steroids, PPIs, and other treatments) are discontinued prior to screening, there should be a washout period of at least 8 weeks prior to screening.

Background medication for EG/EGE (and related treatments) was to remain stable throughout the run-in period and the initial 52 weeks of study treatment (ie, 24-week Part A and first 28 weeks of Part C) unless a change is medically indicated.

Following approval of Amendment 4, background medication for EG/EGE (and related treatments) can be changed at the discretion of the investigator in those patients that choose to continue and receive 24 weeks of open-label benralizumab treatment. Background medication use will be recorded on the eCRF. The justification and rationale for treatment changes should be documented in the eCRF source notes.

6.5.2 Dietary Restrictions

Participants may have dietary restrictions as part of the clinical management of their EG/EGE during the study as long as the diet restrictions have been stable for at least 6 weeks prior to the run-in period and there is agreement not to change the diet restriction for the first 52 weeks

of study intervention, unless medically indicated. The justification and rationale for diet changes should be documented in the source notes and diet questionnaire (Section 8.1.6).

Following approval of Amendment 4, investigators may consider relaxing dietary restrictions while continuing benralizumab, as clinically indicated, in those patients that continue with 24 weeks of open-label benralizumab treatment as part of the Part D.

The reintroduction of previously avoided foods has the potential to trigger an anaphylactic reaction (Ho and Chehade 2018). For clearer assessment of causality for any anaphylactic reactions that may be reported, foods should not be reintroduced one week before or one week after dosing of benralizumab.

6.5.3 Restricted Medication

The medication restrictions that apply during the study are summarized in Table 8.
Unless specifically indicated, all conditions apply from enrollment throughout the study duration. If, at discretion of the Investigator, a participant needs treatment with any disallowed medication or changes in background medications for EG/EGE and related treatments, it is recommended that the Investigator contact the AstraZeneca study physician to discuss justification.

Table 8 Concomitant Medication and Treatments

Medication	Allowed/ Restricted/ Prohibited	Details
Background (maintenance) medication for EG/EGE, including steroids, proton pump inhibitors, and antiemetics, and steroid treatments used for asthma or allergies that are inhaled or administered intranasally	**Allowed**	Maintained at the same dose and schedule for at least 4 weeks prior to the run-in period and throughout the study 52-week treatment period. Following approval of Amendment 4, patients continuing with 24-week open-label treatment in Part D have no restriction.
Rescue corticosteroid medication for EG/EGE	**Restricted**	A brief course of systemic or enteric-coated steroids is allowed, see section 6.5.4. Rescue corticosteroid medication for EG/EGE would constitute treatment failure in the primary analyses.
Systemic corticosteroids (tablets, suspension, or injections; (eg prednisone, prednisolone or related products) for reasons other than EG/EGE	**Restricted**	Not allowed within 8 weeks prior to screening and within 4 weeks prior to endoscopy during the study. Throughout the treatment period, allowed for treatment of an AE (eg, asthma) where there is no alternative treatment available, for no more than 7 days.

Table 8 Concomitant Medication and Treatments

Medication	Allowed/ Restricted/ Prohibited	Details
Other immunosuppressive medication (including but not limited to: methotrexate, cyclosporine, azathioprine)	**Restricted**	Allowed for treatment of an AE where there is no alternative treatment available for the duration of <4 weeks. If longer treatment is required, this should be discussed with the study physician to decide on the participant's disposition. Disallowed within 8 weeks prior to screening and for other reasons throughout the study.
Immunoglobulin or blood products	**Prohibited**	Not allowed 30 days prior to screening and during the study.
Any other marketed or investigational biologic	**Prohibited**	Disallowed if taken for any reason within 4 months or 5 half-lives, whichever is longer, prior to screening and during the study Not recommended within 12 weeks (5 half-lives) after the last dose of investigational product.
Any investigational non-biologic drug	**Prohibited**	Disallowed within 30 days or 5 half-lives (whichever is longer) prior to screening, during the treatment period, and is not recommended within 12 weeks (5 half-lives) after the last dose of investigational product
Subcutaneous allergen immunotherapy	**Restricted**	Allowed if on stable therapy started at least 30 days prior to screening and stable dose is maintained during the study It is recommended that participant does not receive SCIT on the same day as investigational product administration.
Oral and/or sublingual allergen immunotherapy	**Prohibited**	Disallowed within 8 weeks prior to screening and during the treatment period
Live attenuated vaccines	**Prohibited**	Disallowed within 30 days prior to randomization, during the treatment period and for 12 weeks (5 half-lives) after the last dose of investigational product
Inactive/killed vaccinations (eg, inactive influenza)	**Restricted**	Not recommended within the 7 days before or within 7 days after any investigational product dosing study visit. Injection site for vaccine should be distant to preceding or next injection site of IP.

6.5.4 Rescue Medicine

In response to severe gastrointestinal symptoms that the participant cannot tolerate, corticosteroids, including an increased dose over the participant's maintenance dose if they are receiving maintenance treatment with corticosteroids, can be given as rescue medication, but use should be limited to as short a course as possible. If, at discretion of the Investigator, a participant needs treatment with any disallowed medication or changes in background medications as rescue for EG/EGE, it is recommended that the Investigator contact the AstraZeneca study physician to discuss justification. Rescue medication for EG/EGE would constitute treatment failure in the primary analyses. Rescue medication will not be provided by the sponsor but are obtained locally. The date of rescue administration as well as the name and dosage regimen must be recorded.

6.6 Dose Modification (not applicable)

Modification of the dose of benralizumab is not permitted.

6.7 Intervention after the End of the Study

After the end of the study, the patient should be given standard of care therapy, at the discretion of the Investigator, per local practice.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

7.1.1 Reasons for Discontinuation of Investigational Product

Participants may be discontinued from investigational product in the following situations.

- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment
- An AE that, in the opinion of the Investigator, contradicts further dosing
- Severe non-compliance with the Clinical Study Protocol
- If it is discovered that a patient does not meet all the eligibility criteria but was randomized in error, the Investigator should inform the study physician immediately to discuss potential safety concerns and if the investigational product should be discontinued.
- Pregnancy
- Development of any study-specific criteria for discontinuation:
  - Anaphylactic reaction to the investigational product requiring administration of epinephrine

- Development of helminth parasitic infestations requiring hospitalization
- Confirmed reactivation of hepatitis B virus
- If a participant misses 2 or more doses (consecutively or non-consecutively) of investigational product within a 1-year period, a conversation between the Investigator and the AstraZeneca study physician should take place to review the participant's adherence to treatment and decide on the participant's further disposition.

Before a decision to discontinue a participant from investigational product is instituted, the study physician should be consulted regardless of the reason for discontinuation. The Investigator should contact the participant if a decision to stop investigational product is taken. A participant that decides to discontinue investigational product will always be asked about the reasons and the presence of any AEs. The date of last investigational product dose, the date of investigational product discontinuation decision and the reasons for discontinuation should be documented in the eCRF. Conditions that require administration of investigational product to be temporarily withheld are described in Section 6.1.3.3. Discontinuation of investigational product will be registered in the RTSM.

See Table 1 to Table 3 for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.2 Procedures for Early Discontinuation of Investigational Product

7.1.2.1 Early discontinuation of study treatment

All patients who prematurely discontinue IP should return to the study site for an IPD visit within 4 weeks (±3 days) after the last dose of IP and an FU visit 4 weeks (±7 days) after the last dose of IP for procedures described in Table 1 to Table 3. The IPD visit replaces the nearest scheduled visit after IP discontinuation. Patients will return the PRO device at the IPD visit if applicable. Patients who have discontinued IP during Part A are not eligible to enter Part C or Part D.

7.1.3 Procedures for Handling Incorrectly Enrolled or Randomized Patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be randomized or receive IP. There can be no exceptions to this rule. Patients who are enrolled but who do not meet all eligibility criteria must not be randomized and must be withdrawn (screen failed) from the study.

When a patient does not meet all the eligibility criteria but is randomized in error or incorrectly started on IP, the Investigator should inform the AstraZeneca study physician immediately to discuss potential safety concerns and the best interests of the patient and decide whether IP should be continued or discontinued.

If the agreed decision is to discontinue IP, patients should be encouraged to complete IPD and FU visits, ie, follow-up for 4 weeks after last IP dose (if received) (Section 7.1.2).

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

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of withdrawal from the study, if possible, an IP Discontinuation visit should be conducted, as shown in the schedule of activities. See Table 1 to Table 3 for what 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.
  - Endoscopy should be performed at the discretion of the Sponsor and only if ≥12 weeks have elapsed since the prior endoscopy.
- If the participant withdraws consent for disclosure of future information, the sponsor 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 ICF and local regulations. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow up

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

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

- 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 and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). 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. Should the participant be unreachable at the end of the study the participant should be considered to be lost to follow up with unknown vital status at end of study and censored at latest follow up contact.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in Table 1 to Table 3. Protocol waivers or exemptions are not allowed.
- The Investigator will ensure that data are recorded on the eCRF. The Web Based Data Capture (WBDC) system will be used for data collection and query handling.
- The Investigator ensures the accuracy, completeness, 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 eCRF. A copy of the completed eCRF will be archived at the study site.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified Table 1 to Table 3, 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 count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in Table 1 to Table 3.

8.1 Efficacy Assessments

8.1.1 Histopathology and Tissue Eosinophil Counts

Note: following the approval of Amendment 4 (CSP version 5), biopsies are NOT required at any clinic visit, although investigators may perform endoscopies and collect biopsies as part of their normal standard of care. The text below concern assessments prior to implementation of Amendment 4.

One of the dual-primary endpoints in the study is the proportion of participants with a histologic response at 24 weeks defined as ≤6 eosinophils/hpf in the stomach gastric levels and/or ≤15 eosinophils/hpf across duodenal levels. During the study, biopsies were planned to be conducted at Visit 1 (Week -8 to -4), Visit 8 (Week 24), and Visit 15 (Week 52). Esophagogastroduodenoscopy will be performed according to local medical practice. Eight gastric biopsies should be targeted for collection from separate areas of the gastric antrum (four samples) and the gastric corpus (four samples); four duodenal biopsies, with at least two from the second part of the duodenum. Additionally, 4 biopsies should be taken from the esophagus: two from the proximal esophagus and two from the distal esophagus. The biopsies will receive blinded pathology review of tissue eosinophil counts and histopathology from an independent physician. Details pertaining to biopsy collection are provided in the Laboratory Manual. To confirm eligibility at Visit 2, the Visit 1 biopsy results will be communicated to the site.

Additional pathology findings will also be captured on biopsy specimens. A histology scoring system may be applied and recorded independently for all available esophageal, gastric, and duodenal specimens by blinded pathology review.

Helicobacter pylori will be evaluated on gastric biopsies from Visit 1 (Week -8 to -4) by pathology review.

8.1.2 Endoscopic Reference System Scores

Note: following the approval of Amendment 4 (CSP version 5), there are no study-mandated endoscopy procedures. The text below concern assessments prior to implementation of Amendment 4.

During study-mandated endoscopy procedures, the endoscopic manifestations of EG/EGE, including erosions/ulcerations, granularity, raised lesions, erythema, friability, fold thickness and pyloric stenosis, will be scored by the endoscopist using the Eosinophilic Gastritis Endoscopic Reference System (EG-REFS) from three areas of the stomach (antrum, body, and fundus). Endoscopic appearance of the duodenum will also be characterized.

The Eosinophilic Esophagitis Endoscopic Reference System (EREFS) is a scoring system for assessing the presence and severity of major endoscopic findings in the esophagus, including

esophageal edema, rings, exudates, furrows, and stricture. A global (EREFS) should be obtained that scores the most severe esophageal abnormality in the criteria scoring system.

Each of these GI scoring tools will have an additional separate overall global disease activity scoring assessment (0 normal –10 extremely diseased).

The EGREFS including duodenal findings and EREFS will be centrally-read from video recordings and Investigator-read during the upper endoscopies. Centralized imaging data assessments and scoring from expert physician review will be performed for all endoscopies. Standardized methods for training Investigators on the application of these scoring systems to ensure the collection of quality data using this measure will be implemented. Details on the scoring will be provided to Investigators in a separate manual.

The sites will remove patient-identifying information from the imaging data header prior to sending the imaging data to the central reader.

8.1.3 Patient Reported Outcomes

Note: following the approval of Amendment 4 (CSP version 5), participants will cease performing PRO assessment at their next clinic visit (ie, Part D Visit 20) and return their handheld PRO devices. The text below concern PRO assessments prior to implementation of Amendment 4.

Participants will complete all PRO assessments using a handheld device. The handheld device (or the web-based backup, in case of device failure) will be the only accepted source of PRO data. Participants will be required to complete a training module before taking the device home. 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 device will be programmed at Visit 1 with reminder alarms for the daily PROs. Study site staff will be able to adjust alarms for specific participant needs as required.

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

Participants are expected to bring the device to every Part A site visit. To reduce bias, review of compliance with the assessments, completion of any available assessments, and logging of the visit on the handheld device should be completed prior to any other study procedures. Compliance with the assessment schedule should be reviewed weekly throughout the study.

Participants with low compliance should be reminded to complete their assessments through follow-up phone calls and during site visits. Correcting poor compliance is required to ensure sufficient data are available for supporting the dual-primary endpoint of this study.

The timing and frequency for each PRO is presented Table 4. PRO assessments end at Visit 21 when the handheld device will be returned to the study site.

8.1.3.1 Symptom Assessment for Gastrointestinal Eosinophilic Diseases

The Symptom Assessment for Gastrointestinal Eosinophilic Diseases (SAGED) instrument was developed to measure gastrointestinal symptoms in participants diagnosed with EG/EGE. The SAGED instrument, comprising 8 items, measures the severity of abdominal pain, nausea, bloating, early satiety, lack of appetite, vomiting, and diarrhea, and frequency of vomiting. Severity for each concept is assessed using an 11-point numerical rating scale (where 0 = 'none' and 10 = 'worst imaginable'). Frequency of vomiting is reported as number of episodes of vomiting within the past 24 hours.

The SAGED instrument is a daily diary to be completed by participants each evening to record their symptoms during the past 24 hours. It will be completed by the participant every evening starting on the evening following Visit 1 as described in Table 4.

The SAGED score (range: 0-50) includes the items measuring severity of abdominal pain, nausea, bloating, early satiety and lack of appetite. The severity of vomiting and severity of diarrhea scores (range: 0-10) are considered separately. Frequency of vomiting is reported as a count.

8.1.3.2 Bristol Stool Form Scale

The Bristol Stool Form Scale is a frequently used diagnostic tool designed to evaluate human feces based on the shape and consistency of the stool (Lewis and Heaton 1997). There a 7 stool types, which are dependent upon the amount of time in which it spends in the colon:

1. Separate hard lumps, like nuts (hard to pass)
2. Sausage-shaped, but lumpy
3. Like sausage, but with cracks on its surface
4. Like a sausage or snake, smooth and soft
5. Soft blobs with clear cut edges (passed easily)
6. Fluffy pieces with ragged edges, a mushy stool
7. Watery, no solid pieces.

Types 3, 4, 5 are considered optimal. Types 1 and 2 indicate constipation, and Types 6 and 7 indicate diarrhea.

Participants were to be asked every evening to classify the stool type of each bowel movement they have had during the past 24 hours, starting on the evening following Visit 1 until the end of study (Visit 15, Week 76).

8.1.3.3 Dysphagia Symptom Questionnaire

The Dysphagia Symptom Questionnaire (DSQ) is a PRO measure validated for patients age 12 and older with dysphagia related to eosinophilic esophagitis (Dellon et al 2013b). The presence and severity of dysphagia symptoms in the past 24 hours are captured in a 4-item questionnaire.

Questions 1 and 2 utilize yes/no response capture if the patient consumed solid food that day (yes/no; unscored) and instances of food going down slowly or becoming stuck in the throat or chest (scored 0 for no and 2 for yes). Question 3 asks about the severity of dysphagia, based on actions the patient took to relieve the dysphagia at its worst point during the day. It ranges from 0 (dysphagia cleared up on its own) to 4 (patient sought medical attention for dysphagia). Question 4 asks the patient to report the worst pain experienced while swallowing food over the past 24 hours (no pain [0] to very severe pain [4]).

The total DSQ score ranges from 0 to 84, with a lower score indicating less severe dysphagia. Questions 2 and 3 are the only questions that contribute to the total DSQ score. The score is calculated by multiplying the daily scores of questions 2 and 3 by 14 days and dividing by the number of days in the past 14 days with no missing data. Question 4 is a standalone item intended to be evaluated separately. The DSQ can only be scored if there are at least 8 days with no missing data. Using anchor-based methods, the minimal clinically important differences and clinically important difference in DSQ score (mean absolute change) were estimated to be −6.5 points and −13.5 points, respectively (Hudgens et al 2017). Using DSQ Question 2, dysphagia-free days over each 28-day period following randomization will also be summarized.

The DSQ will be completed by the participant every evening starting on the evening following Visit 1, as described in Table 3.

8.1.3.4 Patient Assessment of Gastrointestinal Disorders Symptom Severity Index

The Patient Assessment of Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM) measures symptom severity in patients with upper gastrointestinal disorders. The standard recall version used in this study asks the patient to report the severity of symptoms over the past two weeks.

The instrument is composed of 20 items, which form 6 sub-scales: heartburn/regurgitation

(7 items), nausea/vomiting (3 items), post-prandial fullness/early satiety (4 items), bloating (2 items), upper abdominal pain (2 items), and lower abdominal pain (2 items). Subscale scores are calculated by averaging across items comprising the subscale; scores vary from 0 (none or absent) to 5 (very severe). The total PAGI-SYM score is calculated by taking the mean of the subscale scores. Higher scores indicate greater symptom severity.

The PAGI-SYM will be completed initially in the clinic at Visit 1 and Visit 2 and then at home every 4 weeks after Visit 2 as described in Table 4.

8.1.3.5 Patient-Reported Outcome Measurement Information System Short Form – Fatigue 7a

The Patient-Reported Outcome Measurement Information System (PROMIS) Short Form – Fatigue 7a consists of 7 questions assessing the severity of the patient's fatigue-related symptoms and the impact of these symptoms on health-related quality of life. The questions have a 7-day recall period, and the response options are on a 5-point Likert scale ranging from 1 (never) to 5 (always).

The standardized T-score (range 0-100) is obtained by rescaling the raw total score using the score conversion table. The mean T-score for the reference population of US adults is 50; the standard deviation of the reference population is 10. Higher T-scores represent greater fatigue.

The PROMIS Fatigue Short Form 7a assessment will be completed initially in the clinic at Visit 1 and Visit 2 and then at home every 4 weeks after Visit 2 as described in Table 4.

8.1.3.6 Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life

The Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QoL), the health-related quality of life counterpart to PAGI-SYM, measures disease-specific health-related quality of life impacts in patients with upper gastrointestinal disorders. It is comprised of 30 items and five sub-scales: daily activities (10 items), clothing (2 items), diet and food habits (7 items), relationships (3 items), and psychological well-being and distress (8 items). Patients are asked to rate the impacts of their gastrointestinal symptoms over the past two weeks on a scale ranging from 0 (none of the time) to 5 (all of the time).

Subscale scores are calculated by averaging across items comprising the subscale after reversing all scores. The total PAGI-QoL score is calculated by averaging across subscale scores. Lower scores reflect worse health-related quality of life.

The PAGI-QoL assessment will be completed initially in the clinic at Visit 1 and Visit 2 and then at home every 4 weeks after Visit 2 as described in Table 4.

8.1.3.7 Short Form 36-item Health Survey, Version 2, Acute Recall

The Short Form 36-item Health Survey, Version 2, acute recall (SF-36v2) is a 36-item

questionnaire on functional health and well-being. The recall period is 1 week. Responses to 35 of the 36 items are used to compute 8 domain scores and 2 component summary measures. The remaining "Health Transition" item asks participants to rate how their current state of health compares to their state of health 1 week ago. The Heath Transition item is not used to calculate the domain scores.

The 8 domains are: Physical Functioning, Role Limitations due to Physical Health, Bodily Pain, General Health Perceptions, Vitality, Social Functioning, Role Limitations due to Emotional Problems, and Mental Health. The component summary measures, Physical Component Summary (PCS) and Mental Component Summary (MCS), are computed from domain scores to give a broader metric of physical and mental health-related quality of life. The transformed score range for each of the 8 domains and for PCS and MCS is 0-100; higher scores indicate better health state. The change from baseline in PCS, MCS, and domain scores will be calculated.

The SF-36v2 assessment will be completed initially in the clinic at Visit 1 and Visit 2 and then at home every 4 weeks after Visit 2 as described in Table 4.

8.1.3.8 Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions

The Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions Version 2 (WPAI+CIQ) consists of questions about how health and health-related issues impact the ability to work, attend classes, and perform regular daily activities. The questionnaire relates to the previous 7 days. The WPAI+CIQ will be used to measure self-reported productivity loss.

This study uses the version of the instrument designed to measure the impact of a specific health problem (SHP). All instances of "problem" in the source text are replaced with "eosinophilic gastritis and/or eosinophilic gastroenteritis" to specify that the participant should respond with EG/EGE symptoms in mind.

The WPAI+CIQ assessment will be completed initially in the clinic at Visit 1 and Visit 2 and then at home every 4 weeks after Visit 2 as described in Table 4.

8.1.3.9 Patient Global Impression of Severity

Patient Global Impression of Severity (PGI-S) is a single item designed to capture the participant's perception of overall EG/EGE symptom severity over the past 14 days using a 4-point categorical response scale (none, mild, moderate, or severe).

The PGI-S assessment will be completed initially in the clinic at Visit 1. It should be repeated at home every 2 weeks after Visit 1 until Visit 2 is confirmed. The assessment will be completed at Visit 2 if no PGI-S assessment was completed within the last 24 hours. PGI-S

will then be repeated at home every 2 weeks after Visit 2 as described in Table 4.

8.1.3.10 Patient Global Impression of Change

Patient Global Impression of Change (PGI-C) is a single item assessment to capture the participant's perception of change in their EG/EGE symptoms. The participant is asked to report the degree to which their EG/EGE symptoms have changed since entering the treatment period using a 7-point scale (much better, moderately better, a little better, about the same, a little worse, moderately worse, or much worse).

The PGI-C assessment will be completed by participants every 2 weeks, starting 2 weeks after Visit 2 as described in Table 4.

8.1.3.11 Patient Global Impression of Benefit-Risk

The Patient Global Impression of Benefit-Risk (PGI-BR) is a 5-item questionnaire assessing the participant's perception of the overall benefits and risks of treatment. The 5 items assess: overall trial experience, efficacy, side effects, convenience and overall assessment of the benefits and harms of treatment. Items are rated on 5- or 6-point verbal rating or Likert-type scales.

The PGI-BR assessment will be completed by participants Visits 8 (Week 24) and 15 (Week 52) and after discontinuation if applicable as described in Table 4.

8.1.4 Clinical Global Impression of Severity

Clinical Global Impression of Severity (CGI-S) is a single item designed to capture the clinician's perception of the participant's overall disease severity at the time of the visit using a 6-point categorical response scale (no signs and/or symptoms to very severe signs and/or symptoms).

The answer will be entered in the eCRF at Week 0 and Week 24 of Part A (Table 1) and all visits in Part D (Table 3).

8.1.5 Clinical Global Impression of Change

Note: following the approval of Amendment 4 (CSP version 5), investigators will cease assessing the Clinical Global Impression of Change.

Clinical Global Impression of Change (CGI-C) is a single item assessment to capture the clinician's perception of change in the participant's health status. The clinician is asked to report the degree to which the participant has changed since entering the treatment period during the randomization study period using a 7-point scale (very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse). For the open label extension period, the clinician will report the degree to which the participant has changed since entering the open label extension period.

The answer will be entered in the eCRF at Part A and Part C visits as described in Table 1 and Table 2.

8.1.6 Diet Questionnaire

The Investigator or designee were to interview participants about their current diet restrictions at every visit. The information will be entered via a standardized diet questionnaire on a web portal.

8.1.7 Qualitative Patient Interview Sub-study

Note: following the decision to close enrollment of this study, it was also decided to discontinue the qualitative patient interview sub-study, with no further enrollment or interviews. The text below describes procedures used prior to that decision.

Adult participants who complete the ICF in select languages will be invited to participate in a qualitative patient interview sub-study. Up to 45 participants will be enrolled in the sub-study, which consist of interviews at three timepoints (baseline, end of double-blind treatment, and open label). The interviews will be non-interventional and will collect data on participants' experiences with EG/EGE, the study treatment, and non-pharmacological interventions for EG/EGE (eg, diet and lifestyle modifications). Interviews will be performed via telephone contact on a one-to-one basis. The duration of each interview is approximately 90 minutes.

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

Participants will be introduced to the sub-study during the informed consent process using the participant communication materials attached to the Qualitative Patient Interview Sub-study Manual. Interested participants will indicate their willingness to participate via the master ICF. Participants will be contacted according to procedures described in the Qualitative Patient Interview Sub-study Manual.

Each participating participant will be interviewed at the following timepoints:

- Baseline: between Visit 2 and Visit 3, to capture experiences before starting study treatment and/or in the first few months of study treatment
- Open-label extension period: between Visit 9 and Visit 11, to capture experiences after at least one month of benralizumab treatment
- Middle of open-label extension: after Visit 20, to capture experiences after at least 11 months of benralizumab treatment.

During each interview, participants will be asked a set of open-ended questions with probes to explore their symptoms, their experiences with study treatment, and their EG/EGE-related diet and lifestyle modifications. The interview discussion guide is provided as an appendix to the

Qualitative Patient Interview Sub-study Manual.

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

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

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

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

8.1.8 Eosinophilic Gastrointestinal Disease Diary

The Eosinophilic Gastrointestinal Disease Diary is an exploratory free text diary assessing participants' health-related quality of life. Participants may write about their symptoms and quality of life impacts using an app on their handheld PRO device. Completion of the diary is optional. Though the software will use occasional notifications to encourage the participant to enter data, there is no predetermined schedule of assessment. The diary is accessible at any time during the study in which participants have the handheld device, and participants may write up to once per day. **Note: following the approval of Amendment 4 (CSP version 5), participants will return their handheld PRO devices at their next clinic visit (ie, Part D Visit 20).**

8.2 Safety Assessments

Planned time points for all safety assessments are provided in Table 1 to Table 3.

8.2.1 Physical Examinations

- A complete physical examination will be performed in accordance with the schedule of activities and include assessments of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, muscular-skeletal (including spine and extremities) and neurological systems.
- A brief physical examination will be performed in accordance with the schedule of activities and will include, at a minimum, assessments of general appearance, lungs, cardiovascular system, and abdomen (liver and spleen).

- The participant's height and weight will be measured in accordance with the schedule provided in Table 1 through Table 2. The participant's weight will be recorded in kilograms and height will be recorded in centimeters.

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.

8.2.2 Vital Signs

Pre-dose vital signs (pulse rate, blood pressure, respiratory rate, and temperature) will be performed at timelines as specified in the Schedule of Activities.

It is recommended that vital signs are assessed before any interventional study procedures (blood test collection, investigational product administration), and prior to administration of maintenance therapy, if possible.

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 should 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 will be obtained before blood pressure.

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

Body temperature will be measured in Celsius; oral measurement is preferred, but other methods are acceptable as per local standards of care.

8.2.3 Electrocardiograms

A single 12-lead electrocardiogram (ECG) will be obtained at Visit 2 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals. The ECG will be taken in the supine position, after the participant has been resting for at least 5 minutes and prior to investigational product administration. The ECG results will be interpreted locally.

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

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the visits indicated in Table 1 to Table 3. All protocol-required laboratory

assessments, as defined in the table, must be conducted in accordance with the Laboratory Manual and the schedule of activities indicated in Table 1 to Table 3.

For information on methods of collection, assessment, labelling, storage, and shipment of samples, see the separate Laboratory Manual.

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 center 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 on the appropriate eCRF.

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

The following laboratory variables will be measured.

Table 9 Laboratory Safety Values

Clinical Chemistry		Hematology	Urinalysis
• Alanine aminotransferase	• Creatine kinase	• Hematocrit	• Appearance
• Albumin	• Creatinine	• Hemoglobin	• Blood
• Alkaline phosphatase	• Gamma-glutamyl transpeptidase	• Mean corpuscular volume	• Color
• Aspartate aminotransferase	• Glucose	• Platelet count	• Glucose
• Blood urea nitrogen	• Phosphorus	• Red blood cell count	• Ketones
• Calcium	• Potassium	• White blood cell count (absolute and differential)[a]	• Microscopy, including white and red blood cells
• Chloride	• Sodium		• pH
• Cholesterol, total	• Total bilirubin		• Protein/Albumin
• CO_2[b]	• Uric acid		• Specific gravity

[a] Eosinophil, basophil, and monocyte counts and differentials will be redacted from the central laboratory reports starting from Visit 2 (see Section 6.3.3).

[b] Measured as bicarbonate.

8.2.5 Pregnancy Testing

The following tests are applicable to female participants only and will be conducted as per the schedule provided in Table 1 through Table 3, as applicable.

- Follicle-stimulating hormone: The test will be performed at Visit 1 only to confirm postmenopausal status in women <50 years of age who have been amenorrheic for ≥12 months. This test is to be sent to and analyzed at the central laboratory.
- Serum beta-human chorionic gonadotropin: The test will be performed at Visit 1 for WOCBP. This test is to be sent to and analyzed at the central laboratory. Urine human chorionic gonadotropin: To be performed at the study site for all females (according to the schedule of assessments in Table 1 through Table 3) **before investigational product** administration using a dipstick except for those females who are NOT of childbearing potential as defined in inclusion criterion 8. This kit is to be provided by the central lab and analyzed locally at the sites. A positive urine test result must be confirmed with serum beta human chorionic gonadotropin analyzed at the central laboratory. Between on-site pregnancy testing, the patient is encouraged to monitor for pregnancy, and, if pregnant, should contact the site and should not administer IP.

Note: Patients should be strongly encouraged to monitor for pregnancy during the study and report a pregnancy to the site as soon as possible.

8.2.6 Other Safety Assessments

Serology

Blood samples for the hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), hepatitis C antibody (anti-HCV), and the HIV-1 and HIV-2 antibodies will be taken according to Table 1 through Table 3. The analysis will be performed at the central laboratory. Any low-positive or indefinite results must be confirmed prior to determining the participant's eligibility.

For participants that are HBsAg positive or anti-HBc positive at Visit 1, hepatitis D antibody and hepatitis B virus DNA testing will be performed. For those participants that are HBsAg positive or anti-HBc positive, alanine aminotransferase and hepatitis B-virus DNA may be analyzed at scheduled on-site visits to monitor for hepatitis B reactivation.

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

8.3 Adverse Events and Serious Adverse Events

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

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

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

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

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

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

AEs will be collected from time of signature of the IFC throughout the treatment period and including the follow-up period.

SAEs will be recorded from the time of signing of the IFC.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix B. The Investigator will submit any updated SAE data to the Sponsor 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 sponsor.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant’s last AE assessment in the study are 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 AEs at the end of the study, if judged necessary.

Adverse event variables

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix B. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

The following variables will be collected for each AE:

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

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

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

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- Seriousness criteria
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedures
- Causality assessment to other medication

8.3.3 Causality Collection

The investigator should assess causal relationship between investigational product 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 should 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 to the Clinical Study Protocol.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or guardian or reported in response to the open question from the study site staff: '*Have you/the child 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 Clinical Study Protocol mandated laboratory tests and vital signs will be summarized in the Clinical Study Report.

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

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

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

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 Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new or more severe gastrointestinal symptoms or new gastroduodenal endoscopic findings should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

8.3.7 Disease Under Study

Symptoms of disease under study are those which might be expected to occur as a direct result of EG/EGE. These events may include abdominal pain, nausea, bloating, vomiting severity,

early satiety, loss of appetite, and diarrhea. Events which are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the investigational product.

8.3.8 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedures. All SAEs will be recorded in the eCRF.

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

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

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

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

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

8.3.9 Pregnancy

Patients should be strongly encouraged to monitor for pregnancy during the study and report a pregnancy to the site as soon as possible.

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for if the pregnancy is discovered before the study participant has received any study intervention.

8.3.9.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, the investigational product should be discontinued immediately and the pregnancy reported to AstraZeneca.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product 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) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.8) 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 pregnancy outcome form is used to report the outcome of the pregnancy.

8.3.10 Medication Error, Drug Abuse, and Drug Misuse

8.3.10.1.1 Timeline

If an event of medication error, drug abuse, and drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 calendar 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 completed within **1** (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 8.3.8) and **within 30 days** for all other events.

8.3.10.1.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an investigational medicinal product or AstraZeneca non-investigational medicinal product that either causes harm to the participant or has the potential to cause harm to the participant.

The definition of a medication error can be found in Appendix B 4.

8.3.10.1.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of investigational medicinal product or AstraZeneca non-investigational medicinal product for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

8.3.10.1.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of investigational medicinal product or AstraZeneca non-investigational medicinal product for medicinal purposes outside of the authorised product information, or for unauthorised investigational medicinal products or AstraZeneca non-investigational medicinal product, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

8.3.10.1.5 Reporting of Overdose

Refer to Section 8.4 for definition and treatment of overdose.

8.3.11 Device Constituent Deficiencies

In a combination drug-device IMP (e.g. 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.

SADE is defined as any Device Constituent Deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

- For device constituent deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
- A remedial action is any action other than routine maintenance or servicing of a device constituent where such action is necessary to prevent recurrence of a device constituent deficiency. This includes any amendment to the device constituent design to prevent recurrence.
- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the device constituent deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

8.3.11.1 SADE 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.

8.3.12 Management of investigational product-related toxicities

Appropriate drugs, such as epinephrine, H1 and H2 antihistamines, and corticosteroids, and medical equipment to treat acute anaphylactic reactions should be available at the study site, and study personnel should be trained to recognize and treat anaphylaxis (see Lieberman et al 2010). Details on anaphylaxis management are provided in Appendix F 4.

Anaphylaxis will be defined as a serious reaction that is rapid in onset and may cause death. 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 1 of the following: a) respiratory compromise; b) or 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 F.

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

Serum tryptase or other blood or urine testing (drawn 90 +/- 30 min after concern for anaphylaxis is identified) relevant to the diagnosis of anaphylaxis may be obtained at a local lab at the discretion of the Investigator. If local testing of serum tryptase is unavailable, there

will be an option to have the sample tested centrally.

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 diagnoses/symptoms on the relevant AE modules in the CRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module

If an overdose on an investigational product or AstraZeneca non-investigational product occurs in the course of the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives 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 or 5 calendar days** for overdoses associated with an SAE (see section 8.3.8) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

Note: following the approval of Amendment 4 (CSP version 5), no further human biological samples as described in this section will be collected.

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 Clinical Study Report in line with consent and local requirements, after which they will be destroyed/repatriated.

- Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
- Pharmacokinetic samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the Clinical Study Report.

- Remaining anti-drug antibody sample aliquots will be retained at AstraZeneca or its designee for a maximum of 5 years following issue of the Clinical Study Report. Additional use includes but is not limited to further characterization of any anti-drug antibodies, 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 Clinical Study Report.

8.5.1 Pharmacokinetics

- Serum samples will be collected for measurement of serum concentrations of benralizumab as specified in Table 1. It is important that the date, time, and location of each SC injection is recorded for each participant.
- Pharmacokinetic samples will be collected before administration of investigational product, if applicable.
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.
- 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
- Samples collected for analyses of benralizumab concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples will be collected, processed, labelled, stored, and shipped as detailed in the Laboratory Manual.
- The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentration in serum of patients that received benralizumab will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

The bioanalytical laboratory will have access to the randomization list. Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

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 anti-drug antibodies in serum will be collected pre-investigational product administration as detailed in Table 1 and assayed 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.

Anti-drug antibodies samples may also be further tested for characterization of the anti-drug antibody response.

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

8.5.3 Pharmacodynamics

Blood and urine samples will be collected for pharmacodynamic measurements at timepoints specified in Table 1.

For information on storage, re-use, and destruction of pharmacodynamic samples see Section 8.5 and Appendix C.

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of mandatory samples for biomarker analysis

Note: following the approval of Amendment 4 (CSP version 5), no further human biological samples as described in this section will be collected.

Mandatory collection of samples for exploratory biomarker research is a part of this study. Samples for exploratory biomarker research are required and will be collected from all participants in this study as specified in Table 1. Blood (whole blood, serum, and plasma) as well as stomach and/or intestinal tissue will be collected. Samples will be tested in order to evaluate the effect of benralizumab on gene expression (RNA transcript analysis), inflammation, and immunological mechanisms related to the pathogenesis of EG/EGE.

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

8.6.1.1 Serum

Serum samples will be collected as specified in Table 1 to evaluate the pharmacology of benralizumab as well as biomarkers of eosinophil recruitment, activation, and survival (eg, absolute eosinophil count, CCI [redacted]). Additional markers of cellular inflammation and/or activation may be assessed including, but not limited to, those associated with humoral

autoimmunity (total serum IgE), T cell subsets (eg, CCI), eosinophil granule proteins (eg,CCI), epithelial cell damage (eg,CCI), or activation of inflammatory cells includingCCI . The results from such studies will not be reported in the CSR but in separate reports or publications as appropriate.

Serum samples will be collected according to the schedules presented in Table 1 for analysis of serum tryptase levels. The analysis will be performed at the central laboratory.

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

8.6.1.2 Tissue Histology and Immunostaining

Biopsies will be collected at screening, Week 24, and Week 52. Biopsies will be taken from sites within the stomach and/or small intestine identified during endoscopy by site physicians. At the time of each EGD, pts will also have biopsies taken of the esophagus, 2 each proximal and distal, for monitoring of esophageal eosinophilia during the trial.

Biopsies will be collected and processed locally at the clinical sites as described in detail in the Laboratory Manual.

Staining of the biopsies will be conducted at an appropriate contract lab and/or at AstraZeneca. The gastrointestinal biopsies will be stained for chemical markers for the detection and enumeration of inflammatory cell types such as eosinophils, mast cells, and basophils. Other molecules that may be directly or indirectly involved in the mechanism of action of benralizumab (including, but not limited to,CCI) and/or the pathophysiology of EG/EGE may be investigated.

8.6.1.3 RNA Transcriptome Research

Transcriptome studies (blood and biopsy) will be conducted. Transcriptomic studies of serum and/or biopsies collected from gastrointestinal mucosal tissue will be conducted using microarray, RNA-sequencing, and/or alternative equivalent technologies, which facilitate the simultaneous measurement of the relative abundances of as many as thousands of RNA species, resulting in a transcriptome profile for each tissue sample. This will enable the evaluation of transcriptome profiles that will provide molecular insight into mechanisms underlying tissue pathology, identification of features associated with pathology conserved across subjects or across areas of the GI tract within a given subject, as well as the mechanism of action of benralizumab and how its clinical efficacy correlates with changes in gastrointestinal tissue transcriptome.

Details on biopsy acquisition and processing for transcriptomics will be included in the lab manual.

8.7 Optional Genomics Initiative Sample

Collection of optional samples for Genomics Initiative research is also part of this study and is subject to a separate consent in the ICF addendum, and local regulations.

A blood sample for DNA isolation will be collected from adult participants who have consented to participate in the genetic analysis component of the study at Visit 2 (Table 1). Adolescents are not included in this option. Participation is optional; participants who do not wish to participate in the genetic research may still participate in the study. Samples can be collected at any time after the ICF has been signed.

Details on processes for collection, shipment, storage and destruction of these samples are provided in Appendix D and in the Laboratory Manual.

8.8 Healthcare Resource Utilization

EG/EGE-related and other GI-disease complications-related healthcare resource utilization data will be collected in the eCRF by the Investigator and study-site personnel for all participants throughout the study. Protocol-mandated visits, procedures, tests, and encounters are excluded.

At visits when healthcare use is being collected, as specified in Table 1 through Table 3, the Investigators retrospectively collect any EG/EGE-related and other GI disease complications-related healthcare resource utilization information. At baseline, healthcare resource utilization will be collected with a 6-month recall period. At all subsequent visits, any EG/EGE-related and other GI disease complications-related healthcare resource utilization information will be collected with a recall period of 'since last HRU assessment during the scheduled visit'.

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

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days or length of stay, including duration by wards [eg, intensive care unit])
- Outpatient medical encounters and interventions (including specialist visits, General Practitioner visits, home health care visits, and emergency room visits, etc.)
- Number and type of diagnostic and therapeutic tests and procedures

9 STATISTICAL CONSIDERATIONS

The analysis of the study will be performed when all patients have completed their last visit in the study. Data from this analysis will be summarized in a synoptic CSR.

9.1 Statistical Hypotheses

No hypothesis testing will be performed given the decision to terminate recruitment to the study, resulting in the intended sample sizes required not being recruited.

9.2 Sample Size Determination

The original sample size calculations for the study were based on the change from baseline in SAGED score at Week 24 dual primary endpoint. Changes in the other dual primary histological response rate endpoint required smaller sample sizes as larger relative differences are assumed (10% placebo response versus 80% benralizumab response).

Part A intended to enroll approximately 50 patients with EG (with or without duodenal involvement). Eligible patients with duodenal only disease were also to be included whilst enrolling the required 50 EG patients, with no minimum requirement on the number of duodenal only patients. A minimum of 60 and a maximum of 80 patients in the overall population in Part A were targeted. Thirty patients per arm in the overall population, and 25 patients per arm with gastric disease would provide >85% and >80% power for statistical significance at the 10% 2-sided level for each population respectively, if the true treatment effect for the change from baseline in SAGED score is a standardized effect size (difference in means/ standard deviation) of 0.75. A standardized effect size is used as the variability of the SAGED score is not known yet. An effect size of 0.75 is a similar relative effect size as that observed in the antolimab Phase 2 trial (Dellon et al 2020). Approximately 20 adolescent patients (12 to 17 years of age) with either EG or duodenal only disease were targeted for inclusion in Part A.

The final sample size for the study is limited to 12 patients due to closure of recruitment to the study.

9.3 Populations for Analyses

The following populations are defined:

Table 10 Populations for Analysis

Population/Analysis set	Description
Enrolled	All participants who sign the ICF
All patients analysis set	All patients screened for the study, to be used for reporting of disposition and screening failures
Safety analysis set	The safety analysis set consists of all patients who have received at least one dose of investigational product. Erroneously treated patients (eg, those randomized to one treatment but actually given the other treatment) are accounted for in the treatment group of the treatment they actually received. A patient who has on one or several occasions received active

Population/Analysis set	Description
	investigational product is classified as active. Safety summaries will be based on this analysis set and for whom any post-dose data are available.
Open-label benralizumab analysis set	All patients who receive at least 1 dose of benralizumab after the end of the double-blind treatment period

9.4 Statistical Analyses

Analyses will be performed by AstraZeneca or its representatives. Any deviations from the analyses outlined here will be reported in the CSR.

9.4.1 General Considerations

As recruitment to the study has been terminated and the final sample size is too low to perform originally planned analysis, analyses will consist of descriptive summaries and figures of safety data for the double-blind placebo-controlled period (Part A) and the open-label periods (Parts C and D) as well as select patient listings of demographic and baseline characteristics, safety and key efficacy data. No statistical analyses or hypothesis testing will be performed.

All available data will be included in data presentations, regardless of use of rescue therapy, restricted medications for EG/EGE or treatment discontinuation.

9.4.2 Efficacy

All available (from Part A and Part C) peak eosinophil count (eos/hpf) data will be listed by patient including whether patients achieved a histological response at available visits, defined as ≤6 eosinophils/hpf in the stomach and/or, ≤15 eosinophils/hpf in the duodenum, as applicable based on disease area involvement at enrollment.

All available (from Parts A and C) SAGED score data will be listed by patient including individual abdominal pain, nausea, bloating, early satiety and loss of appetite severity item scores and the bi-weekly SAGED score calculated as the 14-day mean of the daily sum of the item scores.

Listings of other efficacy endpoints may be produced as required including all available data from Parts A, C, and D. Individual patient data may be presented graphically as appropriate.

Available efficacy data collected in relation to EG-REFs, EoD-REFs, PGI-S/C, CGI-S/C will be listed by patient (from the point of protocol amendment onwards only PGI-C data is collected during Part D but data already collected from patients in Part C will be included as available).

9.4.3 Safety

Safety data presentations will be performed using the safety analysis set.

The first presentation of safety data will include only data from the double-blind, placebo-controlled first 24 weeks of the study (Part A double-blind period). Patients will be summarized according to the treatment they received (benralizumab or placebo).

Safety data from the open-label benralizumab parts of the study (Part C and Part D) will be reported separately from Part A.

Safety data will be presented using descriptive statistics, figures, and data listings. Full details will be provided in the SAP.

In general, the baseline value for safety analyses is the last non missing value prior to administration of the first dose of investigational product.

9.4.3.1 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.

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

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

AE listings for the safety analysis set will cover details for each individual AE, including information on the relationship to investigational product as assessed by the investigator, maximum intensity, seriousness, death and events leading to discontinuation of investigational product, as well as other action taken related to investigational product.

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

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

Treatment Emergence

The following events are considered treatment emergent:

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

9.4.3.2 Clinical Safety Laboratory Assessments

Laboratory data for hematology and clinical chemistry will be Listed. 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.

9.4.3.3 Vital Signs and Weight

Vital sign parameters will be listed for all patients during the study.

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

9.4.4 Other Analyses

9.4.5 Methods for multiplicity control

As no hypothesis testing will be performed and no statistical comparisons of benralizumab versus placebo will be made there is no adjustment for multiplicity necessary.

9.5 Interim Analyses

No interim analyses are planned for this study.

9.6 Data Monitoring Committee

For details on the Independent Data Monitoring Committee, see Appendix A 5.

Note: With the approval of Amendment 4, the open-label dosing in Part D will not require the use of an IDMC.

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH Good Clinical Practice Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a contract research organization, but the accountability remains with AstraZeneca.
- 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

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the [Investigator's Brochure or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.

- A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.

If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.

In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.

- AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.

The investigator should have a process in place to ensure that:

- The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
- A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, the US Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICFs during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.
- The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.
- **Patients who participate in Part D will be required to sign a supplemental ICF specific for Part D.**

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Independent Data Monitoring Committee

An independent DMC consisting of 2 clinicians (including at least 1 EG/EGE expert) and a statistician will be used for this study to monitor overall patient safety. The Independent Data Monitoring Committee will receive participant profiles including safety data and unblinded participant laboratory results on a regular basis and will meet to discuss the data as needed. Based on their review, the Independent Data Monitoring Committee may recommend changes to the study design or conduct or that individual participants be discontinued from the study for safety reasons.

The Independent Data Monitoring Committee will communicate decisions/recommendations to an internal (Sponsor) Executive Committee that will consist of representatives from regulatory affairs, clinical development, biostatistics and patient safety and will remain blinded to data. The committee will decide on the implementation of the decisions/recommendation and will communicate back their actions and justification to the Independent Data Monitoring Committee.

Further details, composition and operation of the Independent Data Monitoring Committee are described in a separate Independent Data Monitoring Committee charter.

The safety of all Sponsor clinical studies is closely monitored on an ongoing basis by the Sponsor representatives in consultation with AstraZeneca's Patient Safety department.

Note: With the approval of Amendment 4, the open-label dosing in Part D will not require the use of an IDMC.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com, http://www.clinicaltrials.gov, and https://www.clinicaltrialsregsiter.eu, as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH Good Clinical Practice, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the data monitoring plan.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open, and it's opening date will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or ICH Good Clinical Practice guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRB/IECs, the regulatory authorities, and any contract research organizations used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

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

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events (AEs) for **malignant tumors** reported during a study should generally be assessed as **Serious AEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious AE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself an serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of

intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough

information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an investigational medicinal product or AstraZeneca non-investigational product that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- **Was identified and** intercepted before the participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error

- Participant accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of investigational medicinal product or AstraZeneca non-investigational product for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site (DES) using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- ·The dug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of investigational medicinal product or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised investigational medicinal products or AstraZeneca non-investigational medicinal products, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes

- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the ICF.

The investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

Appendix D Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant´s DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

- All adult participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol and provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Previous allogeneic bone marrow transplant
  - Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection
  - Healthy Volunteers and pediatric patient samples will not be collected for the Genomics Initiative.

Withdrawal of Consent for Genetic Research

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main Clinical Study Protocol.

Collection of Samples for Genetic Research

- The blood sample for this genetic research will be obtained from the participants at randomization (Visit 2). Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and Storage of DNA Samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years, from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated Organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).
- The link between the participant enrollment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

- The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed Consent

- The genetic component of this study is optional and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the participant must sign and date both the ICF for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated ICFs must be given to the participant and the original filed at the study center. The Principal Investigator is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyses the samples.
- AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organizations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Appendix E Best Practice Guidelines for Completing PRO Assessments

Participants will complete PRO assessments at home using a handheld device. PRO assessments must be collected in a systematic way to ensure data integrity. The following best practice guidelines should be followed when collecting PRO data via handheld device:

- Provide the right environment
  - Participants should complete the PRO questions in a quiet and private location without help from others.
- Purpose of the PRO assessments
  - Discuss the purpose of the PRO assessments with the participants. Reinforce that these are standardized questions designed to capture the participant experience in the study.
  - Inform participants that each PRO assessment is independent of the others. Some questions may be very similar or seem repeated, but it is important to answer each question independently.
- Help with procedural questions
  - Make sure the participant understands how to complete the PRO assessment. Assessment instructions are usually self-explanatory, but staff may answer questions about procedural issues like what it means to "tick a box".
- Avoid bias: do not clarify the meaning of questions or responses
  - Sometimes participants will ask site staff to clarify the meaning of a question or response. To avoid introducing any bias, politely tell the participant that you cannot clarify items. Remind them that there are no right or wrong answers. Inform the participant that they should select the response that best answers the question as they understand it.
  - If a participant becomes unable to independently use the handheld device during the treatment period of the study (eg, unable to read due to vision problems), then the participant should be exempted from completing PRO questionnaires used for efficacy endpoints and may continue in the study with external help for symptom severity and background/rescue medication use questionnaires completion. Participant's exemption in this regard must be pre-approved by an AstraZeneca study physician/delegate and appropriately documented.
- No time limits
  - Although most PRO assessments require only a few minutes to complete, the participant should be given as much time as is needed.

- Train the participant on handheld device usage
  - Train participants on how to use the handheld device using the materials and training provided by the device vendor.
  - Provide guidance on whom the participant should call if they have problems with the device.
- Monitor compliance
  - Minimizing missing data is a key aspect of study success. Compliance with device completion must be checked weekly (at a minimum) to ensure that the participant is completing the assessments as scheduled. Follow-up with participants via phone and at the visits is required to ensure sufficient data are available for supporting the dual-primary endpoint of this study.

Appendix F Anaphylaxis: Definition, Signs, Symptoms and Management

F 1 Introduction

As with any antibody, allergic reactions to dose administration are possible. The World Health Organization has categorized anaphylaxis into 2 subgroups, which are clinically indistinguishable: immunologic (IgE-mediated and non-IgE-mediated [eg IgG and immune complex-mediated]) and nonimmunologic. The clinical criteria for defining anaphylaxis for this study are listed in Section F 2 of this Appendix. A guide to the signs and symptoms and management of acute anaphylaxis is provided in Section F 3 of this Appendix. Appropriate drugs, such as epinephrine, antihistamines, corticosteroids, and medical equipment to treat anaphylactic reactions must be immediately available at study sites, and study personnel should be trained to recognize and treat anaphylaxis according to local guidelines.

If an anaphylactic reaction occurs, a blood sample for serum tryptase should be collected as at 90 minutes ± 30 minutes after the event; analysis for serum tryptase will be performed at a local laboratory. If local testing of serum tryptase is unavailable, there will be an option to have the sample tested centrally. Other blood or urine testing relevant to the diagnosis of anaphylaxis may be obtained at a local lab at the discretion of the Investigator.

F 2 Clinical Criteria for Defining Anaphylaxis and Immune Complex Disease

Anaphylaxis

In adults, anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST 1 OF THE FOLLOWING:
   (a) Respiratory compromise (eg dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).
   (b) Reduced blood pressure or associated symptoms of end-organ dysfunction (eg hypotonia [collapse], syncope, incontinence).
2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   (a) Involvement of the skin-mucosal tissue (eg generalized hives, itch-flush, swollen lips-tongue-uvula).
   (b) Respiratory compromise (eg dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).

(c) Reduced blood pressure or associated symptoms (eg hypotonia [collapse], syncope, incontinence).

(d) Persistent gastrointestinal symptoms (eg crampy abdominal pain, vomiting).

3 Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours): Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that patient's baseline.

Immune Complex Disease

Immune complex disease or Hypersensitivity Type III is evoked by the deposition of antigen-antibody or antigen antibody-complement complexes on cell surfaces, with subsequent involvement of breakdown products of complement, platelets, and polymorphonuclear leukocytes, and development of vasculitis; serum sickness and nephritis are common.

F 3 Signs and Symptoms and Management of Acute Anaphylaxis

Anaphylaxis is an acute and potentially lethal multi-system allergic reaction in which some or all of the following signs and symptoms occur:

Other earlier or concomitant signs and symptoms can include:

- Itchy nose, eyes, pharynx, genitalia, palms, and soles
- Rhinorrhea
- Change in voice
- Metallic taste
- Nausea, vomiting, diarrhea, abdominal cramps and bloating
- Light-headedness
- Headache
- Uterine cramps
- Generalized warmth

F 4 Management of Acute Anaphylaxis

F 4.1 Immediate intervention

1 Assessment of airway, breathing, circulation, and adequacy of mentation.

2 Administer epinephrine intramuscularly every 5-15 minutes, in appropriate doses, as necessary, depending on the presenting signs and symptoms of anaphylaxis, to control signs and symptoms and prevent progression to more severe symptoms such as respiratory distress, hypotension, shock and unconsciousness.

F 4.2 Possibly appropriate, subsequent measures depending on response to epinephrine

(a) Place participant in recumbent position and elevate lower extremities.

(a) Establish and maintain airway.

(b) Administer oxygen.

(c) Establish venous access.

(d) Normal saline intravenous for fluid replacement.

F 4.3 Specific measures to consider after epinephrine injections, where appropriate

(a) Consider epinephrine infusion.

(b) Consider H1 and H2 antihistamines.

(c) Consider nebulized β_2-agonist (eg albuterol [salbutamol]) for bronchospasm resistant to epinephrine.

(d) Consider systemic corticosteroids.

(e) Consider vasopressor (eg dopamine).

(f) Consider glucagon for patient taking β-blocker.

(g) Consider atropine for symptomatic bradycardia.

(h) Consider transportation to an emergency department or an intensive care facility.

(i) For cardiopulmonary arrest during anaphylaxis, high-dose epinephrine and prolonged resuscitation efforts are encouraged, if necessary.

Appendix G Changes Related to Mitigation of Study Disruptions

Note: Changes below should be implemented only during study disruptions due to any of or a combination 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) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the Sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

G 1 Consent/Reconsent/Assent/Re-assent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Consent/reconsent/assent/re-assent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections G 2to G 5. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

G 2 Rescreening of Patients To Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened patients. The investigator should confirm this with the designated study physician.

In addition, during study disruption there may be a delay between confirming eligibility of a patient and either enrollment into the study or commencing of dosing with investigational product. If this delay is outside the screening window specified in Table 1 the patient will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a patient in addition to that detailed in Section 5.4. The procedures detailed in Section 5 must be undertaken to confirm eligibility using the same screening/enrollment number as for the patient.

G 3 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified Health Care Professional from the study site or third-party vendor service will visit the patients home or other remote location as per local standard operating procedures (SOPs), as applicable. Supplies will be provided for a safe and efficient visit. The qualified

Health Care Professional will be expected to collect information per the Clinical Study Protocol.

G 4 Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix, the term telemedicine visit refers to remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs, concomitant medication, diet questionnaire, review compliance of PRO assessments, and healthcare resource utilization to be reported and documented. Scheduled blood sample collection and endoscopies will be performed as soon as the participant can safely attend subsequent site visit.

G 5 At-home or Remote Location Investigational Product Administration Instructions

If a site visit is not possible, at-home or remote location administration of investigational product may be performed by a qualified Health Care Professional, provided this is acceptable within local regulation/guidance, or by the participant or his/her caregiver. The option of at-home or remote location investigational product administration ensures patients safety in cases of a pandemic where participants may be at increased risk by traveling to the site/clinic. This will also minimize interruption of investigational product administration during other study disruptions, eg, site closures due to natural disaster.

G 5.1 At-home or Remote Location investigational product Administration by a Qualified Health Care Professional or Third Party Vendor Service

A qualified Health Care Professional from the study site or third party vendor service should administer the investigational product at the participant's home or other remote location according to the Clinical Study Protocol. All necessary supplies and instructions for administration and documentation of investigational product administration will be provided. Additional information related to the visit can be obtained via a telemedicine or home visit.

G 5.2 At-home or Remote Location Investigational Product Administration by the Participant or His/her Caregiver

Prior to at-home or remote location investigational product administration the investigator must assess the participant or his/her caregiver to determine whether they are appropriate for at-home or remote location administration of investigational product. Once the participant or his/her caregiver is deemed appropriate for at-home or remote location administration, he/she must receive appropriate training. All necessary supplies and instructions for administration

and documentation of investigational product administration will be provided. More information related to the visit can be obtained via a telemedicine or home/remote visit.

G 5.3 Data Capture During Telemedicine or Home / Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified Health Care Professional from the study site or third party vendor service, or by the participant themselves, eg, details of self-administration, PRO, signs and symptoms.

Appendix H Abbreviations

Abbreviation	Explanation
AE	Adverse event
eCRF	Electronic Case Report Form
DSQ	Dysphagia Symptom Questionnaire
EG	Eosinophilic gastritis
EGE	Eosinophilic gastroenteritis
EG-REFS	Eosinophilic Gastritis Endoscopic Reference System
hpf	High powered field
IATA	International Airline Transportation Associations
ICF	Informed Consent Form
ICH	International Council for Harmonization
IP	Investigational Product
IRB/IEC	Institutional Review Board/Independent Ethics Committees
PCS	Physical Component Summary of the SF-36v2
PAGI-QoL	Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life
PAGI-SYM	Patient Assessment of Gastrointestinal Disorders Symptom Severity Index
MCS	Mental Component Summary of the SF-36v2
PGI-C/S/BR	Patient Global Impression of Change/Severity/Benefit-Risk
PRO	Patient-reported outcome
PROMIS	Patient-Reported Outcome Measurement Information System
Q4W	Every 4 weeks
Q8W	Every 8 weeks
RTSM	Randomisation and Trial Supply Management
SAGED	Symptom Assessment for Gastrointestinal Eosinophilic Diseases
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SoA	Schedule of activities
SF-36v2	Short Form Health Survey Version Short (Acute Recall)
WOCBP	Women of childbearing capacity
WPAI+CIQ	Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions

Appendix I Protocol Amendment History

The Summary of Changes Table for the current revision is located directly before the Table of Contents.

Amendment 3 (CSP ver 4.0): 15-September-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 because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment.
The primary rationale for this amendment is to include the free text questionnaire (Eosinophilic Gastrointestinal Disease Diary) for exploratory descriptive analyses.

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial /Non-substantial**
0 Schedule of Activities	Updated Tables 1-4 to reflect changes in assessment schedules, as applicable	Consistency with main text of CSP and clarity	Non-substantial
8.1.3.6 Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life	Edited description of PAGI-QoL	Error correction	Non-substantial
8.1.8 Eosinophilic Gastrointestinal Disease Diary	Added description of new assessment	Added new assessment	Non-substantial
8.2.4 Clinical Laboratory Safety Assessments	Added albumin to clinical chemistry labs in Table 9	Additional safety assessment	Non-substantial
8.2.6 Other Safety Assessments	Clarified instructions for follow-up testing for HBV reactivation	Clarity	Non-substantial

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial /Non-substantial**
0 Schedule of Activities 6.1.3.6 Optional Remote Visits for Patients Doing At-Home or Remote-Location Investigational Product Administration 8.2.5 Pregnancy Testing	Reduced urine pregnancy testing requirements to quarterly, rather than every visit after Week 24 (during open-label treatment). All relevant sections updated with new guidance	Updated internal guidance for benralizumab	Non-substantial
8.3.12 Management of investigational product-related toxicities Appendix F Anaphylaxis: Definition, Signs, Symptoms and Management	Clarified requirements for serum tryptase analysis	Clarity	Non-substantial
8.3.9.1 Maternal Exposure	changed wording from "congenital abnormality" to "congenital anomaly"	Updated guidance and CSP template	Non-substantial
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarised	Non-substantial

Amendment 2 (CSP ver 3.0): 04-Mar-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 because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment.
The primary rationale for this amendment is to include minor clarifications to ensure correct interpretation of the protocol.

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial /Non-substantial**
8.1.1. Histopathology and Tissue Eosinophil Counts 8.1.2. Endoscopic Reference System Scores	Corrected description of Week 1	To ensure that in-text description of assessments aligns with Schedule of Activities table.	Non-substantial
8.1.7. Qualitative Patient Interview Sub-study	Number of patients in sub-study changed from '30' to 'up to 45'.	Correction from previous version	Non-substantial
8.1.1. Histopathology and Tissue Eosinophil Counts	Reworded to state that at least two of the four required duodenal biopsies should be obtained from the lower part of the duodenum	Clarification allows for obtaining of biopsies from the upper duodenum according to clinician or investigator discretion	Non-substantial
8.2.2. Vital Signs	Added language permitting non-oral measurements of body temperature	Allows for other methods of measuring body temperature that may be more acceptable per local standards of care, and aligns with other benralizumab studies.	Non-substantial
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarised	Non-substantial

Amendment 1 (CSP ver 2.0): 23-Feb-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 because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment.
The primary rationale for this amendment is to update the description of the PGI-S tool, which has been changed from a 6-point to a 4-point scale. Details of the collection and analysis of healthcare research utilization data have also been updated. In addition, some minor clarifications were made to ensure correct interpretation of the study protocol.

Summary of Changes to the Clinical Study Protocol			
Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial /Non-substantial**
1.1.Synopsis	The word 'corticosteroid' was added to the objectives and endpoints table	Clarification of the rescue medication use objective and to align with the protocol text.	Non-substantial
0.Schedule of Activities	Removed the healthcare resource utilization assessment, CGI-S, and CGI-C from the unscheduled visit	Streamlining of required assessments at the unscheduled visits	Non-substantial
3. Objectives and Endpoints	The word 'corticosteroid' was added to the objective for rescue medication use in Table 6	Alignment with protocol text	Non-substantial
3. Objectives and Endpoints	Reworded text of healthcare resource utilization objective and endpoint	To provide additional clarity and detail around the healthcare resource utilization data	Non-substantial
5.4.Screen Failures	Corrected the numbers of the inclusion/exclusion criteria that are not allowed to be considered for re-screening.	Correction of a typo in previous version	Non-substantial
8.1.3.9. Patient Global Impression of Severity	Changed the PGI-S scale from a 6-point to a 4-point scale (none/mild/moderate/severe), and clarified that the PGI-S asks participants to consider the severity of their EG/EGE symptoms.	Revised scale will help participants select meaningful responses.	Non-substantial
Section 8.1.3.10. Patient Global Impression of Change	Clarified that the PGI-C asks participants to consider change in their EG/EGE symptoms.	Revised wording will help participants select meaningful responses.	Non-substantial
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarised	Non-substantial

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