A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Efficacy of Benralizumab (Anti-ILRA) in Subjects with Eosinophilic Gastritis

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Clinical Study Protocol

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A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL TO EVALUATE THE EFFICACY OF BENRALIZUMAB (ANTI-IL5RA) IN SUBJECTS WITH EOSINOPHILIC GASTRITIS

Sponsor: Dr. Marc Rothenberg

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
2	11 November 2017		
3	17 January 2018		
4	23 Oct 2018		
5	25 Feb 2019		
6	30 Apr 2019		
7	18 Mar 2020		
8	03 Apr 2020		

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

PROTOCOL SYNOPSIS

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL TO EVALUATE THE EFFICACY OF BENRALIZUMAB (ANTI-IL5RA) IN SUBJECTS WITH EOSINOPHILIC GASTRITIS

Principal Investigator

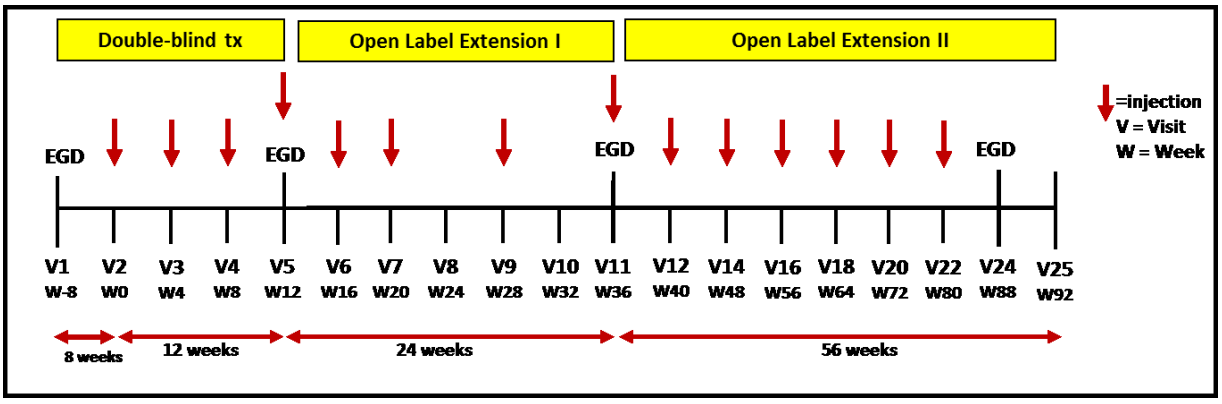
Marc Rothenberg, MD, PhD

Study site(s) and number of subjects planned

Cincinnati Children's Hospital Medical Center, 26 subjects planned

Study period		Phase of development
Estimated date of first subject enrolled	August 2017	II/III
Estimated date of last subject completed	March 2022	II/III

Study Design



Note: OLEII injections will take place every 4 or 8 weeks, based on clinical relevance per PI. In the double blind and OLE periods, participants affected by postponed EGDs due to COVID-19 may receive additional injections (every 4 or 8 weeks) until the EGDs can be performed.

Objectives

Primary Objective:	**Outcome Measure:**
To assess the efficacy of repeat subcutaneous (SC) doses of benralizumab, compared with placebo, to reduce eosinophilic inflammation in the gastrointestinal tract of patients with EG.	Induction of disease remission defined by the percentage of patients that achieve histological remission in the stomach as defined by peak eosinophil counts less than 30/hpf. Comparison between drug vs placebo will be the primary measurement endpoint.

Secondary Objective:	**Outcome Measure :**
To assess changes in endoscopic score before and after treatment with benralizumab	Change in endoscopic score from pre- to post-treatment with benralizumab or placebo as measured by EREFS for EoE and Lanza Score for EG.
To assess changes in histologic features before and after treatment with benralizumab	Change in histologic score from pre- to post-treatment with benralizumab or placebo as measured by HSS for EoE and EG and ED Biopsy Evaluation Forms for EG or EGE
To assess changes in blood eosinophil counts before and after treatment with benralizumab	Change in blood eosinophil count before and after treatment with benralizumab or placebo as measured by CBC with differential.
To assess changes in clinical symptoms before and after treatment with benralizumab	Change in symptoms from pre- to post-treatment with benralizumab or placebo as measured by PROs -SODA (for EG) -PEESSv2, PedsQL 3.0, EESAI, EoE-QOL-A, PROMIS (for EoE)
To evaluate esophageal, gastric, and duodenal tissue transcriptome changes following benralizumab treatment.	Baseline predictors and changes in expression of genes as assessed by whole genome RNA sequencing
To assess changes in peak eosinophil counts in biopsies before and after treatment with benralizumab	Change in peak eosinophil count in biopsies (esophageal, gastric, and/or duodenal, as applicable) pre- vs. post-treatment with benralizumab or placebo

Safety Objective:	**Outcome Measure :**
To evaluate the safety and tolerability of Benralizumab in subjects with EG	AEs/SAEs Vital signs Physical exam Collection of blood chemistry and hematology Urinalysis Pregnancy testing

Target subject population
Male and female subjects between the ages of 12-60 with histologically active EG.

Duration of study
3 months during the double blind treatment and up to 20 months during the open label extensions. Due to COVID-19, some participants may remain in the study up to an additional 3 months.

Investigational product, dosage and mode of administration
Benralizumab 30 mg or placebo
Subcuteaneous injection

Statistical methods

The planned total sample size of 24 subjects is justified based on previously published studies. Based on trials of other therapies in EoE, it is reasonable to assume that an eosinophil count at or below 30 eos/hpf for the stomach is considered an adequate response. It is estimated that a response rate in the placebo group will be no more than 10%. The estimated benralizumab response rate is 70%. To detect a difference between these two response rates, we need a total of 24 completed patients, or 12 patients per arm, to reach 80% statistical power. To account for possible dropouts, we will enrol at least 26 patients. At the end of OLE, we will use descriptive statistics to analyze the OLE data including histology, eosinophil counts, PROs etc.

SUMMARY OF CHANGES

Page no.	Sections	Change description
17 27 33 35 37	1.3 Study design 4. Study plan 4.2 Treatment period 4.4 OLE I 4.5 OLE II	Due to COVID-19 travel restrictions, investigational product injections and some safety procedures may occur for double blind and open label visits at the patient's local provider. Local providers may administer injections at visits 4,6,7,9 and 12-23 per PI discretion. Safety procedures that may occur at local provider or local lab include urine pregnancy test, urinalysis, vitals, and CBC with differential per PI discretion When IP administration and safety procedures occur at local providers, lab results and date/time of injection and other records will be provided to study staff post visit.
25	3.8 Post injection monitoring	Post injection monitoring will occur at local providers who are medically trained to perform this monitoring including monitoring for hypersensitivity reactions. Study staff will confirm that local providers have standard treatments for hypersensitivity reactions in stock. Reactions related to injections will be logged by local providers.
50	7.4 Storage of IP	Local providers who receive and store IP for local administration will confirm IP storage temperatures for study staff. To minimize risk and monitoring burden, IP will be shipped 1-2 days before injection.
50	7.6 Accountability	Date and quantity of IP dispensed for shipment to local providers will be maintained in drug accountability records. Local providers will provide study staff with date/time of IP injection.
53	9.1 Training of study staff and local providers	Local providers must show competency in subcutaneous injections and post injection monitoring (e.g., currently providing injections in clinical practice).

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	Anti-drug Antibodies
ADCC	Antibody-Dependent Cell-mediated Cytotoxicity
AE	Adverse event
ANOVA	Analysis of variation
CBC	Complete blood count
CCHMC	Cincinnati Children's Hospital Medical Center
CFR	Code of Federal Regulations
COVID-19	Coronavirus Disease 2019
(e)CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
ED	Eosinophilic Duodenitis
EGE	Eosinophilic Gastroenteritis
EGD	Esophagogastroduodenoscopy
EGID	Eosinophilic Gastrointestinal Disorder
EoE	Eosinophilic Esophagitis
EoE-QOL-A	Adult Esophagitis Quality of Life Questionnaire
EOT	End of Treatment
EREFS	Endoscopic Reference Score
EESAI	EoE Adult Symptom Score Activity Index
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HPF	High power field
HSS	Histology Scoring System
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroids

Abbreviation or special term	Explanation
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine system (levonogestrel)
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LABA	Long-Acting β2-Agonists
LSLV	Last Subject Last Visit
MRO	Medical Review Officer
MTA	Material Transfer Agreement
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
OLE	Open Label Extension
PEESSv2	Pediatric EoE Symptom Score, version 2
PROMIS	Patient-Reported Outcomes Measurement Information System
PGx	Pharmacogenetic research
PHI	Protected Health Information
PI	Principal Investigator
PPI	Proton Pump Inhibitor
PROs	Patient reported outcome metrics
QOL	Quality of Life
SAE	Serious adverse event
SAR	Serious adverse reaction
SODA	Severity of Dyspepsia Assessment
TEAEs	Treatment-emergent adverse events
UGI	Upper Gastrointestinal series
WOCBP	Woman of child bearing potential

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Eosinophilic gastrointestinal diseases (EGID) include eosinophilic esophagitis (EoE), eosinophilic gastritis (EG), eosinophilic duodenitis (ED) and eosinophilic colitis (EC). Symptoms of EGID include vomiting, abdominal pain, dysphagia, food impactions, and diarrhea, and generally dependent upon which gastrointestinal segment is involved. Patients with gastrointestinal eosinophilia in multiple gastrointestinal segments are referred to as eosinophilic gastroenteritis (EGE) patients and typically complain of upper abdominal pain, nausea and vomiting. Commonly-reported symptoms of EoE include dysphagia, vomiting, reflux, food aversion, and food impaction [1-3]. Preliminary studies suggest that most patients with EoE do not have extra-esophageal eosinophilia whereas most patients with EG also have involvement of the esophagus. There are no FDA approved drugs for any of these disorders. Diagnostically, EoE is defined by consensus criteria that requires esophageal-specific inflammation of $\geq$ 15 eosinophils per high power field (hpf), as obtained from two to four biopsies from either the proximal or distal esophagus, that is not mitigated by the use of proton pump inhibitor (PPI) therapy [2]. The diagnosis of eosinophilic gastritis (EG) requires $\geq$ 30 eosinophils per hpf in at least 5 hpfs, and eosinophilic duodenititis (ED) requires >52 eosinophils/hpf.

EGID are complex clinical entities requiring coordinated care within the fields of both Allergy and Gastroenterology. Current treatment modalities involve either elimination diet therapy, swallowed topical corticosteroid therapy, or a combination of both. These treatments are efficacious, but require continuous use, as a majority of patients recrudesce if treatment is not maintained. Concerns about the potential risks of chronic steroid use, as well as a desire to find more tolerable and/or convenient methods of treatment, have driven the search for other potential therapies.

Interleukin 5 (IL-5) is a cytokine produced by type-2 T helper cells, innate lymphocyte type 2 cells, and mast cells that serves as a key mediator in eosinophil activation. Drugs, such as the monoclonal antibodies against IL-5, mepolizumab and reslizumab, have been evaluated as potential therapies for eosinophilic disorders, due to their ability to reduce eosinophilic inflammation [4]. These two drugs are now FDA approved for eosinophilic asthma but not other eosinophil-associated diseases [5]. Significant numbers of eosinophils have been found to remain in the tissue after neutralization or experimental genetic deletion of IL-5 [6], suggesting the need for therapies that target other potential pathways for eosinophil activation.

Benralizumab is a monoclonal antibody that binds to the alpha chain of the IL-5 receptor (IL-5Ra) [7]. This receptor is expressed not only by mature eosinophils, but also by eosinophil progenitor cells and basophils. Benralizumab is a humanized, recombinant IgG1κ monoclonal antibody. Benralizumab has been engineered to be afucosylated, or without a fucose sugar residue, which enhances the interaction of benralizumab with its binding site. This results in heightened antibody-dependent cell-mediated cytotoxicity (ADCC) function [8]. Benralizumab targets eosinophils and other cells expressing IL-5Rα in the circulation and residing in tissues for ADCC and results in depletion of eosinophils in the circulation, bone marrow and tissues.

Benralizumab also targets eosinophil precursors in the bone marrow for ADCC. Thus, benralizumab may potentially be more effective than the monoclonal antibodies against IL-5 itself.

IL-5 is one of several cytokine mediators involved in eosinophil development, activation, proliferation, and survival. The concentration of this cytokine in affected tissues is increased in patients with asthma and in other diseases such as EGIDs. Findings from clinical trials have shown efficacy and safety of treatment with monoclonal antibodies against IL-5 in patients with asthma and have led to the approval of mepolizumab and reslizumab in the USA and Europe as add-on maintenance treatment for patients with severe asthma aged 18 years (reslizumab) or 12 years and older (mepolizumab) with an eosinophilic phenotype [5]. Benralizumab induces direct, rapid, and nearly complete depletion of eosinophils by lysis through enhanced ADCC involving natural killer cells [9]. This mechanism is in contrast to current treatments, which target IL-5 directly and act through a passive (i.e. indirect) mechanism that ultimately results in eosinophil reduction but not depletion. Benralizumab has a broad efficacy profile for patients with severe, uncontrolled asthma with eosinophilic inflammation [10]. In a phase 2b study, benralizumab 100 mg SQ every 8 weeks for 1 year seemed to reduce exacerbation rates compared with placebo (0.34 vs 0.57; 41% reduction, 80% CI 11–60; p=0.096) for patients with uncontrolled asthma treated with medium-dosage or high-dosage inhaled corticosteroids (ICS) and long-acting β2-agonists (LABA) (ICS plus LABA). A lower 20 mg dosage was also efficacious in reducing exacerbation rates (0.30 vs 0.68 in placebo, 57% reduction, 80% CI 33–72; p=0.015) in patients with blood eosinophil counts of at least 300 cells per mcL [11]. Results from this study prompted the decision to investigate a 30 mg dosage in phase 3 trials. A double-blind, double-dummy designed study (ages 12-75) confirmed the efficacy and safety of benralizumab for patients with severe asthma and elevated eosinophils, which were uncontrolled by high-dosage ICS plus LABA, and provided support for benralizumab to be an additional option to treat this disease in this patient population. Indeed, usage of benralizumab has recently been approved by the FDA for eosinophilic asthma in 12 year olds and older [12].

1.2 Rationale for study design, doses and control groups

Benefit/risk and ethical assessment

1.2.1 Risks of Investigational Product as cited in Investigator Brochure

Risk of serious infection

Nonclinical pharmacology studies show that benralizumab binds to eosinophils through the IL-5Rα, and blocks the binding of the ligand, IL-5, to the receptor. Benralizumab, through Fc engagement exhibits increased ADCC, resulting in depletion of eosinophils. In two reports, strains of transgenic mice that were deficient in eosinophils were created and both had normal immunological and hematological profiles except for the absence of eosinophils in their blood and tissues. Neither report indicated an increase in susceptibility to viral or bacterial infections for these gene-manipulated mice [13-15].

Observations of eosinophil-deficient, gene-modified mice including (1) IL-5 knockout; (2) IL-5Rα knockout mice; and (3) normal mice treated with anti-IL-5 mAb, demonstrated that

disruption of eosinophil function or elimination of the eosinophil itself did not cause perturbation of the animal's normal immunological constitution.

To mitigate the potential risk of serious infections (defined as infections that are life threatening, requiring IV antibiotics or hospitalization) eligibility criteria will be included in clinical study protocols to exclude vulnerable subjects, and subjects in studies will be monitored with complete blood counts including differential white cell count throughout the study; and through standard AE/SAE monitoring in clinical studies.

Risk of helminth infection

A theoretical risk of depleting eosinophils is interference with expulsion of helminthic parasites. A report in the literature showed that ablation of eosinophils with anti-IL-5 antibody in mice enhanced the survival of *Trichinella spiralis* [16]. On the other hand, depletion of eosinophils in other murine *T spiralis* infection models have shown no effect [17] or even a detrimental effect [18] on the ability to clear helminth infections. The importance of eosinophils in the control of helminth infections in humans is also uncertain. To mitigate the potential risk of helminth infections, eligibility criteria will be included in clinical study protocols to exclude vulnerable subjects and subjects in studies will be monitored through standard AE/SAE monitoring in clinical studies. If patients become infected while receiving treatment with Benralizumab and do not respond to anti-helminth treatment, treatment with Benralizumab will be discontinued until infection resolves.

Potential risks common to any monoclonal antibody

a. Potential risk of hypersensitivity/allergic reactions

As with the administration of any foreign protein, acute allergic reactions and hypersensitivity reactions may occur, may be severe, and may result in death. Acute allergic reactions and hypersensitivity reactions may include hypotension, laryngeal edema, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, mental status changes, and unresponsiveness.

There is a rare possibility of acute or late drug reaction (mild temporary abnormality of liver and renal function tests), kidney stones and reactivation of herpes zoster.

There are specific requirements within each protocol for observing subjects for AEs and for monitoring vital signs before, during, and after administration of benralizumab if hypersensitivity or allergic reactions are present.

b. Potential risk of infusion-related reaction

Infusion-related reactions may be defined as any signs or symptoms experienced by subjects during the infusion of pharmacologic or biologic agents or any event occurring on the first day of drug administration. Clinical manifestations of these reactions vary. Anaphylactic or anaphylactoid reactions are the most severe forms of infusion-related reactions and may result in death. Infusion-related reactions usually develop within 2 hours of the start of investigational

product administration and often resolve within 24 hours after completion of investigational product administration. Signs/symptoms may include the following: urticaria, arthralgia, bronchospasm, wheeze, cough, dizziness, dyspnea, fatigue, headache, hypertension, hypotension, myalgia, and vomiting [19, 20].

c. Potential risks associated with immune reactivity

The administration of a mAb can result in the formation of anti-drug antibodies (ADA). The occurrence of ADA could result in immune complex disease or hypersensitivity type III (defined as disease resulting from immune-complex formation divided broadly into 3 groups: those due to persistent infection, those due to autoimmune disease, and those caused by inhalation of antigenic material) with manifestations such as serum sickness, nephritis, and vasculitis, or altered benralizumab levels or activity. Therefore, subjects will be monitored for clinical manifestations that may be associated with the formation of specific antibodies to benralizumab generated during clinical studies.

To date, no confirmed cases of immune complex disease have been observed and no appearance of a relationship between ADA and treatment-emergent adverse events (TEAEs) has been established.

d. Potential risk associated with malignancy

Since benralizumab targets eosinophils for destruction, it is important to understand what physiological impact eosinophil depletion may have in relation to carcinogenicity risk. While eosinophils have been found in association with solid tumours, especially tumours of epithelial origin (breast and colon) [21], the role eosinophils may have in tumour growth, if any, remains unclear. While some clinical studies have suggested the presence of eosinophils may be a positive prognostic indicator of cancer patient survival, a definitive link has not yet been established [22, 23].

To mitigate the potential risk of malignancies, eligibility criteria will be included in clinical study protocols to exclude vulnerable subjects and subjects in studies will be monitored through standard AE/SAE monitoring in clinical studies.

1.2.2 Risks of Study Procedures

Esophagogastroduodenoscopy (EGD)

Endoscopy with biopsy is a well-established procedure, with few patients experiencing unexpected or serious complications. Biopsies are routinely collected from the esophagus, stomach, and duodenum during endoscopy, and biopsies from all of these sites will be collected during endoscopic procedures for this study.

The risks associated with collecting additional esophageal and gastrointestinal biopsies (up to a total of four obtained from each of the proximal and/or distal esophagus and stomach and duodenum) for research at the time of the endoscopy include: bleeding at the site of tissue (biopsy) collection, and a small chance of perforation (hole) of the stomach, duodenum, or esophagus. Perforation is the most severe gastrointestinal complication, but generally it is self-

resolving and poses no life-threatening risk. Transient bacteremia as a result of diagnostic UGI endoscopy has been reported at rates as high as 8%, but the frequency of infectious endocarditis and other clinical sequelae is extremely low, such that current American Heart Association and American Society for Gastrointestinal Endoscopy guidelines do not recommend antibiotic prophylaxis with diagnostic UGI endoscopy solely to prevent infectious endocarditis [24]. The risk of aspiration during endoscopy is miniscule.

To minimize the risks of collecting additional biopsies during endoscopy, the procedure will be performed or supervised by a skilled endoscopist, and additional biopsies will only be collected if the endoscopist feels it is appropriate to do so. Some samples that are collected during an endoscopy for research purposes may be frozen and shipped to other hospitals, institutions, and testing companies for analysis. Data may also be shared. The data and/or samples will be de-identified per the Health Insurance Portability and Accountability Act (HIPAA) and have no protected health information (PHI) associated with them. The data and/or samples will be used in a collaborative relationship between institutions, or testing companies receiving the data and/or samples. All of these samples will be shared under a Material Transfer Agreement (MTA), or other applicable agreement.

Blood Draws

Risks associated with the collection of blood include bleeding, bruising, swelling, dizziness, fainting, and infection at the site of blood draw. Blood draws will be performed by individuals with expert skills in phlebotomy. To minimize the additional risks associated with phlebotomy, blood will be obtained during the standard placement of intravenous lines when possible. The amount of blood drawn will adhere to institutional policy.

Histologic Scoring Tools

The histology scoring tools are used to evaluate biopsies containing eosinophils for various features (ex: basal layer hyperplasia, dilated intercellular spaces, surface epithelial alteration, apoptotic epithelial cells), eosinophilic inflammation (peak count, eosinophil abscess, eosinophil surface layering), and lamina propria (fibrosis). There is no risk associated with the utilization of the histology scoring tools.

Patient Reported Outcome (PRO) Metrics

Participants will be asked to complete several metrics, including disease-specific symptom scores and QOL measures in order to address their symptoms and problems / feelings related to eating. There are no foreseeable physical discomforts or significant risks related to completing the PROs. However, some questions may be difficult or uncomfortable for participants to answer, and participants may refuse to answer any questions that they are uncomfortable with. Participants may also feel inconvenienced by completing the questionnaires. The participant questionnaires typically take approximately 15 to 20 minutes to complete. All participants will be given ample time to complete the questionnaires.

Other Risks

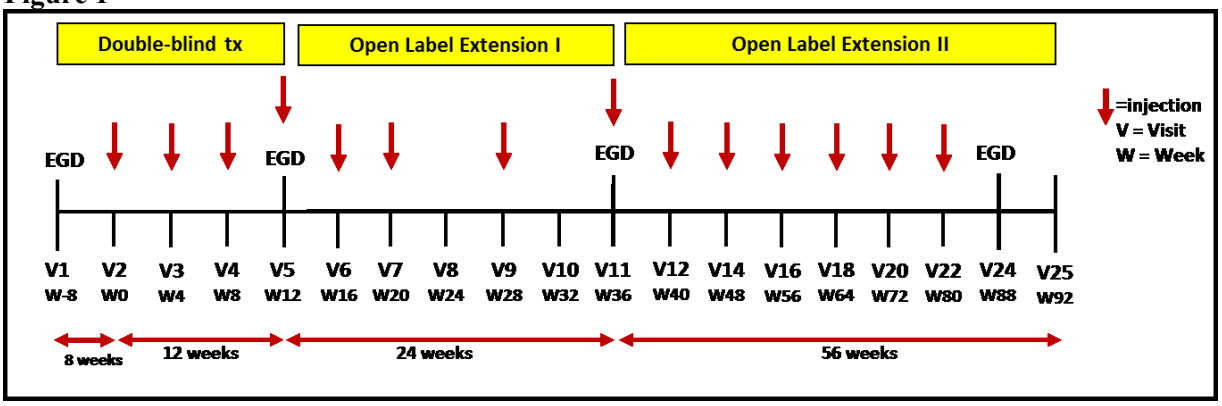
There is a slight risk that data containing PHI may be inadvertently shared. All data will be protected to the greatest extent possible. Electronic data will be maintained only on password-protected systems on secure networks. Paper data will be kept in locked file cabinets and/or storage rooms. All data will be deidentified prior to being shared, and will only be shared with necessary parties for study purposes.

It is possible that there are other unforeseen risks that we are not yet aware of.

There are no guaranteed benefits associated with study participation. Subjects may experience reduced symptoms as a result of treatment. Subjects who complete the treatment period, whether on study drug or placebo, will be eligible to receive the drug during an open label extension.

1.3 Study Design

Figure 1



- OLE II injections will take place every 4 or 8 weeks, based on clinical relevance per PI. Due to COVID-19, OLE I injections may also take place every 4 or 8 weeks.
- Participants affected by postponed EGDs due to COVID-19 may receive additional injections (every 4 or 8 weeks) until the EGDs can be performed.
- Participants who are unable to travel due to restrictions and risks related to COVID-19 may receive injections and safety assessments at a local provider per PI discretion

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To assess the efficacy of repeat subcutaneous (SC) doses of benralizumab, compared with placebo, to reduce eosinophilic inflammation in the gastrointestinal tract of patients with EG.	Induction of disease remission defined by the percentage of patients that achieve histological remission in the stomach as defined by peak eosinophil counts less than 30/hpf. Comparison between drug vs placebo will be the primary measurement endpoint.

2.2 Secondary objectives

Secondary Objective:	Outcome Measure :
To assess changes in endoscopic score before and after treatment with benralizumab	Change in endoscopic score from pre- to post-treatment with benralizumab or placebo as measured by EREFS for EoE and Lanza Score for EG
To assess changes in histologic features before and after treatment with benralizumab	Change in histologic score from pre- to post-treatment with benralizumab or placebo as measured by HSS for EoE and EG and ED Biopsy Evaluation Form for EGE
To assess changes in blood eosinophil counts before and after treatment with benralizumab	Change in blood eosinophil count before and after treatment as measured by CBC

To assess changes in clinical symptoms before and after treatment with benralizumab	Change in symptoms from pre- to post-treatment with benralizumab or placebo as measured by PROs -PEESSv2, PedsQL 3.0, EESAI, EoE-QOL-A (for EoE) -SODA (for EG) -PROMIS
To evaluate esophageal, gastric, and duodenal tissue transcriptome changes following benralizumab treatment.	Baseline predictive transcripts and changes in expression of genes as assessed by whole genome RNA sequencing
Comparison between peak eosinophil counts before and after drug or placebo	Change in histological features including peak eosinophil count in biopsies (esophageal, gastric, and/or duodenal, as applicable) pre- vs. post-treatment with benralizumab or placebo

2.3 Safety objectives

Safety Objective:	**Outcome Measure :**
To evaluate the safety and tolerability of Benralizumab in subjects with EG	AEs/SAEs Vital signs Physical exam Collection of blood chemistry and hematology, and coagulation Urinalysis Pregnancy testing

3. SUBJECT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

3.1 Inclusion criteria

Informed Consent: Able to give written informed consent prior to participation in the study, which will include the ability to comply with the requirements and restrictions listed in the consent form. Subjects must be able to read, comprehend, and write at a level sufficient to complete study related materials.

Males and females between the ages of 12-60 years

Confirmed diagnosis of EG involving stomach; involvement of eosinophilic inflammation in other gastrointestinal segments will be allowed but not required or sufficient.

Histologically active EG at time of screening, with a peak Gastric count of ≥ 30 eos/hpf in at least 5 hpfs.

Must be symptomatic (defined as having experienced symptoms within 4 weeks prior to enrollment). Clinical symptoms (i.e., abdominal pain, bloating, vomiting, diarrhea) must be severe enough to impact daily life (e.g., school/work attendance, social activities) ≥ 2 times in 3 of the 4 weeks prior to enrollment despite treatment (such as diet, proton pump inhibitors or corticosteroids). See addendum number 1, page 59.

Blood eosinophilia (defined as having an absolute eosinophil count > 0.5 K/ mcL of blood) at least once during the 6 months prior to enrollment.

Must be on baseline anti-EG/EGE therapy as long as there is agreement to not change their dosage unless medically indicated; OR, must have failed anti-EG/EGE therapy in the past, including diet therapy.

Female subjects: Women of childbearing potential (WOCBP) must use an effective form of birth control (confirmed by the Investigator). Effective forms of birth control include: true sexual abstinence, a vasectomized sexual partner,

Implanon, female sterilization by tubal occlusion, any effective IUD intrauterine device/IUS levonogestrel Intrauterine system, Depo-Provera(tm) injections, oral contraceptive, and Evra Patch(tm) or Nuvaring(tm). WOCBP must agree to use effective method of birth control, as defined above, from enrollment, throughout the study duration and within 16 weeks after last dose of IP, and have negative serum pregnancy test result on Visit 0.

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 amenorrheic for 12 months prior to the planned date of visit -1 without an alternative medical cause. The following age-specific requirements apply:

Women <50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone (FSH) levels in the postmenopausal range.

Women ≥50 years old would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatment.

All male subjects who are sexually active must agree to use an acceptable method of contraception (condom with or without spermicide, vasectomy) from Visit 0 until 16 weeks after their last dose.

3.2 Exclusion criteria

Concurrent *H. pylori* gastritis or parasitic infection

Other gastrointestinal disorders such as Crohn's disease, inflammatory bowel disease, or Celiac disease, eosinophilic granulomatosis with polyangiitis (EGPA), drug hypersensitivity or connective tissue rheumatological disorders,

Esophageal stricture that prevents the easy passage of a standard endoscope

Use of any investigational biologic drug within 6 months prior to screening

Hypereosinophilic syndrome, defined by multiple organ involvement (with the exception of atopic disease or EGID) and persistent blood absolute eosinophil count ≥1500/mcL.

History of cancer: Subjects who have had basal cell carcinoma, localized squamous cell carcinoma of the skin, or in situ carcinoma of the cervix are eligible provided that the subject is in remission and curative therapy was completed at least 12 months prior to the date informed consent, and assent when applicable was obtained. Subjects who have had other malignancies are eligible provided that the subject is in remission and curative therapy was completed at least 5 years prior to the date informed consent, and assent when applicable, was obtained.

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

Pregnant or nursing

Receipt of any investigational non-biologic within 30 days or 5 half-lives prior to visit 0, whichever is longer.

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

Any other medical illness that precludes study involvement

Positive hepatitis B surface antigen, or hepatitis C virus antibody serology, or a positive medical history for hepatitis B or C. Subjects with a history of hepatitis B vaccination without history of hepatitis B are allowed to be enrolled.

Patients who are currently receiving or have previously received benralizumab or any other type of anti-interleukin therapy (i.e. mepolizumab, reslizumab, lebrikizumab etc.) within the last 6 months or 5 half-lives whichever is longer.

History of anaphylaxis to any biologic therapy or vaccine.

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

3.3 Subject enrollment and randomization

We plan to recruit at least of 26 subjects, between the ages of 12-60 years. Potential subjects will be screened during an 8-week screening period. An EGD with biopsies will be performed to determine study eligibility, and subjects will be enrolled based on the presence of active disease and their ability to meet the study inclusion and exclusion criteria.

The screening EGD can be performed up to 8 weeks prior to enrollment. In this case, biopsies collected for clinical purposes in Cincinnati Children's Hospital or University of Cincinnati medical center, will be blinded and re-analyzed by Dr. Margaret Collins, to determine study eligibility. In case the EGD is performed in a different site, clinical biopsies will be sent to Dr. Collins for evaluation, after authorization of release of medical information and specimens is accepted from the subject.

Qualifying subjects will be blindly randomized 1:1 to either study drug (benralizumab) or placebo, and will receive monthly 30 mg doses of study treatment for 2 months (for a total of 3 injections). Participants affected by postponed EGDs due to COVID-19 may receive additional injections (every 4 weeks) until the EGD is performed. Randomization ratio will be kept at 1:1 for users of systemic and/or swallowed corticosteroids, compared to non-users.

During the treatment period, subjects will be monitored for adverse events/reactions and will complete patient reported outcome metrics to track their symptoms and general wellbeing. Subjects and study staff will remain blinded to the results of the complete blood count (CBC) so that they are not biased by an apparent drop in eosinophil counts. At the end of the treatment period, a repeat endoscopy with biopsies will be performed to assess the change in peak eosinophil count from pre- to post-treatment. Subjects and research study staff will remain blinded to the endoscopy results until completion of the double blind phase of the study. An Open Label Extension (OLE) will include four additional injections of Benralizumab, followed by an end of treatment endoscopy. Participants affected by postponed EGDs due to COVID-19 may receive additional injections (every 4 or 8 weeks) until an EGD is performed. Extended OLE (OLE II) will allow up to 13 additional injections and a final research endoscopy. Participants affected by postponed EGDs due to COVID-19 may receive additional injections (every 4 or 8 weeks) until an EGD is performed. Subjects will continue to be monitored for 30 days as a safety follow-up. At the end of the 30 day follow-up period, study participation will conclude.

Given the nonspecific nature of the symptoms in EG and the known dissociation of histology and symptoms in other eosinophilic disorders, presence or absence of symptomatic responses alone will not be sufficient to assess therapy effectiveness, and thus endoscopy is a necessary part of both clinical care and therapeutic trial monitoring.

3.4 Procedures for handling incorrectly enrolled or randomized subjects

Incorrectly enrolled or randomized subjects will be withdrawn from the study at the direction of the study sponsor.

3.5 Methods for assigning treatment groups

Approximately 26 patients will be randomized in a 1:1 ratio to receive benralizumab or placebo. Randomization will be accomplished via a central randomization scheme provided by the study sponsor/principal investigator, Dr. Marc Rothenberg, to the study pharmacist (or qualified designee).

3.6 Methods for ensuring blinding

The investigators, study staff, pathology review pathologist, and study subjects will all remain blinded to treatment assignment throughout the trial. The medical review officer (MRO), study monitor, and any other personnel designated by the sponsor (Dr. Rothenberg as PI of the study) who have regular contact with the study site will remain blinded to all treatment assignments. Individuals not involved in the conduct of the trial who have been designated by the sponsor (e.g. Data Safety Monitoring Board members) may have access to unblinded data as necessary for safety review or other data review. Blinded study drug kits coded with a medication numbering system will be used. In order to maintain the blind, lists linking these codes with product lot numbers will not be accessible to individuals involved in study conduct.

Study site personnel will be blinded to the peripheral eosinophil results during the double blind phase of the study so as to prevent unintentional bias due to changes in blood eosinophil counts. The MRO will have access to the CBC results for data safety review. Beginning in the open label extension, peripheral eosinophil counts from the 3rd dose visit (Visit 7) and subsequent visits will be made available to study staff after each visit. This data will be used to determine dosing intervals in OLE II.

Study site personnel will be blinded to the post-treatment double blind endoscopy results until the completion of the double blind phase of the study. Endoscopy results from the open label extensions will be available to study staff after each OLE EGD. Study participants may only receive results of any **post** – OLE endoscopies and peripheral eosinophil counts upon request.

3.7 Methods for unblinding

In the case of medical emergency or other significant medical event (e.g. pregnancy), unblinding of treatment assignment for a subject may be necessary.

For medical emergencies:

- Only the investigator may make the decision to unblind the treatment assignment.
- Unblinding will occur only for the affected subject.
- The study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator.
- The investigator will immediately notify the sponsor that unblinding has occurred.

Barring true emergencies, site personnel, including the PI, should not be provided the treatment assignment data at any time during the conduct of the trial.

3.8 Restrictions

Post injection observation

All subjects will be observed for 1 hour post injection of investigational product for signs of infusion reaction or anaphylaxis during the double blind and OLEI treatment periods. During OLEII, this may be reduced to 30 minutes post injection, if the subject has tolerated previous treatments well. Anaphylaxis will be assessed as per standard protocol and treatment will include subcutaneous epinephrine, antihistamines and /or systemic corticosteroids such as solumedrol or prednisone as clinically indicated. When drug is administered at local providers for patients that cannot travel to the study site due to COVID-19, local providers will follow the above post-injection observation procedures including monitoring for hypersensitivity reactions. Standard protocols for treatment of hypersensitivity reactions will be reviewed by study staff with local provider. Study staff will confirm local providers have standard treatments (epinephrine, antihistamine, corticosteroids) on site and are clinically trained on the administration of treatments for hypersensitivity reactions. Local providers will be asked to log all reactions related to injections and provide to study staff to ensure adverse reactions are recorded in research records.

3.9 Discontinuation of investigational product

3.9.1 Procedures for discontinuation of a subject from investigational product

Study therapy may be prematurely discontinued for any participant for any of the following reasons:

1. At the discretion of the sponsor
2. The PI feels that the study treatment is no longer in the best interest of the participant.

3. The participant experiences an AE that the PI feels warrants discontinuation of the study therapy.

3.10 Criteria for withdrawal

Participants may be prematurely terminated from the study for the following reasons:

1. The participant elects to withdraw consent from all future study activities, including follow-up.
2. Participant develops severe complications from their EoE/EGE (for instance, esophageal strictures).
3. Participant required EGID rescue medicines that the investigator feels are substantial.
4. Participant becomes pregnant.
5. The participant is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).
6. The participant develops an SAE related to therapy.
7. The participant dies.
8. The Investigator no longer believes participation is in the best interest of the participant.

Enrolled participants who start on the initial intervention protocol and prematurely discontinue/withdraw from the study will be replaced if they do not reach the End of Treatment (V5) visit of the study, including the EGD. Additional participants will be enrolled in the same manner as all other participants. Participant numbers will not be re-used. All enrolled participants will be included into intent to treat analysis.

3.10.1 Screen failures

If it has been confirmed that a subject does not meet inclusion and/or exclusion criteria, the subject will be considered a screen failure. Screen failed subjects cannot be rescreened unless the screen failure was due to a concomitant medication that can be discontinued prior to rescreening. Other potential reasons for rescreening (i.e. reasons unrelated to the inclusion/exclusion criteria) must be approved by the study principal investigator prior to rescreening the subject.

3.10.2 Withdrawal of the informed consent

Subjects may choose to withdraw consent at any time during study participation. When a participant withdraws permission, they will no longer be part of the study and no new information about the subject will be gathered for the study except for information related to an adverse event that is related or potentially related to the study.

3.10.3 Early withdrawal

Subjects may be asked to complete an EOT/Early withdrawal visit prior to withdrawal per the discretion of the PI.

3.11 Discontinuation of the study

The principal investigator may discontinue the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the principal investigator will notify the drug manufacturer, and regulatory agencies and the IRB will be notified as appropriate. Additionally, the study entry on clinicaltrials.gov will be updated to reflect that the study has been discontinued.

4. STUDY PLAN AND TIMING OF PROCEDURES

Study Procedures	**Screening**	**Double-Blind Treatment**			**OLE**						
	V1	V2 Baseline	V3	V4†	V5 EOT/EW OLE 1st dose	V6 OLE 2nd dose	V7 OLE 3rd dose	V8 (phone call)	V9†† OLE 4th dose	V10 (phone call)	V11 EOT/EW (***1st dose OLEII
Week (Wk)	Wk -8 to 0	WK 0	4	8	12	16	20	24	28	32	36
Visit Window (in days, d)+	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d
Screening/Baseline:											
Informed Consent	X										
Inclusion/exclusion	X	X									
Medical History/demographics/height	X										
Randomization/Eligibility		X									
Diet Questionnaire		X			X						
Treatment:											
Administer study drug[2]		X	X	X	X**[2]	X**	X[2]		X[2]		X***[2]
Con meds/procedures	X	X	X	X	X**	X**	X	X	X	X	X
Efficacy:											
EESAI[1]	X	X	X	X	X	X**	X	X	X	X	X
GI symptoms and pain interference	X	X	X	X	X	X	X	X	X	X	X

Study Procedures	**Screening**	**Double-Blind Treatment**			**OLE**						
	V1	V2 Baseline	V3	V4†	V5 EOT/EW OLE 1st dose	V6 OLE 2nd dose	V7 OLE 3rd dose	V8 (phone call)	V9†† OLE 4th dose	V10 (phone call)	V11 EOT/EW (***1st dose OLEII
Week (Wk)	Wk -8 to 0	WK 0	4	8	12	16	20	24	28	32	36
Visit Window (in days, d)+	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d
EoE-QOL-A[2]	X	X	X	X	X	X**	X	X	X	X	X
SODA[3]	X	X	X	X	X	X**	X	X	X	X	X
EREFS[4]	X				X						X
PEESSv2[5]	X	X	X	X	X	X**	X	X	X	X	X
PedsQL 3.0[6]	X	X	X	X	X	X**	X	X	X	X	X
PROMIS[7]	X	X	X	X	X	X**	X	X	X	X	X
Lanza Score	X				X						X
Histology Assessments[8]	X				X						X
Safety:											
Weight	X	X	X	X	X	X	X		X		X
Vital signs	X	X	X	X	X	X	X		X		X
Physical Exam	X				X	X*					X
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing:											
Hematology and serum chemistry	X		X		X						X
CBC with Differential					X**	X**	X		X		X
HBsAG	X										
Hepatitis C Ab	X										
IgE	X				X						X
Urinalysis	X		X		X		X		X		X
Pregnancy testing - Serum	X										
Pregnancy testing - Urine	X	X	X	X	X	X	X		X		X

Study Procedures	**Screening**	**Double-Blind Treatment**			**OLE**						
	V1	V2 Baseline	V3	V4†	V5 EOT/EW OLE 1st dose	V6 OLE 2nd dose	V7 OLE 3rd dose	V8 (phone call)	V9†† OLE 4th dose	V10 (phone call)	V11 EOT/EW (***1st dose OLEII
Week (Wk)	Wk -8 to 0	WK 0	4	8	12	16	20	24	28	32	36
Visit Window (in days, d)+	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d
Endoscopy with biopsies[9]	X				X						X
Research samples (whole blood/serum)	X	X	X	X	X	X	X		X		X
Tissue transcriptome (esophagus, stomach, and duodenum)	X				X						X
Stool microbiome	X				X						X

[1]EESAI = eosinophilic esophagitis symptom activity index; [2]EoE-QOL-A = Adult Esophagitis Quality of Life Questionnaire; [3]SODA = severity of dyspepsia assessment; [4]EREFS = endoscopic reference score; EOT = end of treatment; EW = early withdrawal [5]PEESS = Pediatric EoE Symptom Score; [6]PedsQL = Pediatric Quality of Life; [7]PROMIS = Patient Reported Outcomes Measurement System; [8]HSS for esophageal biopsies; EG Biopsy Evaluation form for gastric biopsies; ED Biopsy Evaluation form for duodenal biopsies. [9]SOC qualifying Endoscopy will be a part of screening. EOT of unscheduled endoscopies will be covered by the study.

[2] Study drug administration and related activities= every 4 or 8 weeks, determined ad-lib by the study doctor depending upon symptoms and COVID-19 restrictions

*= Procedures in Visit 5/6 (F/U) which will only be performed if subject does NOT continue to OLE 1

**= Procedures in Visit 5/6 (F/U) which will only be performed if subject is to start OLE 1.

***= drug administration in visit 11 will only be performed if subject chooses to continue to OLE2.

+ visit window is counted from the previous visit and not from the date of enrollment/randomization.

† This visit may be repeated until an EGD can be performed for participants whose EGDs are postponed due to COVID-19.

† † This visit may be repeated until an EGD can be performed for participants whose EGDs are postponed due to COVID-19

Note: study drug administration may occur at local provider per PI discretion at visits 4, 6, 7, and 9 due to COVID-19

Study Procedures	OLE II													
	V12 OLE II	V13 OLE II	V14 OLE II	V15 OLE II	V16 OLE II	V17 OLE II	V18 OLE II	V19 OLE II	V20 OLE II	V21 OLE II	V22 OLE II	V23†† OLE II	V24 EOT/EW EGD	V25 Safety F/U
Week (Wk)	40	44	48	52	56	60	64	68	72	76	80	84	88 or 92	96
Visit window in days (d) +	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d
Diet Questionnaire			X			X							X	X
Administer study drug[1]	X[1]	X	X[1]	X	X[1]	X	X[1]	X	X[1]	X	X[1]	X		
Con meds/procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:														
EESAI[2]						X							X	
EoE-QOL-A[3]						X							X	
GI symptoms and pain interference						X							X	X
SODA[4]						X							X	
EREFS[5]													X	
PEESSv2[6]						X							X	
PedsQL 3.0[7]						X							X	
PROMIS[8]						X							X	
Lanza Score													X	
Histology Assessments[9]													X	
Safety:														
Weight		X		X		X		X		X		X	X	
Vital signs	X*	X	X*	X	X*	X	X*	X	X*	X	X*	X	X	
Physical Exam						X							X	
Adverse events	X*	X	X*	X	X*	X	X*	X	X*	X	X*	X	X	
Lab testing:														
Hematology and serum chemistry													X	
CBC with Differential		X		X		X		X		X		X	X	

Study Procedures	OLE II													
	V12 OLE II	V13 OLE II	V14 OLE II	V15 OLE II	V16 OLE II	V17 OLE II	V18 OLE II	V19 OLE II	V20 OLE II	V21 OLE II	V22 OLE II	V23†† OLE II	V24 EOT/EW EGD	V25 Safety F/U
Week (Wk)	40	44	48	52	56	60	64	68	72	76	80	84	88 or 92	96
Visit window in days (d) [+]	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d	±4 d
IgE						X							X	
Urinalysis													X	
Pregnancy testing – Urine	X*	X	X*	X	X*	X	X*	X	X*	X	X*	X	X	
Endoscopy with biopsies[10]													X	
Research samples (whole blood/serum)	X*	X	X*	X	X*	X	X*	X	X*	X	X*	X	X	
Tissue transcriptome (esophagus, stomach, and duodenum)													X	
Stool microbiome														

1 Study drug administration and related activities= every 4 or 8 weeks, determined ad-lib by the study doctor depending upon symptoms, CBC and discussion with patients.; 2EESAI = eosinophilic esophagitis symptom activity index; 3EoE-QOL-A = Adult Esophagitis Quality of Life Questionnaire; 4SODA = severity of dyspepsia assessment; 5EREFS = endoscopic reference score; 6PEESSv2 = Pediatric EoE Symptom Severity; 7PedsQL = Pediatric Quality of Life; 8PROMIS = Patient Reported Outcomes Measurement System; 9HSS for esophageal biopsies; EG Biopsy
Evaluation form for gastric biopsies; ED Biopsy Evaluation form for duodenal biopsies. 10Endoscopy with biopsies in visit 24 will be performed at week 88 or week 92, depending on the treatment interval.
* assessments to be done if subjects are in cchmc
[+] visit window is counted from the previous visit and not from the date of enrollment/randomization.
† † This visit may be repeated until an EGD can be performed for participants whose EGDs are postponed due to COVID-19.
Note: study drug administration may occur at local provider per PI discretion at visits 12-23 due to COVID-19

4.1 Enrollment/Screening period

Visit 1

- Informed Consent
- Inclusion/Exclusion
- Medical history/demographics/height
- Concomitant medications/procedures GI symptoms and pain interference
- endoscopy with biopsies (Standard of care if performed prior to consent)
- PROs (EESAI, EoE-QOL-A, SODA, PedsQL, PEESS, PROMIS)
- Endoscopic and Histologic metrics (EREFS, HSS, Lanza Score, EG Biopsy Evaluation Form, ED Biopsy Evaluation Form)
- Physical Exam, Vital Signs, Weight
- Clinical labs (hematology and serum chemistry, urinalysis, IgE, HBsAg, Hepatitis C Ab)
- Pregnancy testing: serum and urine
- Adverse Events
- Research samples (whole blood/serum, plasma, endoscopic biopsies, stool microbiome)

4.2 Treatment period

Visit 2 (Baseline Week 0)

- Administer study drug
- Inclusion/Exclusion
- Randomization
- Concomitant medications/procedures
- GI symptoms and pain interference
- PROs (EESAI, EoE-QOL-A, SODA, PedsQL, PEESS, PROMIS)
- Vital Signs, Weight
- Diet Questionnaire
- Adverse Events
- Pregnancy Testing: urine
- Research samples (whole blood/serum/plasma)

Visit 3 (Week 4)

- Administer study drug
- Concomitant medications/procedures
- GI symptoms and pain interference
- PROs (EESAI, EoE-QOL-A, SODA, PedsQL, PEESS, PROMIS)
- Vital Signs, Weight
- Adverse Events
- Pregnancy Testing: urine
- Clinical labs (hematology and serum chemistry, urinalysis)
- Research samples (whole blood/serum/plasma)

Visit 4 (week 8)†

- Administer study drug
- Concomitant medications/procedures
- GI symptoms and pain interference
- PROs (EESAI, EoE-QOL-A, SODA, PedsQL, PEESS, PROMIS)
- Vital signs, weight
- Adverse Events
- Pregnancy Testing: urine
- Research samples (whole blood/serum/plasma)

† This visit may be repeated until an EGD can be performed for participants whose EGDs are postponed due to COVID-19. Participants may have study drug administered by their local providers due to COVID-19 travel restrictions and travel risks. In these cases, adverse events and concomitant meds will be assessed by study team via telephone/telemedicine prior to the visit to local provider. Pregancy testing and vitals will occur by local provider or local lab per PI discretion. Results from testing will be provided to the study staff directly from the local provider (via medical record release when necessary). Date and time of study drug injection and post injection monitoring results will also be provided to study staff from the local provider.

Visit 5 (Week 12 - End of Treatment/Early Withdrawal)

- Concomitant medications/procedures
- GI symptoms and pain interference
- PROs (EESAI, EoE-QOL-A, SODA, PedsQL, PEESS, PROMIS)
- Physical Exam, Vital Signs, Weight
- Diet Questionnaire
- Adverse Events

- Pregnancy Testing: urine
- Endoscopy with biopsies
- Endoscopic and Histologic metrics (EREFS, HSS, Lanza score, EG Biopsy Evaluation Form, ED Biopsy Evaluation Form)
- Clinical labs (hematology and serum chemistry, urinalysis, pregnancy testing, IgE)
- Research samples (whole blood/serum, plasma, stool microbiome)

4.3 Follow-up period

Visit 6 (Week 16 Follow-Up)

- Physical Exam, Vital Signs, weight
- Adverse Events
- Pregnancy testing: urine
- Clinical labs (hematology and serum chemistry, urinalysis, IgE)

4.4 Open Label Extension I (OLE I)

Study subjects who complete the 12 week treatment phase (whether on drug or placebo) will be allowed into an extension study, where 3 doses of Benralizumab will be administered every four weeks, and 1 more dose will be administered at an 8 week interval. Study drug may be administered at 8 week intervals due to COVID-19 restrictions or PI discretion depending upon symptoms. General laboratory studies and patient reported outcomes will be measured regularly. Endoscopy will be performed four weeks after the last dose of the study drug. The first dose in the OLE phase will be administered at visit 5 of the double treatment phase, for subjects who choose to do so.

Visit 5 (OLE I Week 12, 1st dose)

- Administer study drug
- Concomitant medications/procedures
- GI symptoms and pain interference
- PROs (EESAI, EoE-QOL-A, SODA, PedsQL, PEESS, PROMIS)
- Adverse Events
- Research samples (whole blood/serum, plasma)

Visit 6 (OLE I Week 16, 2nd dose)

- Administer study drug
- Concomitant medications/procedures
- GI symptoms and pain interference
- PROs (EESAI, PEESSv2, PedsQL3.0, EoE-QOL-A, SODA, PROMIS)

- Vital signs
- Clinical labs (CBC with differential, pregnancy testing)
- Adverse Events
- Research samples (whole blood/serum, plasma)

Visit 7 (OLE I Week 20, 3rd dose)

- Administer study drug
- Concomitant medications/procedures
- GI symptoms and pain interference
- PROs (EESAI, PEESSv2, PedsQL3.0, EoE-QOL-A, SODA, PROMIS)
- Adverse Events
- Research samples (whole blood/serum, plasma)
- Clinical labs (CBC with differential, urinalysis, pregnancy testing)

Visit 8 (OLE I Week 24, safety follow up phone call)

- Concomitant medications/procedures
- GI symptoms and pain interference
- PROs (EESAI, PEESSv2, PedsQL3.0, EoE-QOL-A, SODA, PROMIS)
- Adverse Events

Visit 9†† (OLE I Week 28 – 4th dose)

- Administer study drug
- Concomitant medications/procedures
- GI symptoms and pain interference
- PROs (EESAI, PEESSv2, PedsQL3.0, EoE-QOL-A, SODA, PROMIS)
- Adverse Events
- Research samples (whole blood/serum, plasma)
- Clinical labs (CBC with differential, urinalysis, pregnancy testing)

†† This visit may be repeated until an EGD can be performed for participants whose EGDs are postponed due to COVID-19

At visits 6, 7, and 9 participants may have study drug administered by their local providers due to COVID-19 travel restrictions and travel risks. In these cases, adverse events and concomitant meds will be assessed by study team via telephone/telemedicine prior to the visit to local provider. Pregancy testing, vitals, urinalysis, and CBC with differential will occur by local provider/lab per PI discretion. Results from testing will be provided to the study staff directly from the local provider (via medical record release if necessary). Date and time of

drug injection and post injection monitoring results will also be provided to study staff from the local provider.

Visit 10 (OLE I Week 32, safety follow up phone call)

- Concomitant medications/procedures
- PROs (EESAI, PEESSv2, PedsQL3.0, EoE-QOL-A, SODA, PedsQL, PEESS)
- GI symptoms and pain interference
- Adverse Events

Visit 11 (OLE I Week 36 - End of treatment EGD or Early Withdrawal)

- Concomitant medications/procedures
- GI symptoms and pain interference
- PROs (EESAI, PEESSv2, PedsQL3.0, EoE-QOL-A, SODA, PROMIS)
- Adverse Events
- Endoscopy with biopsies
- Endoscopic and Histologic metrics (EREFS, HSS, Lanza score, EG Biopsy Evaluation Form, ED Biopsy Evaluation Form)
- Clinical labs (CBC with differential, urinalysis, pregnancy testing)
- Research samples (whole blood/serum)

4.5 Extended Open Label Extension (OLE II)

Study subjects may choose to extend the OLE period, and receive up to 7 additional injections of benralizumab (every8 weeks) or 13 additional injections (every 4 weeks dosing), based on clinical considerations by the treating physician. The default dosing will be every 8 weeks. A research endoscopy will occur in visit 24 (end of treatment). Any other endoscopies will be performed clinically as needed, per the discretion of the PI. Medications will be modified ad lib during the OLE II period.

Visit 11 (Week 36) through Visit 25 (Week 92)

During OLE II, study drug will be administered at either 4 or 8 week intervals, which will be determined ad-lib by the study doctor, depending upon the symptoms, CBC results and discussion with patients. Additional unscheduled clinical tests such as CBC with differential tests (for peripheral eosinophil counts) may be drawn to determine dosing frequency and assess patient wellbeing. If the study drug is given at 8 week interval, then telephone encounter and surveys will be completed remotely every four weeks. For participants whose EGDs are postponed due to COVID-19, additional injections may be given until an EGD can be performed.

The below activities are done when indicated in the study plan table (section 4):

- Concomitant medications/procedures
- GI symptoms and pain interference
- PROs (EESAI, EoE-QOL-A, SODA, PedsQL, PEESS, PROMIS)
- Vital Signs, Weight
- Adverse Events
- Pregnancy Testing: urine
- Endoscopy with biopsies
- Endoscopic and Histologic metrics (EREFS, HSS, Lanza score, EG Biopsy Evaluation Form, ED Biopsy Evaluation Form)
- Physical exam (Due to COVID-19, physical exams not associated with EGDs may be conducted via telephone or telemedicine)
- Clinical labs (hematology and serum chemistry, urinalysis, pregnancy testing, IgE)
- Research samples (whole blood/serum, plasma, stool microbiome)

At visits 12 - 23 participants may have study drug administered by their local providers due to COVID-19 travel restrictions and travel risks. In these cases, adverse events and concomitant medications will be assessed by study team via telephone/telemedicine prior to the visit to local provider. Pregancy testing, vitals, and CBC with differential will occur by local provider/lab per PI discretion. Results from testing will be provided to the study staff directly from the local provider (via medical record release if necessary). Date and time of drug injection and post injection monitoring results will also be provided to study staff from the local provider.

5. STUDY ASSESSMENTS

5.1 Efficacy assessments

Severity of Dyspepsia Assessment (SODA)

Since instruments are not available to date for adult EG, this study will use the Severity of Dyspepsia Assessment (SODA) scale as a validated instrument to assess dyspepsia related health [25].

EREFs

The EREFs measures EoE esophageal mucosal inflammatory and remodeling features as identified during endoscopy. The score includes a total of 17 items related to the presence and

severity of esophageal features. Specific esophageal features assessed include: rings (absent, mild, moderate, severe, not applicable); stricture (yes, no, not applicable); diameter of the stricture (if applicable); exudates (absent, mild, severe), furrows (absent, present); edema, (absent, present); crêpe paper esophagus (absent, present); overall general appearance incorporating all endoscopically identified EoE findings (ie, fixed rings, strictures, whitish exudates, furrowing, edema, and crêpe paper mucosa). Mucosal changes associated with gastroesophageal reflux disease will also be recorded using the Los Angeles classification system for erosions (No Erosions or LA Classification A, B, C, D). The EREFS is a validated scoring system for the assessment of inflammatory and remodeling features of disease using both overall scores and scores for each individual characteristic [26]. The EoE-EREFS should be performed by the physician who performs the endoscopy procedure.

Lanza Score

The Lanza score is an endoscopic grading system used to evaluate for gastritis. It has been used in therapeutic trials and is based on the 0-7 scale with 0=no lesions and 7= >3mm ulcer scale. Since no system has been developed/used to date for EG, this score will be used to assess adult EG [27].

HSS (EoE)

The HSS is a scale developed by Collins, et al. [28] to express the severity and extent of abnormalities in the gastrointestinal (GI) tract that often accompany eosinophilic inflammation. The HSS evaluates esophageal biopsies for various features (e.g. basal layer hyperplasia, dilated intercellular spaces, surface epithelial alteration, apoptotic epithelial cells), eosinophilic inflammation (peak count, eosinophil abscess, eosinophil surface layering), and lamina propria (fibrosis).

Eosinophilic Gastritis (EG) and Eosinophilic Duodenitis (ED) Biopsy Evaluation Forms

Histological evaluation forms, with the goal of capturing features of eosinophilia relevant to the affected tissue as well as other features indicative of mucosal health and inflammation, have been developed by expert pathologist Dr. Margaret Collins. These forms will be utilized to evaluate the gastric and duodenal biopsies from subjects with extraesophageal eosinophilia.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

The following laboratory variables will be measured:

Table 2 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma) with Differential
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-Alkaline phosphatise (ALP)
B-Platelet count	S/P-Aspartate transaminase (AST)
	S/P-Alanine transaminase (ALT)
Urinalysis (dipstick)	S/P-Albumin
U-Hb/Erythrocytes/Blood	S/P-Potassium
U-Protein/Albumin	S/P-Calcium, total
U-Glucose	S/P-Sodium
	S/P-Creatine kinase (CK)
	Blood urea nitrogen (BUN)
	Differential: Neutrophils, Lymphocytes, Monocytes, Basophils, Eosinophils

5.2.2 Physical examination

A thorough physical examination will be performed at the time points indicated in Table 1. Any abnormalities that may be present, according to the patient's medical history, should be assessed. Due to COVID-19, physical exams not associated with EGDs may be conducted via telephone or telemedicine.

5.2.3 Vital signs

Vital signs, including heart rate, blood pressure, and respiration rate will be measured at the time points indicated in Table 1.

5.2.3.1 Pulse and blood pressure

Heart rate and blood pressure will be measured with the patient in sitting position, after the patient has been resting for at least 5 minutes.

5.2.3.2 Body temperature

Body temperature will be measured at the time points indicated in Table 1.

5.2.4 Other safety assessments

Pregnancy testing will be performed for all women of childbearing potential. Serum or urine pregnancy testing will be performed at the time points indicated in Table 1. A serum FSH test will be performed if there is a question regarding menopausal status.

5.3 Other assessments

5.3.1 Patient reported outcomes

5.3.1.1 EESAI: for subjects with EoE and EG

The EESAI is a validated index developed at University Hospital Inselspital (Berne, Switzerland) [29], which is a part of the international EESAI study group. The EESAI includes items related to the intensity and frequency of dysphagia, the influence of specific food groups on dysphagia symptoms, and other symptoms independent of eating or drinking (e.g., heartburn, acid regurgitation, and chest pain). The total EESAI PRO score ranges from 0 to 100. The EESAI PRO utilizes 24-hour and 1-week recall periods. In this study, a 1-week recall period will be utilized. This questionnaire will be administered to both adolescents and adults.

5.3.1.2 EoE-QOL-A: for subjects with EoE and EG

The EoE-QOL-A is a validated disease-specific questionnaire used to assess health-related quality of life in patients with EoE [30]. The instrument that will be used in this study, the EoE-QOL-A v.3.0, includes 30 items related to established domains such as social functioning, emotional functioning, and the impact of disease on daily life experiences. The EoE-QOL-A has a 1-week recall period. Items are graded on a 5-point scale: 'Not at All,' 'Slightly,' 'Moderately,' 'Quite a bit,' and 'Extremely'. This questionnaire will be administered to both adolescents and adults.

5.3.1.3 PEESS®v2.0: For pediatric subjects (≤ 18 years old)

The PEESS® v2.0 is a content-validated metric that seeks to capture EoE-specific symptoms directly from children with EoE (8–18 years of age) and from their parents (2–18 years of age) [31]. From parent/participant interviews, four domains were established: dysphagia, gastroesophageal reflux disease (GERD), nausea/vomiting and pain. The range for these PEESS® v2.0 scores is 0 to 100, with a higher score being indicative of more frequent and/or severe symptoms for total score, and the dysphagia, GERD, nausea/vomiting and pain domains. A 30 day recall will be used. This questionnaire will be administered to all pediatric patients.

5.3.1.4 PedsQL 3.0: for pediatric subjects (≤ 18 years old) with EoE and EG

The PedsQL 3.0 is a disease-specific measure of health-related quality of life for pediatric patients diagnosed with EoE [32] . This questionnaire will be administered to all pediatric patients.

5.3.1.5 PROMIS: Patient Reported Outcomes Measurement Information System

The PROMIS assessments selected for this study are multi-purpose, short-form health surveys with 29 (for adults) and 25 (for peds) questions, that will be used with EG patients. It yields a high profile of general well being.

5.3.2 Other

5.3.2.1 Diet Questionnaire

The diet questionnaire is a tool used to track participants' diets before and after treatment. Since participants are asked not to change their diet during trial participation, this questionnaire allows for an evaluation of whether or not a participant's diet did change during the trial.

5.3.2.2 Complete Blood Count (CBC) with differential

CBCs will be performed to measure changes in participants' blood eosinophil counts pre- and post-treatment.

5.3.2.3 GI Symptoms and Pain Interference

The GI symptoms and pain interference tool is a series of questions administered to patients to quantify symptoms. The tool is used to determine eligibility at screening and to track clinical symptoms during the study.

5.4 Pharmacokinetics

5.4.1 Collection of samples

Not applicable

5.4.2 Determination of drug concentration

Not applicable

5.4.3 Storage and destruction of pharmacokinetic samples

Not applicable

5.5 Pharmacodynamics

Not applicable

5.5.1 Collection of samples

Not applicable

5.5.2 Storage, re-use and destruction of pharmacodynamic samples

Not applicable

5.6 Pharmacogenetics

Not applicable

5.6.1 Collection of pharmacogenetic samples

Not applicable

5.6.2 Storage, re-use and destruction of pharmacogenetic samples

Not applicable

5.7 Biomarker analysis

5.7.1 Storage, re-use and destruction of biological samples

Tissue samples for transcriptome evaluation will be stored in RNAlater reagent (Qiagen) in individual tubes at -80ºC until RNA or protein isolation is performed; isolated RNA and protein will then be stored at -80ºC. Tissue samples for eosinophil counts will be collected in tubes containing 10% formalin and will be stored at room temperature until they are embedded in paraffin using routine procedures; paraffin blocks will then be stored at room temperature. Serum samples will be aliquoted into several tubes and stored at -80ºC until proteomic and/or biomarker analysis is performed. Stool samples will be stored in individual tubes at -80ºC in a freezer until DNA is isolated from such samples; DNA will then be stored at -20ºC. Research blood cell samples will be aliquoted into several tubes and stored at -80ºC until used for biomarker analysis and/or reprogramming into induced pluripotent stem cells. Re-use of samples may occur if the entire sample or material isolated or derived from the sample is not depleted during a particular analysis. In this case, the remainder of the sample or material derived from the sample will be stored at the appropriate temperature until additional analysis is performed. Samples or material isolated or derived from samples will be destroyed only if a subject withdraws consent and gives written notice of his/her request for destruction of samples collected prior to the withdrawal of consent.

5.7.2 Labelling and shipment of biological samples

Unique biological samples will be stripped of protected health information and labeled with a unique barcode linked to the protected health information of the corresponding patient. Any material derived or isolated from the original sample will be labeled with the same barcode as the original sample. Shipment of biological samples, if necessary, will be performed in accordance with federal guidelines for shipment of biological materials and will be coordinated by personnel who are trained to comply with these guidelines. The shipping conditions (e.g., temperature of shipment) will be chosen according to the most appropriate storage conditions for the given samples being shipped.

5.7.3 Chain of custody of biological samples

Biological samples obtained by the study physician or other qualified medical professional will be delivered to clinical research coordinators. The clinical research coordinators will deidentify the samples and then deliver them to designated laboratory personnel, who will then process and store the samples. All personnel in the chain of custody will be qualified to handle the designated tasks and will have successfully completed any required appropriate training.

5.7.4 Withdrawal of Informed Consent for donated biological samples

If a subject withdraws consent for donated biological samples, any existing samples provided by the subject will be retained unless notified otherwise by the subject. The subject must provide

written notice of this withdrawal of consent and include their request for destruction of existing samples.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

Safety will be evaluated throughout the study. Evaluation for AEs, review of concomitant medications, and review of protocol restrictions will occur at the beginning of each visit.

6.1 Definition of adverse events

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

The term AE is used to include both serious and non-serious AEs. An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the Visit 1 that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)

Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be preexisting and should be documented on the medical history CRF.

6.2 Definition of Serious Adverse Event (SAE)

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

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

6.3 Causality assessment

The Investigator will assess causal relationship between Benralizumab and each adverse event, 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 a causal relationship will also be assessed for other concomitant medications, study procedures, and comparator study drugs. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

6.4 Recording of adverse events

6.4.1 Time period for collection of adverse events

Adverse events (including SAEs) will be collected from the time of consent until a subject completes study participation, or until 30 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study.

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the participant.
- Interviewing the participant
- Receiving an unsolicited complaint from the participant.

In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Definition of adverse events.

Throughout the study, the investigator will record adverse events and serious adverse events on the appropriate AE/SAE CRF, regardless of the relationship to study therapy regimen or study procedure.

6.4.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last AE assessment in the study will be followed up by the investigator for as long as medically indicated, but without further recording in the CRF.

AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of study, if judged necessary

6.4.3 Variables

The following variables should be collected for each AE;

- *AE (verbatim)*

- *The date when the AE started and stopped*
- *CTCAE grade (*Grade 1 = mild adverse event, Grade 2 = moderate adverse event, Grade 3 = severe and undesirable adverse event, Grade 4 = life-threatening or disabling adverse event, Grade 5 = death.)
- *Whether the AE is serious or not*
- *Investigator causality rating against the Investigational Product*
- *Action taken with regard to investigational product*
- *AE caused subject's withdrawal from study (yes or no)*
- *Outcome*

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

- *Date AE met criteria for serious AE*
- *Date Investigator became aware of serious AE*
- *AE is serious due to...*
- *Date of hospitalisation*
- *Date of discharge*
- *Probable cause of death*
- *Date of death*
- *Autopsy performed*
- *Causality assessment in relation to Study procedure(s)*
- *Description of AE.*

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. 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. 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.

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the CRF. 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.

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report (CSR). 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 or are the reason for discontinuation of treatment with the investigational product.

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

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.

Since the most common adverse effects previously noted for Benralizumab has been breathing difficulty, nasopharyngitis, upper respiratory infection, headache, bronchitis, sinusitis, influenza and pharyngitis, surveillance for these events will be undertaken. Any of these events that fulfil the criteria of an AE as judged by the investigator should be reported using the standard procedures for assessing severity, causality and seriousness.

6.5 Reporting of serious adverse events

All SAEs have to be reported to AstraZeneca, whether or not considered causally related to benralizumab, or to the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 60 days after the last dose of benralizumab. The investigator is responsible for informing the IRB as per local requirements.

The investigator and other site personnel must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AZ. A copy of the MedWatch/AdEERs report must be faxed or email to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

When reporting to AstraZeneca, a cover page should accompany the MedWatch/AdEERs form indicating the following:

- Investigator Sponsored Study (ISS)
- The investigator IND number assigned by the FDA
- The investigator’s name and address

- The trial name/title and AstraZeneca ISS reference number (ESR- 16-12419)

Investigative site must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.

Send SAE report and accompanying cover page to AstraZeneca by email to AE Mailbox Clinical Trial (TCS) <AEMailboxClinicalTrialTCS@astrazeneca.com> or by fax to 1-302-886-4114 (US Fax number). Email is the preferred method.

Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events at least on a monthly basis.

6.6 Overdose

Overdose in itself is not considered to be an AE or SAE.

Investigator/site staff are responsible for recording and reporting overdose in accordance with the clinical study protocol instructions. All overdoses with AstraZeneca product are collected and reported to AstraZeneca. Overdoses associated with SAEs will be reported according to SAE reporting described in section 6.5. All other overdoses can be sent to AstraZeneca at least on a monthly basis.

The following information should be provided in the event of an Overdose (Overdose Report Form can be provided upon request):

- Details of the Patient who was dispensed study medication (Randomization code)
- Details of the Patient who took the overdose (demographic information, was patient a study participant?)
- Details of the drug overdose (total daily dose, route, formulation, Overdose start and stop dates)
- Was the overdose accidental or intentional?
- Was the overdose associated with an adverse event (serious or non-serious)
- Provide an Adverse Event description (use same wording as in CRF). Provide start and stop dates of the event, or indicate if the event is ongoing.
- Provide Investigator's signature and date.

6.7 Pregnancy

All female patients of child-bearing potential should receive blood and urine pregnancy screening tests during the baseline assessment and should receive a urine test at each study visit. If any female patient is found to be pregnant during the study she should be withdrawn and study medication should be immediately discontinued. If the pregnancy occurs during

administration of active study drug the pregnancy should be reported immediately to the study investigators.

Should the pregnancy occur during or after administration of the study drug the investigator must inform the subject of their right to receive treatment information. Healthy controls do not need follow-up.

Pregnancy in itself is not considered to be an AE or SAE. However, if the subjects become pregnant during the study, Investigator/site staff are responsible for recording and reporting pregnancies and their pregnancy outcomes until pregnacy resolution in accordance with the clinical study protocol instructions.

6.7.1 Maternal exposure

All reports of pregnacy with benralizumab (with or without associated SAE, AE or no symptoms) are collected and reported to AstraZeneca. If the pregnancy is accompanied by an SAEs (e.g. events of congenital abnormality/birth defect, spontaneous miscarriage or ectopic pregnancy, or any complications in the subject which meet the criteria for a serious adverse event), it should be reported according to the SAE reporting requirement. All other maternal exposure reports can be sent to AstraZeneca at least on a monthly basis.

Normal births and elective abortions without complications are not considered to be SAEs.

6.7.2 Paternal exposure

If paternal exposure pregnancy occurs in the course of the study, the the investor/site staff should inform AstraZeneca within the same timeframe as the maternal exposure. The female partner of the patient will be asked to consent to allow collection of information and follow-up on the pregnancy. The outcome of the pregnancy is also followed and reported in accordance with the processes written in maternal exposure section.

6.8 Management of toxicities

The study is designed to administer uniform dose of 30mg of benralizumab. In the event of SAEs, the subject will be discontinued from the study and the event reported as mentioned above. Continued enrolment at reduced dosage is not applicable.
Dose Reductions: Not applicable.

6.9 Study governance and oversight

An unblinded medical review officer (MRO) will review all AE data in order to make determinations regarding subject safety and trial continuation.

6.9.1 Steering Committee

Not applicable

6.9.2 Data Monitoring Committee

At least biannually, a data safety monitoring board will review and evaluate the accumulated study data for participant safety, and make recommendations to the study investigators and regulatory agencies (CCHMC IRB, CCHMC IBC, FDA, etc.) concerning the continuation, modification, or termination of the trial.

6.9.3 Scientific Advisory Committee

Not applicable

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Benralizumab	30 mg SC	AstraZeneca
Placebo	Same as benralizumab, without the active substance	AstraZeneca

7.2 Dose and treatment regimens

Benralizumab Drug Product is a sterile liquid solution presented in an accessorized prefilled syringe (APFS) for subcutaneous injection. Each syringe contains 10 mg of benralizumab in a 0.5 volume (nominal) or 30 or 100 mg of benralizumab in a 1.0 mL volume (nominal). The Drug Product is formulated in 20 mM histidine/histidine-HCl, 0.25 M trehalose dihydrate, and 0.006% (w/v) polysorbate 20, pH 6.0 (Table 3).

Table 3 Benralizumab (MEDI-563) composition

Ingredient	Concentration			Unit formula per 10 mg, 30 mg, or 100 mg syringe (nominal)		
Active ingredient						
Benralizumab	20 mg/mL	30 mg/mL	100 mg/mL	10 mg	30 mg	100 mg
Other ingredients						
L-Histidine	9 mM	9 mM	9 mM	0.7 mg	1.4 mg	1.4 mg
L-Histidine HCl monohydrate	11 mM	11 mM	11 mM	1.2 mg	2.3 mg	2.3 mg
Trehalose dehydrate	0.25 M	0.25 M	0.25 M	47 mg	95 mg	95 mg
Polysorbate 20	0.006% (w/v)	0.006% (w/v)	0.006% (w/v)	0.03 mg	0.06 mg	0.06 mg

Benralizumab will be administered as a 30 mg SC injection at V3 and once every 4 weeks for 2 months (for a total of 3 injections) during the double blind portion of the study.
Benralizumab will be administered as a 30 mg SC injection at V5 and once every 4 or 8 weeks during the open label extensions.

7.3 Labelling

A numbering system will be used to label the blinded IP. A list linking the label number with the product lot number will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, the list will not be accessible to individuals involved in study conduct.

7.4 Storage

The investigational product must be stored refrigerated at 2-8°C (36-46°F) and must not be frozen. The investigational product will be allowed to warm to room temperature prior to administration. Due to COVID-19, drug may be shipped to local providers using cold transport shipping or courier. Local providers will confirm IP is stored at 2-8°C (36-46°F) until the IP is administered. To minimize storage risks, the investigational product will be shipped to local providers 1-2 days prior to the patient's planned local injection.

7.5 Compliance

Drug compliance records must be kept current and must be available for inspection by the sponsor and regulatory authorities.

7.6 Accountability

Drug accountability records must be kept current at all times. The investigator must be able to account for all opened and unopened study drug. Records should contain the following:

Dates, quantity, and study medication

- dispensed to each patient (if applicable) including drug shipped to local provider for patients that cannot travel to the study site due to COVID-19
- returned from each patient (if applicable), and
- disposed of at the site or returned to the manufacturer or designee.

Accountability records must be available for inspection by the AstraZeneca and regulatory authorities. Photocopies must be provided to the sponsor at the conclusion of the study.

7.7 Concomitant and other treatments

Prohibited Medication/Class of drug:	Washout Period Prior to Study Screening (i.e. Study Entry)
Anti-immunoglobulin E [IgE] mAb	6 months
Anti-tumor necrosis factor [TNF] mAb)	6 months
Other investigative biologic	6 months
Anti-IL 5 agents	6 months
Anti-IL 4/13 agents including anti-IL4Ra	6 months
Other investigative drugs or device	1 month

Rescue/Supportive Medication/Class of drug:	Usage:
Study participants should continue their baseline medications and dietary therapy. Rescue medicines for EGID exacerbations are not allowed and will lead to study withdrawal.	N/A
During study visits, participants will be allowed to have EMLA or topical analgesic (Pain Ease or Spray & Stretch) for the purpose of venepuncture/IV insertion	As needed during study visits

7.7.1 Other concomitant treatment

Throughout the study duration, all participants are expected to maintain medications such as a PPI, oral or nasal allergy medications (such as antihistamines and any asthma-related medications) as well as special diets including elimination diets that were prescribed prior to study entry.

8. STATISTICAL ANALYSES

8.1 Statistical considerations

Pertaining to the primary objective of this study, the primary efficacy endpoint is the eosinophil count response rate to the treatments. The comparison of response rates between the benralizumab and placebo groups will be made with a Fisher's exact test of binomial distributions. For secondary endpoints, continuous variables comparisons between the two groups, e.g. change in peak eos counts, change in blood eosinophil count, change in symptom scores from pre- to post-treatment, and change in endoscopic scores from pre- to post-treatment at each study visit (e.g. Weeks 4, 8 and the end of treatment) will be made in a repeated measure ANOVA model, where serial correlation within patients will be accounted for. Proper transformation of data, e.g. logarithmic, or non-parametric methods may be applied to satisfy statistical assumptions. Categorical responses, e.g. response rate will also be compared using a Fisher's exact test, by visit if applicable. Additional exploratory analysis to investigate other

factors' effect on response may also be performed, with generalized linear models with appropriate link functions.

All comparisons are two-sided, and p-value < 0.05 is considered statistically significant. No multiplicity adjustment will be made for this analysis.

Safety measurements, including adverse events will be summarized by descriptive statistics. The total numbers of AE's as well as number of patients with an AE will be summarized via N and percent.

8.2 Sample size estimate

The planned total sample size of 24 subjects is justified based on previously published studies. Based on trials of other therapies in EoE and EGID, it is reasonable to assume that an eosinophil count at or below 15, 30 and 52 eos/hpf in esophagus, stomach and duodenum, respectively, after treatment, is considered an adequate response. It is estimated that in the placebo group, the response rate will be no more than 10%. We assume that the benralizumab group response rate will be about 70%. To detect a difference between these two response rates, we need a total of 24 completed subjects, or 12 subjects per arm to reach 80% statistical power. This is based on a two-sided Fisher's exact test at 0.05 level. We will enroll 26 subjects to account for possible dropouts.

8.3 Definitions of analysis sets

8.3.1 Efficacy analysis set

There will be one efficacy analysis set. That is the intention-to-treat (ITT) set. This comprises all enrolled patients who took at least one dose of study medication.

8.3.2 Safety analysis set

Safety analysis set comprises all patients enrolled in the study.

8.3.3 PK analysis set

N/A

8.3.4 PRO analysis set

PRO analysis sets are the same as Efficacy analysis sets.

8.4 Outcome measures for analyses

The primary efficacy endpoints are the eosinophil count response rate to the treatments. A disease remission is defined by peak eosinophil counts less than 15 for esophagus, less than 30 for stomach, and less than 52 for duodenum. A patient is considered in remission if all applicable counts are in remission range. The rate of remission among all patients is the primary efficacy measure for both treatment groups.

Secondary outcome measures include individual disease remission rate, changes in endoscopic scores from pre to post-treatment as measured by EREFS for EoE and Lanza score for EGE, changes in histologic scores from pre to post-treatment, changes in blood eosinophil count pre and post-treatment, changes in symptom scores from pre to post-treatment measured by EESAI, EoE-QoL-A (for EoE), and SODA (for EGE), and changes in peak eosinophil counts in biospies from pre to post-treatment.

8.5 Methods for statistical analyses

8.5.1 Analysis of the primary variable(s)

The comparison of primary response/remission rates between the benralizumab and placebo groups will be made with a Fisher's exact test of binomial distributions.

8.5.2 Analysis of the secondary variable(s)

For secondary endpoints, continuous variables, e.g. change in peak eos counts, change in blood eosinophil count, change in symptom scores from pre- to post-treatment, and change in endoscopic scores from pre- to post-treatment at each study visit will be analysed and compared in a repeated measure ANOVA model. Proper transformation of data, e.g. logarithmic, or non-parametric methods may be applied to satisfy statistical assumptions. Categorical responses, e.g. response rate will also be compared using a Fisher's exact test.

Safety endpoints, i.e. adverse events (by organ system and preferred terms), SAEs, as well as demographic variables will be summarized by treatment groups. The total numbers of AE's as well as number of patients with an AE will be summarized via N and percentages.

8.5.3 Subgroup analysis (if applicable)

No subgroup analysis is planned, other than a per-protocol analysis of efficacy.

8.5.4 Interim analysis

No interim analysis is planned.

8.5.5 Sensitivity analysis (if applicable)

Logistic regression models will be explored in the primary efficacy endpoint analysis, namely the remission rate. In addition to treatment groups, other terms may be included in the regression model, e.g. gender, age, and baseline eosinophil count, to assess the sensitivity of the primary results.

8.5.6 Exploratory analysis (if applicable))

Additional exploratory analysis may be conducted for the exploratory objective measures.

9. STUDY AND DATA MANAGEMENT

9.1 Training of study site personnel and local providers

All study staff listed on the site delegation log must be trained on the conduct of the study prior before engaging in any study-related activities

Due to COVID-19, drug may be administered by local providers to some patients. Local providers medically trained to administer subcutaneous injections (RNs, MDs, PharmD) will provide the study injections. Local providers will be asked to provide evidence of competency in subcutaneous injections and/or injection certification to the study staff. Local providers must show competency in monitoring for post injection reactions.

9.2 Monitoring of the study

The Principle Investigator will designate a study monitor who will visit the study site prior to enrollment of the first patient, and periodically throughout the study. The monitor will compare CRF entries with the corresponding source documents, as outlined in the ICH guidelines. The study monitor may also review subject ICFs, patient recruitment and follow-up documentation, AEs, SAEs, and concomitant therapy; along with records of dispensation of study drug, compliance, and accountability. A copy of the drug dispensing log must be provided to the sponsor upon request.

9.2.1 Source data

Study staff must prepare and maintain adequate and accurate records of each subject's study participation (i.e. source documents). All source documents must be kept on file with the CRFs. (CRFs may be either paper or electronic [eCRF]). CRFs and source documents must be available at all times for inspection by authorized representatives of the Principle Investigator regulatory agencies.

9.2.2 Study agreements

If the PI chooses to close out the study site (for example, due to lack of subject enrollment within a reasonable period of time, violation of the study agreement, breach of protocol, early attainment of study enrollment targets, etc.), the PI will notify involved individuals in writing.

The appropriate regulatory agencies must be informed according to applicable requirements, and adequate consideration must be given to the protection of the subjects' interests.

9.2.3 Archiving of study documents

All essential study documents must be retained by the investigator for at least 3 years after the conclusion or discontinuation of the trial. Prior to destroying any essential documents, the investigator must consult with the PI. If and when destruction is authorized, records must be destroyed in a manner that ensures confidentiality. If an investigator can no longer ensure

archiving, the sponsor and the investigator will agree upon a suitable designation for transferring the essential records.

9.3 Study timetable and end of study

The end of study will be at a follow up visit at Week 16 ±3 days. For subjects who are remote, the follow up visit can be performed at a local site, in which vital signs, physical exam, urine pregnancy and lab work will be performed. Results will be released to CCHMC upon authorization of release of medical information/specimen by the subject.

9.4 Data management

Serious Adverse Event (SAE) Reconciliation

SAEs will be followed until they are resolved, with or without sequlae, or until the end of study participation, or until 30 days after the subject prematurely withdraws from the study (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

Data Management of genotype data

N/A

Data associated with human biological samples

N/A

Management of external data

N/A

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

This study will be conducted using good clinical practice (GCP), as delineated in Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance, and according to the criteria specified in this study protocol.

10.2 Subject data protection

Participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers will be used to collect, store, and report participant information instead of the participant's name. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study sponsor or their representatives.

10.3 Ethics and regulatory review

Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the Cincinnati Children's Hospital Medical Center IRB (CCHMC IRB).

10.4 Informed consent

The Principal Investigator will designate appropriate study staff for performing the informed consent process.

During the consent process, study staff will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The principal investigator or designee listed on the delegation log will review the consent and answer questions. The consent designee must be listed on the delegation log, have knowledge of the study and received training (from the local IRB, PI, or study coordinator) in the consent process. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants (or their legally authorized representative) will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in participants' primary language. A copy of the signed consent form will be given to the participant.

This study will be conducted in compliance with ICH E6 GCP: Consolidated Guidelines pertaining to informed consent. At the first visit, prior to initiation of any study-related procedures, participants will give their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits. If the participant is unable to provide written informed consent, the participant's legally acceptable representative may provide written consent as approved by institutional specific guidelines. The informed consent document must be signed and dated by the participant, or the participant's legally authorized representative, prior to study participation. A copy of the informed consent document must be provided to the participant or the participant's legally authorized representative. Signed consent forms must remain in the participant's study file and be available for verification by the monitor, IRB, and/or regulatory authorities at any time. If participant's legally acceptable representative provides written consent, participants will also give their written assent to participate in the study as approved by institutional specific guidelines for obtaining assent.

The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

10.5 Changes to the protocol and informed consent form

Any amendments to the protocol or consent materials will be approved by the CCHMC IRB before they are implemented.

10.6 Audits and inspections

The study PI or CCHMC representative may subject this trial to quality assurance audits or inspections at any time. In the case of an audit or inspection, the investigator is responsible for the following:

- Informing the sponsor of a planned inspection by regulatory agencies as soon as they become aware of the inspection, and authorizing the sponsor to participate in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Immediately communicating any information arising from inspection by regulatory agencies to the sponsor
- Taking all appropriate measures requested by the sponsor to resolve any problems discovered during audit or inspection

Documents subject to audit or inspection include, but are not limited to:

- all source documents, CRFS, and ICFs
- medical records
- correspondence
- IRB/EC files
- documentation of certification and quality control of supporting laboratories
- records relevant to the study maintained in any supporting pharmacy facilities.

Study material storage data are also subject to inspection. Representatives of CCHMC may observe the conduct of any aspect of the trial or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

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ADDENDUM NUMBER 1: GI SYMPTOMS AND PAIN INTERFERENCE

Inclusion criteria "patient must be symptomatic" will be determined by the following assessment of symptoms and pain interference to a subject's daily life:

IRB# 2017-1701 Benralizumab Study
Subject number:_____
Date of visit:_____

In the past 4 weeks, how have pain and symptoms affected your daily life?
GI symptoms may include Nausea, pain, abdominal discomfort, diarrhea, heartburn, burping, constipation and others.

Ability to Participate in Social Roles and Activities	**Never**	**1 time per week**	**2-3 times per week**	**4-5 times per week**	**6-7 times per week**
How often did pain/symptoms interfere with your regular leisure activities with others, such as playing sports or participating in your hobbies?	☐	☐	☐	☐	☐
How often did pain/symptoms interfere with your day to day activities?	☐	☐	☐	☐	☐
How often did pain/symptoms interfere with your ability to go to work/ school and participate in classes, doing school work at home, chores/tasks you usually do around the home/place of work?	☐	☐	☐	☐	☐
How often did pain/symptoms interfere with your ability to participate in social activities, such as spending time with friends, attending events or parties, or going on dates?	☐	☐	☐	☐	☐
How many times have your symptoms interfered with your daily life in any way?	☐	☐	☐	☐	☐

For inclusion: At least 1 question must be answered with 2-3 time per week and up.

OR,

At least 2 questions must be answered with 1 time per week and up.

Inclusion criteria Pass/Fail (circle)

PI signature:_____ Date:_____