A multi-center, randomized, double blind, parallel-arm, placebo controlled trial of mepolizumab for treatment of adults and adolescents with active eosinophilic esophagitis and dysphagia-predominant symptoms

Protocol Number: 18-0431

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Summary of Changes from Previous Version (Version 5.0 23Jul2019):

Affected Section(s)	Summary of Revisions Made	Rationale
1.2	Updated study schema to reflect final safety assessments.	Clarification
1.3	Updated schedule of activities to more accurately reflect the timing of weekly SDIs.	Clarification
2.2.1	Updated risk information based on most recent package insert, including data from HES and EGPA trials.	Updated per new package insert
4.1	Clarified treatments prohibited during the study treatment period.	Clarification
5.1	Updated inclusion criterion 3 to reflect most recent clinical guidance on PPI trials and allow subjects with a PPI allergy or intolerance to be considered.	Updated per clinical guidance
5.2	Clarified exclusion criterion 3 applies to a course of steroids, defined as >3 days of systemic steroid use. Clarified the time period referenced in exclusion criterion 4 during which dietary changes are prohibited includes the screening endoscopy. New allowance for sponsor-investigator's discretion in the application of exclusion criteria 3 and 5 subjects' with a documented history of steroid non-response.	Clarification
6.5.1	Changed title of section from "Rescue Medications" to "Prohibited Treatments." Added dilation to the list of prohibited treatments and clarified the time period for study exit in case of prohibited treatments.	Clarification
7.1	Added specific criteria for individual subject withdrawal from the study per DSMB request.	Clarification
8.1.3	Clarified biopsy protocol for stomach, duodenum and target areas in adults is up to the investigator's discretion.	Clarification
8.2.1	Clarified timing of weekly SDIs and which assessments are performed during the visit and which the subject performs at home in between visits.	Clarification
8.3	Clarified that VAS scale should be administered, if applicable, at month 8 visit, as noted in the schedule of events.	Clarification
8.8.4.1	Clarified that the CTCAE should be used to evaluate all adverse events, unless the event is not defined in the CTCAE.	Clarification
Entire document	Corrected minor typographical and formatting errors.	Administrative changes
Entire document	Administrative changes to update protocol version number and date, page numbers, and table of contents.	Administrative changes

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SPONSOR-INVESTIGATOR APPROVAL OF PROTOCOL

PROTOCOL TITLE: A multi-center, randomized, double blind, parallel-arm, placebo controlled trial of mepolizumab for treatment of adults and adolescents with active eosinophilic esophagitis and dysphagia-predominant symptoms

PROTOCOL NO: 18-0431

Evan S. Dellon
Sponsor-Investigator

Signed:

DocuSigned by:
Evan Dellon
Signer Name: Evan Dellon
Signing Reason: I approve this document
Signing Time: 21-May-2021 | 13:57 PDT
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Signature

Date: 21-May-2021 | 13:57 PDT

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312).

The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Principal Investigator:

_____
Print/Type Name

Signed:

_____ Date: _____

Signature

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: A multi-center, randomized, double blind, parallel-arm, placebo controlled trial of mepolizumab for treatment of adults and adolescents with active eosinophilic esophagitis and dysphagia-predominant symptoms

Study Description: This multi-center, randomized, double blind, parallel-arm, placebo controlled trial will determine whether mepolizumab is more effective than placebo for improving symptoms of dysphagia and decreasing esophageal eosinophil counts in adults and adolescents with active eosinophilic esophagitis after an initial 3-month treatment course and will also assess the impact of an additional 3-months of treatment.

Objectives:

Primary Objectives:

1. To determine whether mepolizumab is more effective than placebo for improving symptoms of dysphagia as measured by the validated Eosinophilic Esophagitis Symptom Activity Index (EEsAI) in adults and adolescents with active eosinophilic esophagitis after a 3-month treatment course.
2. To determine whether mepolizumab is more effective than placebo for decreasing esophageal eosinophil counts in adults and adolescents with active eosinophilic esophagitis after a 3-month treatment course.

Secondary Objectives:

1. To determine predictors of symptomatic and histologic response to mepolizumab treatment, including potential biomarkers.
2. To assess durability of symptomatic and histologic response to mepolizumab after 6 months of treatment in patients initially randomized to the active medication (this includes a 3-month blinded second phase of treatment).
3. To assess histologic response to a lower dose of mepolizumab treatment in patients initially randomized to the placebo arm (this will be in a 3-month blinded second phase); symptom response will also be assessed in this phase.
4. To assess safety of mepolizumab over 3 and 6 months of treatment (this includes both 3-month study phases).

Outcomes:

Primary Outcome:

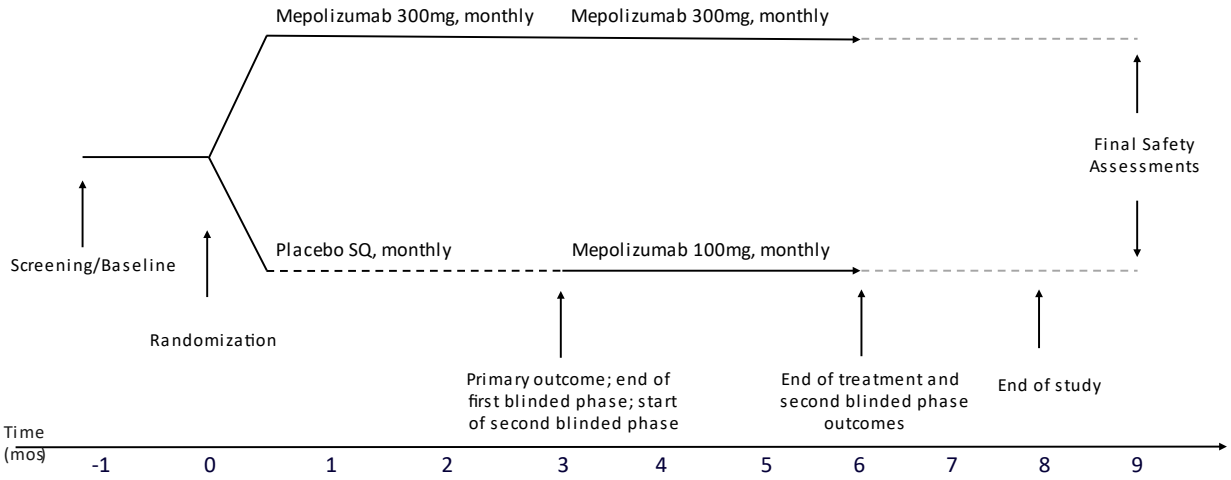
1. Mean change in dysphagia as measured by the EEsAI score (7-day recall) from baseline to 3-months post-treatment.

Secondary Outcomes:

1. Proportion of patients who have clinical remission as defined by an EEsAI score of ≤20.
2. Proportion of patients who have a clinical response, as defined by an EEsAI score decrease of ≥ 20 points.
3. Absolute peak eosinophil count (measured in eos/hpf) after 3-months of treatment.
4. Levels of histologic response after 3-months of treatment including < 15, ≤ 6, and ≤ 1 eos/hpf.

	5. Mean change in severity of endoscopic findings as measured by the EoE Endoscopic Reference Score (EREFS) from baseline to 3-months post-treatment. 6. Mean change in the Straumann Dysphagia Instrument (SDI) from baseline to 3-months post-treatment. Prespecified Exploratory Outcomes 1. Mean change in peripheral blood eosinophil levels from baseline to 3-months post treatment. 2. For patients initially randomized to active medication, the same set of outcomes (as listed above) will be assessed after 6 months of treatment. 3. For patients initially randomized to placebo, a paired analysis will be conducted to compare month 6 to month 3 outcomes. 4. For the same set of outcomes (as listed above), 3-month data for patients initially randomized to active medication (300mg monthly) will be compared to 6 month data for patients initially randomized to placebo and who have completed 3-months of 100mg monthly. This will provide a comparison of the 300mg to the 100mg dose. 5. Adverse events and safety during all time points in the study.
Study Population:	72 adult and adolescent patients with active EoE as measured by both symptomatic and histologic severity.
Phase:	2
Description of Sites/Facilities Enrolling Participants:	4 Unites States sites. Competitive enrollment.
Description of Study Intervention:	Arm 1: Mepolizumab 300 mg SQ monthly for 6 months. Arm 2: Placebo SQ monthly for 3-months followed by mepolizumab 100mg SQ monthly for 3 months. (Note that both arms are blinded for the entire 6 months)
Study Duration:	3 years
Participant Duration:	10 months

1.2 SCHEMA


Mepolizumab 300mg, monthly
Mepolizumab 300mg, monthly
Final Safety Assessments
Screening/Baseline
Placebo SQ, monthly
Mepolizumab 100mg, monthly
Randomization
Primary outcome; end of first blinded phase; start of second blinded phase
End of treatment and second blinded phase outcomes
End of study
Time (mos)
-1
0
1
2
3
4
5
6
7
8
9

1.3 SCHEDULE OF ACTIVITIES (SOA)

Visit	Screening/ Baseline[1] -49 days[10]	Randomization Month 0	Month 1 (+/- 5 days)	Month 2 (+/- 5 days)	Month 3 (+/- 5 days)	Month 4 (+/- 5 days)	Month 5 (+/- 5 days)	Month 6 (+/- 5 days)	Month 8 (+/- 5 days)	Early Termination[6]	30 Day Phone Call[7] 30 days after study discontinuation (+/-5 days)
Procedure											
Informed consent	X										
Demographics	X										
Medical history	X										
EGD with biopsy and EoE Endoscopic Reference Score (EREFS)	X[2]				X			X		X	
EEsAI	X		X	X	X	X	X	X	X	X	
Dysphagia Symptom Screening Questionnaire	X										
Patient Global EoE Assessment	X				X			X		X	
PGIC and PGIS					X			X		X	
VAS Assessment	X[8]				X[8]			X[8]	X[8]	X[8]	
Complete blood count (CBC) w/ differential[9]	X[3]		X	X	X	X	X	X	X	X	
Serum/anti-IL 5 antibodies	X				X			X	X	X	
Physical exam	X				X			X		X	
Vital signs	X	X	X	X	X	X	X	X		X	
Pregnancy test	X	X	X	X	X	X	X	X	X	X	
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	
Adverse event review and evaluation	X	X	X	X	X	X	X	X	X	X	X
48-hour adverse event review and evaluation		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]				
Randomization		X									
Straumann Dysphagia Index (SDI)	X[5]	X[5]	Weekly					X[5]	X[5]	X[5]	
Administer study drug		X	X	X	X	X	X				
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	X	X	X	X

[1]Screening can occur over multiple days, however blood labs should be obtained on the day of the screening EGD if possible. Screening assessments will also be used for baseline measures and will not be repeated at randomization unless indicated above. For the purposes of statistical analysis, this study will consider baseline at the point when symptoms are assessed prior to the study drug being given.
[2]Subjects must be deemed eligible per EEsAI score and dysphagia questionnaire **prior** to undergoing the screening EGD. Sites must obtain approval from the lead site (UNC) prior to performing the screening EGDs. Recent historical EGD information may be allowable in lieu of repeating endoscopic procedures. Dr. Dellon will review requests to use historical EGDs in lieu of the screening EGD on a case-by-case basis.
[3]Screening CBC with differential will be analyzed by local laboratory. Subsequent CBC will be sent to Central Lab for processing.
[4]Subjects will be contacted 48 hours (+ 1 week) after administration of study drug to assess for adverse events via IRB approved methods.
[5]SDI is completed at the screening/baseline visit, month 6, month 8, and early termination (if applicable). Weekly SDIs are completed by the subject at home beginning one week from randomization until the month 6 visit, where the SDI will be completed during the visit. See section 8.2.1
[6]Subjects who prematurely exit the study will be asked to complete an early termination visit.

Visit	Screening/ Baseline[1] -49 days[10]	Randomization Month 0	Month 1 (+/- 5 days)	Month 2 (+/- 5 days)	Month 3 (+/- 5 days)	Month 4 (+/- 5 days)	Month 5 (+/- 5 days)	Month 6 (+/- 5 days)	Month 8 (+/- 5 days)	Early Termination[6]	30 Day Phone Call[7] 30 days after study discontinuation (+/-5 days)
[7]30-day follow-up is completed 30 days after subject is exited from study, including early termination. [8]A VAS should be completed if subject reports any allergic diseases. VAS should be completed for each allergic condition applicable. [9]Unscheduled visits can be scheduled in cases where study assessments need to be re-assessed. Notification and approval from the lead site should be considered before scheduling these visits. [10]Subjects have up to 49 days from screening/baseline prior to randomization to remain eligible for study participation.											

2 INTRODUCTION

2.1 STUDY BACKGROUND AND RATIONALE

Eosinophilic esophagitis (EoE) is a Th2-mediated allergic disease whereby abnormal infiltration of eosinophils into the esophageal mucosa leads to dysphagia, progressive esophageal stenosis, and food impaction.[1-3] First described in the late 1970s[4] and initially felt to be rare,[5] the incidence has increased more than four-fold in the last ten years.[6-9] Because EoE is chronic, the prevalence is also increasing and is now estimated to be at least 1 in 2000.[6, 7, 10-13] Overall, between 5% and 23% of patients undergoing endoscopy for dysphagia will have EoE,[14-18] and more than 50% of patients presenting to an emergency room with food impaction are now diagnosed with EoE.[3, 19] Because of this large burden of disease, health care costs of EoE are also significant, accounting for more than $1 billion annually.[20]

There is currently an urgent need for new treatments for EoE. There are no medications that are Food and Drug Administration (FDA)-approved for EoE,[21] and the current pharmacologic standard of care, swallowed topical steroids, are suboptimal. Topical steroids are asthma preparations such as fluticasone or budesonide that are swallowed rather than inhaled,[22-26] and because a pulmonary-specific medication system is being used to attempt to coat the esophagus to provide an anti-inflammatory effect, results are lacking. For example, up to 50% of patients do not have histologic response to these medications,[27] and emerging data suggest that the effect of steroids in responders may wane over time.[28] Moreover, these medications are not specific to the known pathogenesis of EoE.[29]

The cytokine IL-5 has been shown to play a major role in EoE pathogenesis.[30, 31] IL-5 is increased in patients with EoE, leads to production of IL-13, which in turn stimulates the esophageal epithelium to produce eotaxin-3, a potent chemokine that recruits eosinophils to the esophagus.[32] In experimental models of EoE, blocking IL-5 attenuates the disease state, where as overexpression of IL-5 creates an EoE-like phenotype.[31, 33] Mepolizumab is a recombinant monoclonal antibody that binds IL-5 and has been demonstrated to be highly effective in eosinophilic diseases such as hypereosinophilic syndrome (HES),[34] eosinophilic asthma,[35, 36] and most recently eosinophilic granulomatosis with polyangiitis.[37] Because of its mechanism of action, mepolizumab is a highly promising therapeutic agent for EoE, and has previously been studied in this condition. A small randomized clinical trial (RCT) in 11 adults showed a good histologic effect (55% decrease in mean tissue eosinophil levels in the mepolizumab arm vs 7% decrease in the placebo arm), but variable symptom response.[38] A larger RCT examining three dosing regimens in 59 children also showed a good histologic effect (peak eosinophil count decreased from 118 eosinophils per high-power field [eos/hpf] to 24 eos/hpf in the 2.5 mg/kg arm), but symptoms were relatively mild at baseline and there was no clear overall trend towards improvement.[39] Of note, similar histologic and symptomatic discordance was also observed in a clinical trial of children treated with a different anti-IL-5 antibody.[40]

The counterintuitive results of these studies, where a moderate to robust histologic response was observed in the absence of symptom improvement, can be explained by study design issues. Both studies of mepolizumab used non-validated symptom measures, and a symptom threshold for entry was not required. In addition, the pediatric study utilized a multisymptom instrument, so improvements in one symptom may have been lost if other symptoms worsened. Moreover, both of these studies were performed prior to the strong understanding of best practices for clinical trial conduct that we now have in the field.[41] This includes the need to focus on a single primary symptom, enroll a homogeneous set of patients with highly active disease, account for esophageal remodeling (severe esophageal strictures or narrowing), and restrict baseline esophageal dilation. These latter two points are particularly important

in studies of adults and adolescent with dysphagia-predominant symptoms. In the presence of a stricture that is not dilated, symptoms of dysphagia can persist even with resolution of eosinophilic inflammation. In contrast, symptoms can improve after dilation regardless of persistent esophageal eosinophilia.

Given the strong biologic rationale for anti-IL-5 therapy, advances in knowledge about EoE, increased understanding about optimal RCT design for EoE therapies, and the development and validation of EoE-specific patient-reported outcomes (PRO), it is imperative to revisit mepolizumab treatment for EoE using an optimized clinical trial design and a validated PRO. Our overall hypothesis is that mepolizumab will improve symptoms of dysphagia, as measured by a validated PRO, in adolescents and adults with EoE, as well as improve esophageal eosinophilia, as compared to placebo.

2.2 RISK/BENEFIT ASSESSMENT

2.2.1 KNOWN POTENTIAL RISKS

There are several potential risks or discomforts involved with being in this study. These are outlined below. There may be uncommon or previously unknown risks.

Mepolizumab risks:
Hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred following administration of mepolizumab. These reactions generally occur within hours of administration but in some instances can have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, mepolizumab will be discontinued.

The most common adverse reactions (≥3% and more common than placebo) reported in the first 24 weeks of 2 clinical trials for severe asthma with mepolizumab (and placebo) were: headache, 19% (18%); injection site reaction, 8% (3%); back pain, 5% (4%); fatigue, 5% (4%); influenza, 3% (2%); urinary tract infection, 3% (2%); abdominal pain upper, 3% (2%); pruritus, 3% (2%); eczema, 3% (<1%); and muscle spasm, 3% (<1%).

Systemic Reactions, including Hypersensitivity Reactions: In 3 clinical trials, 3% of subjects who received 100 mg of mepolizumab experienced systemic (allergic and nonallergic) reactions, compared to 5% in the placebo group. Up to 6% (2% in HES, 6% in EGPA) of subjects who received 300mg of mepolizumab experienced systemic (allergic and nonallergic) reactions, compared to up to 1% (0% HES; 1% EGPA) in the placebo group.

Systemic allergic/hypersensitivity reactions were reported by 1% of subjects who received 100mg of mepolizumab, compared to 2% of subjects in the placebo group. Manifestations included rash, pruritus, headache, and myalgia. In EGPA and HES trials using 300mg of mepolizumab, rates of systemic allergic/hypersensitivity reactions were 4% (1% placebo) and 0% (0%), respectively. Manifestations included rash, pruritus, flushing, fatigue, hypertension, warm sensation in trunk and neck, cold extremities, dyspnea, and stridor.

Systemic nonallergic reactions were reported by 2% of subjects who received 100mg of mepolizumab and 3% of subjects in the placebo group. Manifestations included rash, flushing, and myalgia. A majority of the systemic reactions were experienced on the day of dosing. In EGPA and HES trials using 300mg of

mepolizumab, rates of systemic nonallergic reactions were 1% (0% placebo) and 2% (0%), respectively. Manifestations observed included angioedema (EGPA) and multifocal skin reaction (HES).

Injection site reactions (e.g., pain, erythema, swelling, itching, burning sensation) have been reported at a rate of 8% in subjects treated with 100mg of mepolizumab, compared with 3% in subjects treated with placebo. In trials using a 300mg dose of mepolizumab, injection site reactions have been reported at a rate of 15% (13%) in clinical trials for Eosinophilic Granulomatosis with Polyangiitis and at 7% (4%) in clinical trials for Hypereosinophilic Syndrome.

In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in subjects treated with mepolizumab compared to none in placebo.

Eosinophils may be involved in the immunological response to some helminth infections. Patients with pre-existing helminth infections were excluded from participation in the clinical program. Patients with pre-existing helminth infections should be treated for their infection prior to mepolizumab therapy. If patients become infected whilst receiving treatment with mepolizumab, and do not respond to anti-helminth treatment, temporary discontinuation of mepolizumab should be considered.

While clinical experience does not support a role for mepolizumab in the development of malignancies, long-term animal studies have not been performed. Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejecti on. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Therefore, the malignancy risk in humans from an antibody to IL-5 such as mepolizumab is unknown.

When reducing concomitant steroids and/or immunosuppressant treatment, the potential to unmask malignancies should be considered in the management of any subject receiving mepolizumab. Subjects with lymphoproliferative HES or those with an abnormal T-cell phenotype are at increased risk of developing T-cell lymphoma as part of the natural history of the disease. T-cell lymphoma has been reported in HES patients receiving mepolizumab. It is not known if the risk of T-cell lymphoma in susceptible patients is increased by treatment with immunomodulators such as mepolizumab. The risk benefit in these patients should be considered prior to initiation and/or continuation of treatment with mepolizumab.

Mepolizumab is considered to have a low potential for drug-drug interactions because it selectively binds and neutralizes the cytokine IL-5. There are no reports of IL-5 receptors being expressed on hepatocytes. Neutralization of IL-5 is, therefore, not expected to alter gene expression of cytochrome P450 or transporters. Therefore, no formal drug interaction studies have been conducted.

For additional information, please refer to the latest version of the package insert (study Investigator Brochure).

EGD with biopsy risks:

The endoscopy is a well-established procedure with a very low rate of complications. Endoscopy and biopsy are the best methods for monitoring EoE disease activity. People with EoE may normally need repeated endoscopies every year. Briefly, risks include mild discomfort due to gagging while the tube is passed down the throat. Subjects may also experience mild sore throat, chest pain or discomfort,

abdominal pain or discomfort, or painful or difficult swallowing following the procedure. Medicines may ease these problems. Rare risks from an endoscopy include bleeding and infection. There is a very small risk (about 3 in 10,000) of esophageal perforation that could require surgery to repair and a similarly small risk (8 in 10,000) of aspiration that could cause pneumonia.

The number of biopsies taken for this study is within the spectrum of routine clinical practice for esophageal diseases and EoE in particular. Nevertheless, there is a very small risk of perforation or significant bleeding that would require a blood transfusion or other measures to stop the bleeding. To minimize this risk, subjects will be monitored for any bleeding during the biopsy portion of the procedure, and if bleeding is heavy, clinically indicated actions to stop the bleeding will be performed, and further biopsy procurement will be stopped.

There is a risk of adverse reaction to the anesthetic or medication used for the endoscopy. These reactions may require treatment. There may be inflammation of the vein through which medication is given. Subjects with asthma have an increased risk for problems with the anesthesia. An adverse reaction to the medications used for the endoscopy can include difficulty breathing, respiratory depression, low blood pressure, slow heart, excessive sweating, spasms in the larynx, an allergic reaction, such as hives and itching or anaphylaxis.

After the endoscopy, subjects may experience pain in the throat or neck, vomiting, black or bloody stools, pain in the chest or abdomen, or fever.

Venipuncture risks:
There is a small risk of fainting or bruising and a 1/1000 risk of infection at the site where the blood is drawn.

Loss of confidentiality:
There is also a risk of loss of confidentiality.

2.2.2 KNOWN POTENTIAL BENEFITS

The potential benefit of mepolizumab is related to its effect as a treatment for EoE. This medication is able to block eosinophil development and activation, thereby substantially decreasing eosinophil levels both in the blood and in the tissue. This decrease in eosinophils, should, in turn, decrease clinical symptoms related to EoE. Specifically, the cytokine IL-5 has been shown to play a major role in EoE pathogenesis.[30, 31] IL-5 is increased in patients with EoE, leads to production of IL-13, which in turn stimulates the esophageal epithelium to produce eotaxin-3, a potent chemokine that recruits eosinophils to the esophagus.[32] In experimental models of EoE, blocking IL-5 attenuates the disease state, where as overexpression of IL-5 creates an EoE-like phenotype.[31, 33] Mepolizumab is a recombinant monoclonal antibody that binds IL-5 and has been demonstrated to be highly effective in eosinophilic diseases such as HES,[34] eosinophilic asthma,[35, 36] and most recently eosinophilic granulomatosis with polyangiitis.[37] Because of its mechanism of action, mepolizumab is a highly promising therapeutic agent for EoE, and has previously been studied in this condition. A small randomized clinical trial (RCT) in 11 adults showed a good histologic effect (55% decrease in mean tissue eosinophil levels in the mepolizumab arm vs 7% decrease in the placebo arm), but variable symptom response.[38] A larger RCT examining three dosing regimens in 59 children also showed a good histologic effect (peak eosinophil count decreased from 118 eosinophils per high-power field [eos/hpf] to 24 eos/hpf in the 2.5 mg/kg arm), but symptoms were relatively mild at baseline and there was no clear overall trend towards

improvement.[39] In this study, it is likely that mepolizumab will decrease blood and tissue eosinophil counts, and we hypothesize that this will also decrease clinical symptoms of dysphagia.

2.2.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Because the prior studies of this medication in adults and adolescents (who are the target population for this study) have been very small and did not require a symptom threshold for entry, we feel that the current study as designed is required to assess efficacy of this drug. The potential value of information gained, specifically related to a novel therapy for EoE that can be applied for highly symptomatic, and potentially refractory patients, is the basis for exposure to the potential risks of the study. Risks will be minimized by the study design which will have an active and extensive surveillance protocol for adverse events (AEs), as well as close monitoring during and after study drug administration. Finally, the inclusion of a placebo arm is justifiable as there are currently no FDA-approved medications for EoE, and the 3-month long placebo period is very short given the chronic nature of EoE (for example, many patients have a symptom duration of 5-10 years prior to diagnosis).

3 OBJECTIVES AND OUTCOMES

OBJECTIVES	OUTCOMES	JUSTIFICATION FOR OUTCOMES
To determine whether mepolizumab is more effective than placebo for improving symptoms of dysphagia as measured by the validated Eosinophilic Esophagitis Symptom Activity Index (EEsAI) in adults and adolescents with active eosinophilic esophagitis after a 3-month treatment course.	3-month EEsAI score	The EEsAI is a validated and responsive PRO, developed by an international team of EoE experts, that measures dysphagia frequency, dysphagia severity, and food avoidance/modification behaviors, in patients with EoE.[42, 45-47] It has now been used in several clinical trials,[48-51] including recently published abstract data emphasizing the responsive nature of this instrument.[49, 51]
To determine whether mepolizumab is more effective than placebo for decreasing esophageal eosinophil counts in adults and adolescents with active eosinophilic esophagitis after a 3-month treatment course.	3-month peak eosinophil count	The peak eosinophil count is the currently accepted marker of histologic disease activity.

Please see section 9.4 for full description of outcomes.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a multi-center, randomized, double blind, parallel-arm, placebo controlled trial of mepolizumab. After the first 3-month blinded phase, there will be a second 3-month blinded phase where all patients receive active medication, but the dose will be lower in the subjects initially randomized to the placebo arm.

In the first arm, subjects will receive mepolizumab 300 mg SQ monthly for 3 months. In the second arm, subjects will receive a placebo SQ injection monthly for 3 months. Both groups will have the injection administered under direct observation in a clinical setting to ensure proper administration and compliance. Each visit will also provide an opportunity for symptom questionnaires to be completed and for blood samples to be drawn. After 3-months (the time point where the primary outcome is assessed), all subjects initially randomized to active treatment will continue with mepolizumab dosing 300 mg SQ monthly and will remain blinded. All subjects initially randomized to placebo will receive mepolizumab 100mg SQ monthly and will remain blinded.

Of note, no dietary changes, dilations, changes in baseline PPI medication dose, changes in inhaled or intranasal steroid doses, or administration or oral, topical/swallowed, or systemic steroids will be allowed during the study period (from consent through the end of treatment period). Subjects will undergo endoscopy after the first blinded phase (at 3 months) and after the second blinded phase (after 6 months).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

In order to assess whether mepolizumab is effective for improving symptoms and histology in EoE, a randomized, double-blind, placebo-controlled trial is necessary. The inclusion of a placebo arm is justifiable as there are currently no FDA-approved medications for EoE, and the 3-month long placebo period is very short given the chronic nature of EoE (for example, many patients have a symptom duration of 5-10 years prior to diagnosis).

4.3 JUSTIFICATION FOR DOSE

The doses have been chosen based on pharmacologic modelling showing that 100-300 mg of mepolizumab, administered SQ on a monthly basis, is sufficient to suppress eosinophil counts in the blood,[44] and that this often correlates with decreased tissue eosinophilia as well (personal communication, Isabelle Pouliquen). However, prior studies of EoE used much higher does (750mg-1500mg;[38] 2.5-10mg/kg[39]), and dose-response of mepolizumab for EoE treatment and histologic response in esophageal tissue is not known. To bride the existing pharmacologic and clinical data, we have selected the 300mg dose for comparison to placebo for the primary outcome in the first blinded phase of the study, but will also gain response information on the 100 mg dose in the second blinded phase of the study in a planned paired analysis for those initially randomized to placebo.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial across all sites.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Age 16-75*
2. Diagnosis of EoE as per consensus guidelines (including PPI non-response**).[2, 43]
3. Active eosinophilia on esophageal biopsy, with a peak count of least 15 eos/hpf from at least one esophageal level.***
4. Biopsies from the stomach and duodenum that have ruled out alternative etiologies in all children and in adults with abnormal endoscopic findings or when other gastric or small intestinal conditions are clinical possibilities. If these samples have been obtained during a previous endoscopic evaluation and in the judgement of the site-Investigator the patient has not had a clinically significant change that would merit repeat gastric/duodenal biopsies, then prior normal gastric and duodenal biopsies are acceptable to exclude alternate etiologies.
5. Active symptoms of dysphagia with more than 3 episodes of dysphagia over a period of 2 weeks during the screening period, and an Eosinophilic Esophagitis Symptom Activity Index (EEsAI; see below for details) score of ≥ 27 at baseline.****
6. Able to read, comprehend, and sign consent form.
7. Have maintained a stable diet for 6 weeks prior to enrollment.*****
8. Able to maintain a stable diet throughout the duration of the study period. *****
9. Female subjects of childbearing potential who have had their first menses agree to use a highly effective method of birth control during the study and for 30 days after the last dose of study drug. Female subjects with reproductive potential who are using systemic contraceptives (e.g., oral contraceptives, injectable contraceptives, implantable/insertable hormonal contraceptive products, or transdermal patches) to prevent pregnancy must have stable use for ≥28 days prior to screening. See section 5.3 for additional details.

* The rationale for this criterion is that adolescents and adults with EoE have a very similar clinical presentation with dysphagia-predominant symptoms.[21] If we were to enroll younger patients there would be few who would meet the dysphagia threshold, and the symptom metric we will use was not validated in younger patients.[42] Patients of any age can have EoE, but in patients above the age of 75 malignancy is a concern with clinical symptoms of dysphagia, and EoE becomes less common.[12]
** PPI non-response is defined as >15 eos/hpf after at least 6 weeks of high dose administration (40mg total per day or higher) of any approved PPI medication or documented evidence of intolerance or allergy to PPIs. The length of the PPI trial period or documented intolerance/allergy will be determined according to the local clinical standard of care.
***The rationale for this criterion is to ensure high levels of esophageal eosinophilia at baseline. For this study, baseline symptoms are gathered during the screening visit and used as baseline measurements.
**** The rationale for this criterion is to ensure that highly symptomatic patients are enrolled; based on this threshold and prior data related to the EEsAI, we would expect baseline scores for this patient population in the 50-60 range.
***** As dietary restriction is a known effective treatment for EoE, and signs and symptoms of EoE may be highly dependent on eating behaviors, patients should maintain a stable diet for at least 6 weeks preceding enrollment and throughout the duration of the study period.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Esophageal dilation within 8 weeks of the screening endoscopy.
2. Inability to pass a standard upper endoscope (8-10mm) due to esophageal narrowing or stricturing.
3. Swallowed/topical steroids for EoE within 4 weeks of the screening endoscopy, or a course of systemic corticosteroids within 8 weeks of the screening endoscopy.*
4. Not having maintained a stable diet for at least 6 weeks preceding the screening endoscopy.
5. Initiation, discontinuation, or change of dose regimen of PPIs; leukotriene inhibitors; or nasal, inhaled, and/or orally administered topical corticosteroids** for any condition (such as gastroesophageal reflux disease, asthma, or allergic rhinitis) within the 8 weeks prior to the qualifying EGD.
6. Presence of concomitant eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE), eosinophilic colitis (EC), Crohn's disease, ulcerative colitis, or celiac disease.
7. History of malignancy within 5 years prior to screening, except completely treated in situ carcinoma of the cervix and completely treated non-metastatic squamous or basal cell carcinoma of the skin.
8. History of achalasia.
9. Prior esophageal surgery.
10. History of bleeding disorder or esophageal varices.
11. Active parasitic infection or suspicion of an active parasitic infection, which, in the opinion of the site-Investigator, has not been previously evaluated or treated. Subjects presenting with signs of active parasitic infection or suspicion of active parasitic infection as assessed by current diarrhea and/or blood or mucus in stool will be referred to their clinical physician for further testing to rule out parasitic infection.
12. Any other active infections judged at the discretion of the site-Investigator.
13. Any other medical or psychological condition that, in the opinion of the site-investigator, may present an unreasonable risk to the study patient as a result of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments. The specific justification for patients excluded under this criterion will be noted in study documents.
14. Patient or his/her immediate family is a member of the investigational team.
15. Pregnancy or breastfeeding.
16. Women of children bearing potential who are not on highly effective contraception.

*A course is defined as more than 3 days of systemic steroid use. Subjects who have received <3 days of steroids may be eligible if, in the investigator's opinion, the steroid use does not impact the assessment of the underlying EoE disease activity.

**Subjects with a documented history of non-response to steroid treatment for EoE may be eligible if, in the investigator's opinion, the non-EoE steroid treatment would not impact the assessment of the underlying EoE disease activity.

Sponsor-investigator approval is required prior to randomization for subjects who have received <u>any</u> steroids in the 8 weeks prior to the screening EGD or before randomization.

5.3 LIFESTYLE CONSIDERATIONS

Female subjects of childbearing potential who have had their first menses must use a highly effective method of birth control during the study and for 30 days after the last dose of study drug. Medically acceptable regimens to prevent pregnancy must be followed. These include:

- Systemic contraceptives (e.g., oral contraceptives, injectable contraceptives, implantable/insertable hormonal contraceptive products, or transdermal patches). For systemic contraceptives, use must be stable for ≥28 days prior to screening.
- Intrauterine/intravaginal methods (e.g., vaginal contraceptive ring, intrauterine system with hormone release, or copper intrauterine device).
- Bilateral tubal occlusion.
- Vasectomized partner.
- Sexual abstinence.

Female subjects of childbearing potential will have a urine pregnancy test at the screening/baseline visit, as well as at visit months 0, 1, 2, 3, 4, 5, 6, 8, and Early Termination (if applicable) (see section 1.3). Documentation of ongoing contraception or exemption will be completed at each visit. See section 8.9.10 regarding reporting of a pregnancy should this occur during the course of the study.
Subjects who are sexually inactive, had a documented tubal ligation, are at no risk of becoming pregnant, or who have a monogamous partner who is surgically sterilized may be exempted from contraception at the discretion of the site-Investigator. Additionally, female subjects of non-childbearing potential may be exempted from contraception at the discretion of the site-investigator; this may include females who:

- Are diagnosed infertile.
- Have undergone a surgical procedure (total abdominal hysterectomy and or oophorectomy).
- Have undergone menopause (defined as 12 consecutive months without menses and substantiated by an appropriate FSH/LH test for subjects <65 years of age).

The exemption will be documented.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of either insufficient symptoms or insufficient eosinophilic inflammation may be rescreened if there are extenuating circumstances that would influence these factors in the determination of the site-investigator) and sponsor-investigator.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients will be screened at clinic visits or by phone and prior to endoscopy by the study coordinators or other designated personnel at each site. Recruitment materials will also be used to publicize the study, particularly through patient advocate groups and we would expect patients to travel regionally to participate in the study. Once a formal diagnosis of EoE is confirmed as detailed above, the coordinator will assess eligibility, describe the study, and obtain informed consent. All baseline characteristics of interest will be recorded, including a full characterization of all prior EoE treatments and prior treatment responses. For this study, baseline symptoms are gathered during the screening visit and used as baseline measurements. There will be a monetary patient incentive at each visit in order to encourage retention in the study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Mepolizumab is an IL-5 antagonist (IgG1 kappa). IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Mepolizumab binds to IL-5 with a dissociation constant of 100 pM, inhibiting the bioactivity of IL-5 by blocking its binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface. Mepolizumab, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils, which we believe is directly related to the potential benefit in EoE.

6.1.2 DOSING AND ADMINISTRATION

Site pharmacies will be unblinded and responsible for creating and supplying placebo for this study, as well as reconstituting Mepolizumab for dosing in this study. Mepolizumab will be provided to sites in 100 mg per vial as a sterile, single-use, lyophilized product in labeled 10 mL Type I clear glass, stoppered vials. The drug product must be stored in a refrigerator at a temperature of 2° C to 8° C (36° F to 46° F), protected from light. The recommended storage condition and expiry date where required, are stated on the product labels. Aseptic techniques must be used at all times when preparing this sterile product for administration.

Study drug should not be given to subjects if febrile (temperature of 100.4F/38C or greater). Study drug can be administered upon resolution of fever and approval by the site-investigator. Dosing may also be withheld if there are other patient concerns and at the discretion of site-investigators.

The drug product does not contain a preservative. Therefore, it is considered a single dose product. The reconstituted solution should be kept at refrigerated or controlled room temperature (up to 25° C). It should be used as soon as possible and any unused solution remaining after 8 hours should be discarded.

All subjects will receive 3 subcutaneous injections at each dosing visit. The 3 injections will be: 3 injections of 100mg mepolizumab each, or 3 injections of placebo, or 2 injections of placebo and one injection of 100mg mepolizumab depending on randomization and study visit (at the 3-month visit, subjects previously receiving placebo will receive 100mg of mepolizumab). The relation to meals is not important with this medication.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

All supplies of study drug will be accounted for in accordance with GCP. Site-investigators are responsible for ensuring accurate drug accountability records are maintained for the duration of the study. GlaxoSmithKline will provide mepolizumab directly to a central distribution pharmacy which will then ship mepolizumab directly to the site pharmacies. Site pharmacies will be responsible for tracking and requesting study drug. The pharmacy manual provides additional detail regarding disposition and return of expired or unused product.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Each vial of mepolizumab contains 100mg of dry powder that is provided by GlaxoSmithKline and that needs to be reconstituted for injection. Appropriate labels will be applied to the vials by a central pharmacy prior to distribution to the site pharmacies, though once reconstituted and in the syringe ready to inject, the syringes will be masked.

Site pharmacies will be responsible for providing placebo and reconstituting active study drug from mepolizumab supplied by GlaxoSmithKline. A central pharmacy will be utilized to provide Mepolizumab to sites in 100mg vials of dry powder.

At minimum, all study drug will be labeled with the statements:

- “Caution: New Drug--Limited by Federal (USA) law to investigational use”
- “Keep out of reach of children”
- “Investigational drug – to be used by qualified investigators only”

Site pharmacies are responsible for labeling and blinding of all study drug. An example template for use is below:

6.2.3 PRODUCT STORAGE AND STABILITY

The drug product must be stored in a refrigerator at a temperature of 2° C to 8° C (36° F to 46° F), protected from light.

6.2.4 PREPARATION AND ADMINISTRATION

Preparation:

1. Study drug should be reconstituted and administered by a healthcare professional.
2. Reconstitute study drug in the vial with 1.2 mL of Sterile Water for Injection, USP, preferably using a 2- or 3-mL syringe and a 16, 19, or 21-gauge needle. The reconstituted solution will contain a concentration of 100 mg/mL mepolizumab or 1 mL of placebo. Do not mix with other medications. Repeat this 3 times so that there are a total of three 1mL injections of study drug ready for injection for each subject.
3. Direct the stream of Sterile Water for Injection vertically onto the center of the lyophilized cake. Gently swirl the vial for 10 seconds with a circular motion at 15-second intervals until the powder is dissolved. Note: Do not shake the reconstituted solution during the procedure as this may lead to product foaming or precipitation. Reconstitution is typically complete within 5 minutes after the Sterile Water for Injection has been added, but it may take additional time.
4. If a mechanical reconstitution device (swirler) is used to reconstitute study drug, swirl at 450 rpm for no longer than 10 minutes. Alternatively, swirling at 1,000 rpm for no longer than 5 minutes is acceptable.
5. Visually inspect the reconstituted solution for particulate matter and clarity before use. The solution should be clear to opalescent and colorless to pale yellow or pale brown, essentially particle free. Small air bubbles, however, are expected and acceptable. If particulate matter remains in the solution or if the solution appears cloudy or milky, the solution must not be administered.
6. If the reconstituted solution is not used immediately, the reconstituted solution should be kept at refrigerated or controlled room temperature (up to 25°C). It should be used as soon as possible and any unused solution remaining after 8 hours should be discarded.

Administration:

1. For SC administration, preferably using three 1-mL polypropylene syringes fitted with a disposable 21- to 27-gauge x 0.5-inch (13-mm) needle.
2. Obtain subject vitals prior to dosing. If febrile, do not dose.
3. Site pharmacies should supply 3 blinded 1mL syringes of study drug for dosing. Do not shake the reconstituted solution during the procedure as this could lead to product foaming or precipitation.

Administer three 1-mL injections of study drug subcutaneously. Each 1mL injection should be administered at separate sites into the upper arm, thigh, abdomen, or other appropriate location (rotating the injection site each time), avoiding any blood vessels, thickening or tenderness of skin, scares fibrous tissue, stretch marks, bruising, redness, nevi, or other skim imperfection. Location will depend on the specific subject and body habitus, and all three injections need not be in the same area of the body. Injection should be far enough apart to ensure the same site is not injected on more than one occasion. Injection site will be noted by study staff to reference prior to each dose.

Safety Monitoring:

1. Vital signs will be obtained prior to dosing.

2. After completion of dosing, subjects will remain on-site to be monitored for 1 hour. During this time, vital signs will be checked 5, 30, and 60 minutes after injection, and injection sites monitored for adverse reactions. This applies to all dosing visits (initial and subsequent).
3. Subjects will be contacted 48 hours after injection to assess for AEs.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Subjects will be randomized 1:1 to either mepolizumab or a placebo injection. Randomization will be administered centrally but will be at the level of the site using a blocked randomization protocol with computer-generated variable block sizes. At each site, patients will be categorized as either a prior steroid non-responder or not, and then will be randomized within that categorization. The investigational pharmacy at each site will then receive the randomization information and provide study drugs. Allocation will be concealed from all investigators, subjects, and data analysts. The study monitor will be unblinded to treatment assignments and can escalate issues to the medical monitor who can be unblinded if necessary (e.g. in the event of a safety concern or DSMB request). Of note, we will balance the groups for prior steroid non-response but will not be formally stratifying on this variable for power calculations or analysis purposes. Steroid non-response is defined as greater than 15 eos/hpf after a 2-month course of a swallowed/topical steroid at a standard dose (standard dose = 2mg/d of budesonide or 1760 mcg/d of fluticasone).

This is a double-blind study. Subjects, investigators, endoscopists, nurses, statisticians, and study staff will all be masked as to allocation. To maintain the study blind, only unblinded pharmacist(s) at the investigational pharmacy at each site will dispense study drug. The medication will be mixed by the investigational pharmacy, and only blinded syringes with “study drug” will be provided to use in the study. These will either have the correct active dose of mepolizumab or a matched normal saline placebo. In the first blinded phase, subjects randomized to mepolizumab will receive three injections with active medication, and subjects randomized to placebo will receive three injections with placebo. In the second blinded phase, subjects who were initially randomized to mepolizumab will continue to receive three injections of active medication. However, subjects who were initially randomized to placebo will receive one injection of mepolizumab and 2 injections of placebo.

Of note, study personnel will also be blinded to blood and tissue eosinophil counts during the course of the study. The study monitor will receive the unblinded blood results from all sites to enter into the data management system. If there are any values outside of the normal ranges, the study monitor will send to the medical monitor for review. The pathologist who analyzes the tissue eosinophil counts will enter the data directly into the data management system or can provide the results to the study monitor for entry into the data management system.

6.4 STUDY INTERVENTION COMPLIANCE

Compliance with study drug will be recorded on a Case Report Form (CRF) by research or other designated staff at each participating site. This study will utilize electronic CRFs (eCRFs). As the medication is injected subcutaneously in an observed situation on a monthly basis, we can ensure intervention compliance.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the eCRF are concomitant prescription medications, over the counter medications, and supplements.

6.5.1 PROHIBITED TREATMENTS

No dietary changes, dilations, changes in baseline PPI medication dose, changes in inhaled or intranasal steroid doses, or administration or oral, topical/swallowed, or systemic steroids will be allowed during the study period (from consent through the end of treatment period). Esophageal dilation at the screening or month 3 endoscopy will result in study exit. However, dilation may be performed during or after the month 6 endoscopy, if clinically indicated.

If a subject has severe persistent or recurrent symptoms, or experiences a food impaction during the treatment period, rescue medications and procedures to treat EoE are allowed for clinical purposes. The sponsor will not supply rescue medications, and these would need to be prescribed as clinically indicated by the subject's physician. However, if such medications or treatments are required, the participant would be considered a treatment failure and would exit the study. If this happens, and at the discretion of the site-Investigator or sponsor-investigator it is safe and feasible to do so, the subject should return for an early termination visit.

Although the use of rescue medications is allowable at any time during the study, if safe and feasible to do so the use of rescue medications should be delayed until either the 3-month or 6-month assessments are completed. Rescue medications or treatments administered after the month 6 EGD will not result in study exit. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Subjects may choose to withdraw from participation in the study at any time upon their request without penalty. Additionally, the investigator and sponsor may withdraw a subject from the study in the event of an intercurrent illness, adverse event (AE), treatment failure, protocol violation, cure, and for administrative or other reasons. Discontinuation from study treatment does NOT automatically lead to a complete withdrawal from the study. Subjects discontinuing from study treatment are strongly encouraged to complete early termination procedures and safety follow up.

Investigators should withdraw study treatment from subjects if any of the following occur:

- Pregnancy
- Lost to follow up
- Hypersensitivity / systemic allergic reaction to the study treatment requiring administration of epinephrine
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

- Worsening symptoms or disease progression that, in the opinion of the investigator, requires either esophageal dilation or EoE treatment with either topical or systemic steroids during the treatment period
- Any adverse event that, in the opinion of the investigator, precludes safe continuation with the study protocol and study dosing
- Significant study intervention non-compliance, in the opinion of the investigator
- Any condition that, in the judgment of the site-PI or Sponsor, would compromise the ability of the patient to comply with the study protocol or complete the study

Before deciding to discontinue study treatment, the site-PIs should consult the Sponsor-Investigator and study medical monitor, regardless of the reason for discontinuation. Subjects who withdraw and have received at least 1 dose of study drug should return to complete the early termination visit.

The reason for participant discontinuation or withdrawal from the study will be recorded on the eCRF. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will also be replaced such that the goal enrollment at the end of the study can be achieved.

7.2 LOST TO FOLLOW-UP

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

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

- The site will attempt to contact the participant and reschedule the missed visit at the earliest possible time and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the site-investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and/or email contacts, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

To assist with retention, study staff may contact subjects via email if the participant provided an email address at the time of consent. The email will not contain identifying or health related information, rather will request that the participant get in contact with us to complete required study procedures. Subjects may also receive emails directly from the data management system (REDCap) with links to their secure survey.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 SCREENING AND BASELINE

During screening/baseline, the following assessments will be completed. Not all are used to determine eligibility. Baseline symptoms are gathered during the screening visit and used as baseline measurements for this study.

1. Informed consent
2. Demographics
3. Medical history
4. EGD with biopsy and EoE Endoscopic Reference Score (EREFS)*
5. EEsAI*
6. Dysphagia Symptom Screening Questionnaire*
7. Patient Global EoE Assessment*
8. VAS (Visual Analog Scale) Assessment; if applicable for subjects with known allergic diseases
9. CBC with differential*
10. Serum/anti-IL 5 antibodies*
11. Physical exam*
12. Vital signs*
13. Urine pregnancy test*
14. Concomitant medication review
15. Straumann Dysphagia Index (SDI)
16. Adverse event review and evaluation
17. Completion of CRFs

*If eligible, then these assessments performed during the screening phase will also be used for baseline and do not need to be repeated at randomization.
All screening and baseline assessments should be completed prior to and within 49 days of randomization.

8.1.1 SYMPTOM ASSESSMENT FOR ELIGIBILITY

Symptom assessment for eligibility will occur via completion of both the EEsAI questionnaire and a dysphagia questionnaire. These questionnaires should be completed during the screening phase after informed consent is obtained and prior to the screening endoscopy.

8.1.2 QUESTIONNAIRES

The following questionnaires will be completed during screening/baseline and are not used to determine eligibility:

1. Patient Global EoE Assessment
2. VAS (Visual Analog Scale) Assessment
3. Straumann Dysphagia Index (SDI

8.1.3 SCREENING AND BASELINE ENDOSCOPY WITH BIOPSY AND EREFS

Prior to the screening endoscopy, subjects must be deemed eligible per the EEsAI questionnaire and dysphagia questionnaire. Sites must obtain approval from the lead site prior to completing any screening endoscopies for this study. This is to ensure subjects meet symptom requirements to be eligible for the study.

During the screening endoscopy, esophageal biopsies will be obtained from the following locations:

- Distal esophagus (3-5 cm above the Z-line/squamo-columnar junction)
- Proximal esophagus (~15 cm above the Z line and within 10 cm of the esophageal inlet)

Up to 6 esophageal biopsies will be obtained from each location, focusing on areas of endoscopic abnormalities, if present. Biopsies to determine eligibility will be immediately shipped to a Central Lab for analysis.

Additionally, all children (<18 years of age) will have additional biopsies from the stomach (up to 4: 2 from the antrum and 2 from the gastric body) and duodenum (up to 4) taken to rule out alternative etiologies. Similarly, adults (≥18 years of age) with abnormal endoscopic findings or cases where other gastric or small intestinal considerations are clinical possibilities will have biopsies taken from the stomach, duodenum, and/or other targeted areas to rule out alternative etiologies.

Additional details regarding biopsy collection, processing, and shipping instructions can be found in the Manual of Procedures (MOP).

Endoscopic findings will be assessed by each investigator using the EoE Endoscopic Reference Score (EREFS)[50] in 5 classification categories: fixed rings, exudates, furrows, edema, and stricture.

In addition to obtaining the eosinophil counts required for inclusion in the trial and outcome determination, the esophageal biopsies will be used for evaluation of potential diagnostic and pharmacodynamic markers using appropriate laboratory methodology, including but not limited to other histopathologic findings, immunohistochemistry, and transcript profiling. Samples may also be used for future unspecified studies.

If deemed eligible, then biopsies and EoE Endoscopic Reference Score (EREFS) from the screening EGD will also be used as baseline. For this study, baseline symptoms gathered during the screening visit are used as baseline measurements.

8.1.4 SAMPLE COLLECTION

During the screening phase, complete blood count (CBC) with differential will be obtained to determine the baseline peripheral blood absolute eosinophil count.

Screening CBC with differential will be analyzed by local laboratories and results entered into the electronic data capture system. Subsequent CBC with differential will be sent to a Central Lab for analysis and sites will be blinded to results unless abnormal. Blood samples should be obtained on the same day as the EGD.

In addition, on the day of the screening/baseline EGD, a serum sample will be obtained for anti-IL 5 as a baseline measure. Baseline symptoms are gathered during the screening visit and used as baseline measurements. Serum will be sent to the lead site for processing and storage.

Additional details regarding sample collection, processing, and shipping instructions can be found in the MOP.

8.2 RANDOMIZATION VISIT

During the randomization visit, the following will be completed:

1) Confirm eligibility based on screening assessments
2) Vital Signs
3) Urine pregnancy test
4) Concomitant medication review
5) Randomization
6) Administration of study intervention (see section 6 for details)
7) Adverse event review and evaluation
8) 48-hour adverse event review and evaluation
9) Straumann Dysphagia Index (SDI)*
10) Completion of CRFs

8.2.1 STRAUMANN DYSPHAGIA INDEX (SDI)

*The Straumann Dysphagia Index (SDI) will be dispensed during the randomization visit and completed weekly between Month 0 - Month 6. The SDI will be sent electronically for participants who have provided an email address at the time of consent between Month 0 visit and Month 6 visit. SDI should be completed during the visit at Screening and Baseline, Month 6, Month 8, and Early Termination (if applicable). Additional details regarding SDI completion can be found in the MOP.

8.3 VISIT MONTHS 1, 2, 4, AND 5

During visit months 1, 2, 4, and 5, the following will be completed:

1) EEsAI
2) CBC with differential
3) Vital signs
4) Urine pregnancy test
5) Concomitant medication review
6) Administration of study intervention (see section 6 for details)
7) Adverse event review and evaluation
8) 48-hour adverse event review and evaluation
9) Weekly Straumann Dysphagia Index (SDI)
10) Completion of CRFs

8.3.1 SAMPLE COLLECTION

CBC with differential will be sent to a Central Lab for analysis and sites will be blinded to results unless abnormal. Blood samples should be obtained on the same day as the EGD for the screening visit and visit months 3, 6, and early termination.

Additional details regarding sample collection, processing, and shipping instructions can be found in the MOP.

8.4 VISIT MONTHS 3, 6 AND EARLY TERMINATION

During visit months 3, 6, and early termination the following will be completed:

1) Endoscopy with biopsy and EoE Endoscopic Reference Score (EREFS)
2) EEsAI
3) Patient Global EoE Assessment
4) Patient Global Impression of Change (PGIC)
5) Patient Global Impression of Severity (PGIS)
6) VAS (Visual Analog Scale) Assessment; if applicable for subjects with known allergic diseases
7) CBC with differential
8) Serum/anti-IL 5 antibodies
9) Vital signs
10) Physical Exam
11) Urine pregnancy test
12) Concomitant medication review
13) Administration of study intervention (see section 6 for details, 3-month visit only)***
14) Adverse event review and evaluation
15) 48-hour adverse event review and evaluation (3-month visit only)***
16) Straumann Dysphagia Index (SDI)
17) Completion of CRFs

*** No study intervention is given at the month 6 visit or early termination visit, therefore no 48-hour phone call is required for these visits.

8.3.2 ENDOSCOPY WITH BIOPSY AND EREFS

During post-screening endoscopies, biopsies will be obtained from the following locations:

- Distal esophagus (3-5 cm above the Z-line/squamo-columnar junction)
- Proximal esophagus (~15 cm above the Z line and within 10 cm of the esophageal inlet)

Up to 6 biopsies will be obtained from each location, focusing on areas of endoscopic abnormalities, if present. Additional details regarding biopsy collection, processing, and shipping instructions can be found in the MOP.

Endoscopic findings will be assessed by each investigator using the EoE Endoscopic Reference Score (EREFS)[50] in 5 classification categories: fixed rings, exudates, furrows, edema, and stricture.

8.3.3 SAMPLE COLLECTION

The following labs and blood samples will be obtained during the 3- and 6-month visit

1. Safety assessment: Complete blood count (CBC) with differential
2. Research sample: Serum

CBC with differential will be sent to a Central Lab for analysis and sites will be blinded to results unless abnormal. Serum will be sent to the lead site for processing and storage. Blood samples should be obtained on the same day as the EGD.

Additional details regarding sample collection, processing, and GSK instructions can be found in the MOP.

8.4 VISIT MONTH 8

During the month 8 visit, the following assessments will be performed:

1. EEsAI
2. VAS (Visual Analog Scale) Assessment; if applicable for subjects with known allergic diseases
3. Urine Pregnancy Test
4. CBC with differential
5. Serum/anti-IL 5 antibodies
6. Concomitant medication review
7. Adverse event review and evaluation
8. Straumann Dysphagia Index (SDI) – one time on day of visit
9. Completion of CRFs

8.5 30 DAY PHONE CALL

Subjects will be contacted 30 days (+/-5 days) after study exit, including early termination to assess for adverse events.

8.6 UNSCHEDULED VISITS

If the need for a re-assessment of study samples and/or assessments occurs, an unscheduled visit may be scheduled to obtain an additional sample and/or assessment to analyze. In each instance, site should notify study monitor for approval of unscheduled visit.

8.7 SAFETY AND OTHER ASSESSMENTS

The following safety assessments will be performed:

1. Pregnancy test performed at every study visit for women of childbearing potential
2. Symptom assessment at every study visit
3. Adverse event assessment at every study visit, including injection site reactions
4. Vital signs as noted above with study drug administration
5. Adverse event review and assessment completed 48 hours after study drug administration
6. Month 8 visit occurring 3-months after last dose of study drug.
7. 30-day end of study phone call after study completion or early termination.

8.8 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.8.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.8.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the site-investigator or sponsor (UNC), it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention

to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.8.3 ABNORMAL LABORATORY VALUES

In the event of unexplained abnormal laboratory test values which may be clinically significant, based on his/her medical judgment and the clinical setting, the site-investigator will determine whether to repeat the tests and should follow up as appropriate until they have returned to the normal range and/or an adequate explanation of the abnormality is found.

All abnormal laboratory values or test results should not necessarily be reported as AEs.
The criteria for determining whether an abnormal objective test finding should be reported as an AE include the following:

1. Test result is associated with accompanying symptoms (e.g., low red blood cell count [anemia] is accompanied by fatigue, shortness of breath, etc.)
2. Test result requires additional diagnostic testing or medical/surgical intervention
3. Test result leads to a change in study dosing or discontinuation from the trial, significant additional concomitant drug treatment or other therapy
4. Test result is considered to be an AE by the site-investigator or sponsor-investigator.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error should not be reported as an AE.

8.8.4 CLASSIFICATION OF AN ADVERSE EVENT

8.8.4.1 SEVERITY OF EVENT

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 to assess all AEs. For AEs not included in the CTCAE grading system, the following criteria will be used to describe severity of the AE:

- **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2** Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- **Grade 3** Severe; medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- **Grade 4** Life-threatening consequences; urgent intervention indicated.
- **Grade 5** Death related to AE.

8.8.4.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs must have their relationship to study intervention assessed by an investigator who evaluates the event based on temporal relationship and his/her clinical judgment. The degree of certainty about

causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Possibly Related** –There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition. "Possibly Related" means the reasonable possibility that the adverse event, incident, experience or outcome may have been associated with the procedures involved in the research (modified from the definition of associated with use of the drug in FDA regulations at 21 CFR 312.32(a)). Reasonable possibility means that the event is more likely than not related to participation in the research or, in other words, there is a >50% likelihood that the event is related to the research procedures.
- **Somewhat Likely to be Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events) so there is a <50% likelihood that the event is related to the research procedures. Although an AE may rate only as "somewhat likely to be related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "possibly related" or "definitely related", as appropriate.
- **Unlikely to be Related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.8.4.3 EXPECTEDNESS

The site-investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.8.5 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, investigator's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Designated study staff will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the site-investigator or study site staff will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.8.6 ADVERSE EVENT REPORTING

All AEs will be reported in a timely manner to the Lead Site via completion of an adverse event reporting eCRF. Additional information is provided in the MOP.

8.8.7 SERIOUS ADVERSE EVENT REPORTING

The site-investigator will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study outcomes that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All SAEs will be followed until satisfactory resolution or until the site-investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

8.8.8 REPORTING EVENTS TO PARTICIPANTS

Participants will be given any new information in a timely manner that may affect their willingness to continue participation and after approval from IRB.

8.8.9 EVENTS OF SPECIAL INTEREST

Events of special interest (ESI) must be reported within 24 hours of identification. Adverse events of special interest in this study include:

- Food impaction.
- Anaphylactic reactions or acute allergic reactions that require immediate treatment.
- Severe injection site reactions that last longer than 24 hours.
- Any severe infection, any bacterial infection requiring treatment with parenteral antibiotics or treatment with oral antibiotics for longer than 2 weeks, any clinical endoparasitosis, any opportunistic infection, any viral infection requiring antiviral treatment.

Note: Generally, all uncommon, atypical, peculiar, or unusually persistent infections, especially viral infections, should be reported as ESI.

8.8.10 REPORTING OF PREGNANCY

Pregnancy is not considered an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. It is the responsibility of the site-investigator to report the event to the lead site within 24 hours of learning of the pregnancy. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the subject was discontinued from the trial. If a subject becomes pregnant, they will also be withdrawn from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to the Lead Site.

8.9 UNANTICIPATED PROBLEMS

8.9.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others (UPIRSO) to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("Possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research. Reasonable possibility means that the event is more likely than not related to participation in the research or, in other words, there is a >50% likelihood that the event is related to the research procedures.); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.9.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing IRB and to the DCC/study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, investigator's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DCC/study sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 24 hours of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within the timeline specified per policy of the IRB's receipt of the report of the problem from the investigator.

8.9.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Participants will be given any new information in a timely manner that may affect their willingness to continue participation and after approval from IRB.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Efficacy Outcome(s): Mean change in dysphagia from baseline to 3-months post-treatment (as measured by the EEsAI score with 7-day recall).

Hypothesis: Patients treated with mepolizumab will have lower EEsAI scores after 3-months of therapy compared to patients treated with placebo. Given the rapid mechanism of action of mepolizumab related to decreasing eosinophil counts, as well as recent clinical trial literature showing that dysphagia symptoms in EoE improve in a few as 8 weeks with both steroids and biologics, we feel that a 12 week course of mepolizumab is sufficient to demonstrate a symptom response.

Secondary Efficacy Outcome(s): Esophageal eosinophil counts in adults and adolescents with active eosinophilic esophagitis after a 3-month treatment course.

Hypothesis: Patients treated with mepolizumab will have lower esophageal eosinophil counts and higher rates of histologic response (defined with thresholds below 15 eosinophils per high-power field) compared to patients treated with placebo.

9.2 SAMPLE SIZE DETERMINATION

The study is powered for the primary outcome, the EEsAI score, which can range from 0-100, with a score of ≤ 20 indicating clinical remission, and a decrease of ≥ 20 points indicating a meaningful clinical response. Based on this, we estimate that with a sample size of 30 patients in each group we would be able to detect a difference in the mean change in EEsAI score of as little of 17, with a power of 0.9 at an α of 0.05, which would allow us to detect the clinically meaningful difference of 20 (see Table). Assuming a 20% dropout rate, we plan to randomize 36 patients in each group.

Table: Sample size considerations

Estimated mean decrease in EEsAI score after 12 weeks of treatment*				
Placebo	Mepolizumab	α	Power	N per group
10	30	0.05	0.9	22
15	30	0.05	0.9	38
20	30	0.05	0.9	85
10	35	0.05	0.9	14
15	35	0.05	0.9	22
15	***32***	***0.05***	***0.9***	***30***
20	35	0.05	0.9	38
10	40	0.05	0.9	10
15	40	0.05	0.9	14
20	40	0.05	0.9	22

*SD 20 for all

For the secondary outcome of proportion of patients with an EEsAI score ≤ 20 indicating clinical remission, a sample size of 30 in each group would allow us to detect as little as a 40% difference in remission rates between placebo and active therapy with a power of 0.9, a smaller difference that was detected in a recent trial using this metric.[48] This sample size would also provide ample power the for the absolute eosinophil count and EREFS secondary outcomes.

9.3 POPULATIONS FOR ANALYSES

The analysis dataset will be modified intention to treat (ITT), which will include all participants who received study drug and who have 3-month outcome data for EEsAI and endoscopy. We will have a secondary analysis dataset for a sensitivity analysis where the last available EEsAI value will be carried forward for any participants who terminate the study or are lost to follow-up.

The safety analysis dataset will be all participants who received study drug, regardless of follow-up time or other outcomes.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Descriptive statistics will be used to describe the data. Categorical variables will be presented as proportions and means will be presented with standard deviation and range. If the data are not normally distributed, medians and interquartile ranges will be presented rather than means, and non-parametric testing will be used. For inferential tests, a p value < 0.05 will be considered significant and all tests will be two tailed. All statistical estimates (e.g., medians, proportions, incidence rates, mean differences, correlations, etc.) will be tabulated along with corresponding confidence intervals (CIs).

Interpretation of CIs will play a major role as an integral part of the analysis of the data in concert with any statistical hypothesis tests. To avoid over-reliance on p-values, the magnitudes of estimates and the corresponding confidence intervals will be a focus of the analyses. Reasons for missing data will be investigated and recorded for purposes of statistical analyses. Because of the study design and outcome assessment, primary analyses will require exclusion of participants without outcome data. However, we will perform sensitivity analyses for missing data, initially assigning participants lost to follow up to treatment failure, then assigning them to treatment success and comparing the results, a technique that has been successful in prior clinical trials conducted by our group. For all outcomes, the null hypothesis is that there is no difference between the study groups. All hypothesis tests that are observed to be NOT statistically significant will be reported as being inconclusive.

The study statistician on this study will be Joseph Galanko.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY OUTCOMES(S)

The primary outcome will be the mean change in dysphagia as measured by the EEsAI score (7-day recall) from baseline to 3-months post-treatment. Patients will complete this measure at screening (baseline), and then every month throughout the study when they come for their medication injection. This study will consider baseline at the point when symptoms are assessed prior to the study drug being given.

We are focusing on symptoms as the primary outcome as this is the key clinical metric for a PRO-measured treatment response.[41] The EEsAI is a validated and responsive PRO, developed by an international team of EoE experts, that measures dysphagia frequency, dysphagia severity, and food avoidance/modification behaviors, in patients with EoE.[42, 45-47] It has now been used in several clinical trials, including recently published abstract data emphasizing the responsive nature of this instrument.[48] In the first, 59 subjects were randomized to receive an or dispersible budesonide tablet and 29 to placebo.[51] A total of 30 patients (59%) in the active arm achieved an EEsAI score of ≤ 20 compared to just 2 patients (7%) in the placebo arm ($p < 0.0001$). In the second study, which was a study of the anti-IL-4α receptor blocker dupilumab, EEsAI was measured in a subset of patients had EEsAI.[49] The 17 patients who received active treatment had a 36% decrease in the EEsAI score compared to an 11% decrease in the 13 patients who received placebo ($p = 0.085$). These new data support the use of the EEsAI as a primary outcome. The EEsAI score can range from 0 to 100, with higher scores indicated more severe symptoms; a decrease of 20 points is felt to be a meaningful clinical response, and scores ≤20 represent clinical remission.

For the primary outcome, the mean change in dysphagia from baseline to 3-months post-treatment (as measured by the EEsAI score with 7-day recall) will be compared between the mepolizumab and placebo groups using analysis of covariance. In discussion with the study statistician, the main factor that we will include in the primary analysis is the baseline EEsAI score, though in the exploratory analyses we will assess trial site. We will also include the stratification factor (prior steroid response as a covariate as appropriate in the analyses (see below as well).

9.4.3 ANALYSIS OF THE SECONDARY OUTCOMES(S)

Secondary outcomes are as follows:

- The proportion of patients who have clinical remission as defined by an EEsAI score of ≤ 20. This will be compared between groups by chi-square.

- The proportion of patient who have a clinical response, as defined by an EEsAI score decrease of ≥ 20 points. This will be compared between groups by chi-square.
- The absolute peak eosinophil count (measured in eos/hpf) after 3-months of treatment. Eosinophil counts will be measured by our previously validated protocol, with central reading of all biopsy samples at the lead site to ensure a consistent reading approach.[49] This will be compared between groups with a two-sample t-test.
- Levels of histologic response after 3-months of treatment including < 15, ≤ 6, and ≤ 1 eos/hpf. This will be compared between groups by chi-square.
- Mean change in severity of endoscopic findings as measured by the EoE Endoscopic Reference Score (EREFS) from baseline to 3-months post-treatment. EREFS is a validated and responsive endoscopic severity score that assesses the five most common endoscopic features of EoE: exudates, rings, edema, furrows, and strictures.[50, 51] This will compared between the groups using analysis of covariance.
- Mean change in the Straumann Dysphagia Instrument (SDI) from baseline to 3-months post-treatment. The SDI is a direct measure of dysphagia frequency and severity with a 7-day recall period. The score ranges from 0-9, with higher scores indicating more severe dysphagia. This instrument, while not validated, has been shown to be responsive in at least 2 clinical trials.[23, 49] This will compared between the groups using analysis of covariance.

9.4.4 SAFETY ANALYSES

All treatment emergent adverse events will be tabulated and summarized between the study groups and presented in a series of tables using standard Medical Dictionary for Regulatory Activities (MedDRA) terminology.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

We will use descriptive statistics to describe the data for each of the study groups. Categorical variables will be presented as proportions and means with standard deviation and range. We will assess the groups in terms of baseline demographics, comorbidities, prior medications, and disease comparisons.

9.4.6 PLANNED INTERIM ANALYSES

There are no planned interim analyses for this study. The Data and Safety Monitoring Board (DSMB) will review all SAEs as soon as they are reported, and all AEs at the pre-set meeting intervals. If two grade 3 related or possibly related events occur, the DSMB will review all AE data at that time. If there is an unexpected signal or safety concern or newly identified risk that would potentially outweigh the potential benefits of the study drug, then temporary suspension of the study could be considered. See section 10.1.2 for additional details.

9.4.7 SUB-GROUP ANALYSES

In accordance with the first additional aim (“to determine predictors of symptomatic and histologic response to mepolizumab treatment, including potential biomarkers”), we will perform prespecified planned analyses of the primary or secondary outcomes by age, sex, and race/ethnicity, depending on the final characteristics of the population enrolled in the study.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Data will be analyzed in the aggregate, so we are not planning any primary analyses which present individual data by measure or time point. Depending on the results and data distributions, however, this may be done in exploratory fashion.

9.4.9 EXPLORATORY ANALYSES

Prespecified exploratory outcomes are as follows:

- Mean change in peripheral blood eosinophil levels from baseline to 3-months post-treatment. This will be compared between the groups using analysis of covariance.
- For patients initially randomized to active medication, the same set of outcomes (as listed above) will be assessed after 6 months of treatment. This will be compared between the groups using analysis of covariance.
- For patients initially randomized to placebo, a paired analysis will be conducted to compare month 3 to month 6 outcomes. This will use paired t-tests for continuous variables and McNemar's test for categorical variables.
- For the same set of outcomes (as listed above), 3-month data for patients initially randomized to active medication (300mg monthly) will be compared to 6 month data for patients initially randomized to placebo and who have completed 3-months of 100mg monthly. This will provide a comparison of the 300mg to the 100mg dose.
- Adverse events and safety during all time points in the study. This will be compared between groups by chi-square.

Additional Exploratory outcomes are as follows:

- Change in weekly SDI score over the course of the study, and correlation of SDI with the EEsAI score. We will also explore the minimal clinically important differences (MCIDs) of these measures.
- Biomarkers, including serum and tissue levels of cytokines and related factors (IL-5, IL-13, and eotaxin-3 [CCL26]), and eosinophil granule levels (i.e. eosinophil peroxidase or major basic protein) in blood and tissue.
- Antibodies to mepolizumab as a measure of immunogenicity. The study sponsor will assist with these measurements.
- Additional histologic findings, including eosinophil degranulation, microabscesses, basal layer hyperplasia, spongiosis, and lamina propria fibrosis (in samples with adequate subepithelial tissue present).
- Response outcomes (noted above) in prior steroid responders vs. non-responders. Steroid non-response is defined as greater than 15 eos/hpf after a 2-month course of a swallowed/topical steroid at a standard dose (standard dose = 2mg/d of budesonide or 1760 mcg/d of fluticasone). Of note, the randomization is balanced for prior steroid response, but the study is not powered for this exploratory outcome. We will also explore the response outcomes in the context of all prior EoE treatments to understand heterogeneity of treatment response, if present, and will include this stratification factor as a covariate in the above analyses, as appropriate.
- Response outcomes (as noted above) in patients on a restrictive diet vs. an inclusive diet. A restrictive diet will be defined as any diet at baseline (which also must be maintained through the study) that is either limited in foods because of EoE or because of food allergies/intolerances.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the participant's study participation. Consent forms will be IRB - approved and the participant will be asked to read and review the document(s). The investigator or approved study staff will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form(s) and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document(s) prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document(s) will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This trial must suspend screening and enrollment and confer immediately with the DSMB in the event of any of the following:

- A grade 4 (life-threatening consequences; urgent intervention indicated) AE that is related or possibly related to treatment as determined by the sponsor-investigator
- A grade 5 (Death related to AE) AE that is related or possibly related to treatment as determined by the sponsor-investigator
- New information leading to unfavorable risk-benefit judgment of the study drug, e.g., significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions, or other unfavorable safety findings
- A decision that continuation of the trial is unjustifiable for medical or ethical reasons

A grade 3 (severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization) AE that is related or possibly related (per the UNC IRB definition of

relatedness) to the study intervention will be immediately reported to the DSMB for review and screening and enrollment will continue unless the DSMB rules otherwise upon their review of the event. If two grade 3 related or possibly related events occur, screening and enrollment will be suspended at the time of the event and the DSMB will review all AE data at that time. Screening and enrolment may resume pending DSMB determination that it is appropriate to continue.

Upon a determination that continuation of the trial is unjustifiable for medical or ethical reasons, all study activities may be suspended. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator(s), funding agency, the IND sponsor, and regulatory authorities; as applicable. If the study is prematurely terminated or suspended, the investigator will promptly inform study participants, the IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or FDA.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the sponsor(s), and their institutions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor and documented written consent from participants.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, and sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of North Carolina at Chapel Hill. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the University of North Carolina at Chapel Hill research staff will be secured and password protected. At the end of the study, all study databases will be coded and archived at the University of North Carolina at Chapel Hill.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the University of North Carolina at Chapel Hill. After the study is completed, the coded, archived data will continue to be stored at the University of North Carolina at Chapel Hill for use by other researchers including those outside of the study. Permission to store and transmit data and specimens will be included in the informed consent.

With the participant's approval and as approved by local IRBs, coded biological samples will be stored at the University of North Carolina at Chapel Hill. These samples could be used to research the causes of EoE, its complications and other conditions for which individuals with EoE are at increased risk, and to improve treatment. Other researchers will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through direct request to the University of North Carolina at Chapel Hill.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Evan Dellon, MD, MPH	Swathi Eluri, MD, MSCR
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10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest.

An initial meeting for all Committee members and relevant study team members (e.g.: sponsor-investigator, project manager, biostatistician, medical monitor, study monitor) will be held prior to any participant enrollment or start of any Committee activities. This meeting should take place ideally before the initiation of a study and well in advance of the performance of the first review of data.

Subsequent DSMB meetings will be held when 25%, 50% and 75% of the overall enrollment goal is reached and on an as-needed, incident-driven basis (death or serious adverse events) thereafter to ensure patient safety throughout the duration of the trial. When requested by the DSMB, the unblinded medical monitor will be available to attend any necessary "closed" meetings to discuss specific data that may need to be unblinded.

Additional ad-hoc meetings may be called by the Chairperson, the sponsor-investigator, or the project manager. Prior to each meeting, the documents and data needed to hold an efficient meeting will be circulated to the Committee members, as relevant.

Quarterly enrollment reporting will also be required.

Prior to each meeting, the sponsor-investigator and research team will provide the following documents:

- Clinical Trial Protocol, including amendments
- Biostatistical outputs, if available

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Monitoring for this study will be performed by the sponsor.

Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

Independent audits may be conducted to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion. An individualized quality management plan should be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site-investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by the University of North Carolina at Chapel Hill. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site-investigator to use continuous vigilance to identify and report deviations that harmed subject(s) or others or placed subject(s) or others at increased risk within one week of identification of the protocol deviation, or within one week of the scheduled protocol-required activity. All other deviations should be documented in a source document and submitted as reportable events to the sponsor via the eCRF in a timely manner. Protocol deviations meeting reporting criteria

must be sent to the reviewing IRB per their policies. The site-investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. This trial is registered at ClinicalTrials.gov (NCT03656380). Results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

None

10.3 ABBREVIATIONS

ADL	Activities of Daily Living
AE	Adverse Event
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
EEsAI	Eosinophilic Esophagitis Symptom Activity Index
EGD	Esophagogastroduodenoscopy
EoE	Eosinophilic Esophagitis
EREFS	EoE Endoscopic Reference Score
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HES	Hypereosinophilic Syndrome
HPF	High-Power Field
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention to Treat
MCID	Minimal clinically important differences
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MOP	Manual of Procedures
NCT	National Clinical Trial
OHRP	Office for Human Research Protections
PI	Principal Investigator
QC	Quality Control
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SDI	Straumann Dysphagia Instrument
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SQ	Subcutaneous
UP	Unanticipated Problem
UPIRSO	Unanticipated Problem Involving Risk to Subjects or Others
US	United States
VAS	Visual Analog Scale

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