[CEGIR 7810]

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL TO EVALUATE THE EFFICACY OF DUPILUMAB (ANTI-IL4RA) IN SUBJECTS WITH EOSINOPHILIC GASTRITIS

DUPILUMAB EOSINOPHILIC GASTRITIS STUDY (DEGAS)

VERSION 6.0/VERSION DATE 06DEC2023

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SITE INVESTIGATOR SIGNATURE PAGE	
Protocol Number: CEGIR 7810	**Version Number/Date:** V 6.0/ 06Dec2023
PROTOCOL TITLE: A Randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy of dupilumab (anti-IL4rα) in subjects with eosinophilic gastritis	
IND/IDE Sponsor: Marc E. Rothenberg, MD, PhD *[Amend if another IC. Change "IND/IDE Sponsor" to "Study Sponsor" if no IND/IDE]*	
Return Signed Form to: *[A copy of this signature page must be kept for your records. Return the original signed* signature *page (as described below*) by USPS mail or Courier to:]* Cincinnati Children's Hospital Medical Center Regina Yearout 240 Albert Sabin Way, MLC 2010 Cincinnati, Ohio 45229 *[If PPD is not the Regulatory Management Center for this protocol, e.g., for an Investigator Initiated clinical trial, contact the DAIT Regulatory Officer for appropriate mailing address.]*	
I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, 812 and in the International Conference for Harmonisation (ICH) document entitled *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)*. Further, I will conduct the study in keeping with local legal and regulatory requirements. As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the IRB and NIAID. *[*The site Principal Investigator should print, sign, and date at the indicated location below. A written signature is acceptable, and an electronic signature is acceptable in a pdf version of the form.]* _____ **Site Principal Investigator (Print)** _____ _____ **Site Principal Investigator (Signature)** **Date**	

Protocol Synopsis

Title	A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Efficacy of Dupilumab (ANTI-IL4Rα) in Subjects with Eosinophilic Gastritis
Short Title	Dupilumab Eosinophilic Gastritis Study (DEGAS)
Clinical Phase	Phase II
Investigators	Marc E. Rothenberg, MD, PhD, Evan Dellon, MD, Nirmala Gonsalves, MD, Ikuo Hirano, MD
Sites	Multiple sites in the US
Investigational New Drug (IND) Application Sponsor/Number	Marc E. Rothenberg/140499
Study Objectives	**Primary Objective for the Double-Blind Phase (DBP) Population:** To assess the efficacy of repeat subcutaneous (SC) doses of dupilumab, compared with placebo, to reduce eosinophilic inflammation in the stomach of participants with eosinophilic gastritis (EG) with or without esophageal and/or duodenal eosinophilia. **Secondary Objectives for the DBP Population:** To assess the efficacy of dupilumab compared to placebo as measured by: • Patient global impression of severity (PGI-S) • Patient global impression of change (PGI-C) • Proportion of participants achieving threshold response < 30 eos/high powered field (hpf) in 5 hpfs • Eosinophilic Gastritis Endoscopy Assessment (EG-REFS) • Eosinophilic Gastritis Symptom Questionnaire (EG-SQ) **Exploratory Objectives for the DBP Population:** To assess the efficacy of dupilumab compared to placebo as measured by: • Severity of Dyspepsia Assessment (SODA) • Clinician global impression of severity (CGI-S) • Clinician global impression of change (CGI-C) • Quality of Life (QOL) Questionnaires (SF12, PROMIS 29, PROMIS 25) • EoE Endoscopic Reference Score (EREFS) (subjects with esophageal involvement) • Comprehensive assessment of histologic features • Blood and tissue biomarkers and gastric transcripts

	• Peripheral eosinophil counts, hemoglobin & hematocrit, total protein and albumin, total IgE, iron storage panel (iron, ferritin, total iron-binding capacity) • Eosinophilic Gastritis Quality of Life (EG-QOL) • Eosinophilic Duodenitis Endoscopic Reference Score (ED-EREFS) **Exploratory Objective for the Open Label Extension (OLE) Population** Key Objective: To assess the efficacy of repeat SC doses of dupilumab to reduce eosinophilic inflammation in the gastrointestinal tract of participants with EG with or without esophageal and/or duodenal eosinophilia. To assess the efficacy of dupilumab as measured by: • Patient global impression of severity (PGI-S) • Patient global impression of change (PGI-C) • Proportion of participants achieving threshold response < 30 eos/hpf in 5 hpfs • Eosinophilic Gastritis Endoscopy Assessment (EG-REFS) • Eosinophilic Gastritis Symptom Questionnaire (EG-SQ) To assess the efficacy of dupilumab as measured by: • Severity of Dyspepsia Assessment (SODA) • Clinician global impression of severity (CGI-S) • Clinician global impression of change (CGI-C) • Quality of Life Questionnaires (SF12, PROMIS 29, PROMIS 25) • EoE Endoscopic Reference Score (EREFS) (subjects with esophageal involvement) • Comprehensive assessment of histologic features • Blood and tissue biomarkers and gastric transcripts • Peripheral eosinophil counts, hemoglobin & hematocrit, total protein and albumin, total IgE, iron storage panel (iron, ferritin, total iron-binding capacity) • EG-QOL • Eosinophilic Duodenitis- Endoscopic Reference Score (ED-EREFS)
Study Design	This is a phase 2, multi-center, randomized, double-blind, placebo-controlled trial testing the efficacy of dupilumab vs. placebo in eosinophilic gastritis (EG) with or without concurrent esophageal and/or duodenal eosinophilia. Qualifying subjects will be randomized 1:1 to either study drug (dupilumab) or placebo and will receive 600 mg once followed by 300 mg doses every two weeks of study treatment for a total of 6 injections. After the 6th injection subjects may continue into an open-label treatment phase in which dupilumab will be administered every two weeks for a total of 24 weeks.

Primary Endpoint/Outcome for the DBP Population	Relative change from baseline of the peak eosinophil counts in the 5 most eosinophil dense HPFs in the gastric antrum and/or body between drug vs placebo at 12 weeks.
Secondary Endpoints/Outcomes for the DBP Population	Absolute change in the mean of the peak eosinophil counts in the 5 most eosinophil dense HPFs in the gastric antrum and/or body between drug vs placebo at 12 weeks. Absolute change in the patient global impression of severity (PGI-S) score between baseline and post-treatment in dupilumab vs placebo at 12 weeks. Patient global impression of change (PGI-C) score Proportion of participants in dupilumab vs placebo achieving threshold response < 30 eos/hpf in all 5 hpfs identified for the primary endpoint. Absolute change in endoscopic score from pre- to post-treatment with dupilumab or placebo as measured by Eosinophilic Gastritis Endoscopy Assessment at 12 weeks. Absolute change in the total EG-SQ eDiary score between baseline and post-treatment in dupilumab vs placebo at 12 weeks Absolute change in proportion of days of any (1 or more) symptom from pre- to post-treatment with dupilumab vs placebo as measured by the EG-SQ eDiary.
Exploratory Endpoint for the DBP Population	Absolute change in participant reported outcomes from pre- to post-treatment with dupilumab or placebo as measured by additional patient reported outcomes (PROs) including the Severity of Dyspepsia Assessment tool as well as QOL instruments SF-12, PROMIS 29 and PROMIS 25 scores. We will also utilize clinician global impression of severity and clinician global impression of change. Absolute change in proportion of days with each individual symptom and multiple symptoms from pre- to post-treatment with dupilumab vs placebo as measured by the EG-SQ eDiary. Absolute change in each individual EG-SQ eDiary symptom score between baseline and post-treatment in dupilumab vs placebo at 12 weeks. Induction of disease remission defined by the percentage of subjects who achieve histological remission in the stomach as defined by peak eosinophil counts less than 30/hpf in 1, 2, 3 and 4 of the 5 hpfs identified for the primary endpoint. Comparison between drug vs placebo at Week 12 will be the measurement endpoint. Absolute change in histologic score from pre- to post-treatment with dupilumab or placebo as measured by the EG Biopsy Evaluation Form. For those participants who also have esophageal involvement and/or duodenal eosinophilia involvement, we will assess changes in histology

	using the EoE-Histology Scoring System (HSS) and ED Biopsy Evaluation Forms, respectively. Absolute and relative change in blood biomarkers (primarily cytokine levels) and tissue biomarkers as well as gastric transcripts from pre- to post- treatment. Absolute and relative change in blood eosinophil count, hemoglobin, hematocrit, total protein levels, albumin, IgE, iron storage panel (iron, ferritin, total iron-binding capacity) from pre- to post- treatment with dupilumab or placebo. The association of blood and tissue biomarkers and transcripts with drug responsiveness. Assess histological changes in the esophagus and duodenum including peak eosinophil levels. Assess endoscopic changes in the esophagus and duodenum for those participants with involvement of these gastrointestinal segments using the EoE-EREFS and ED-EREFS, respectively.
Exploratory Endpoint/Outcome for the OLE Population	There will be two key time points evaluated for the OLE. First, we will examine the overall change across the study (baseline to OLE/EOT (Week 24)). Second, we will examine change during the open label phase (DBP/EOT (Week 12) to OLE/EOT (Week 24)). These time points apply to the endpoints listed below: <u>Key Endpoint/Outcome</u> Relative change of the peak eosinophil counts in the 5 most eosinophil dense HPFs in the gastric antrum and/or body <u>Additional Endpoints</u> Absolute change in the mean of the peak eosinophil counts in the 5 most eosinophil dense HPFs in the gastric antrum and/or body Absolute change in the patient global impression of severity (PGI-S) score Patient global impression of change (PGI-C) score Proportion of participants achieving threshold response < 30 eos/hpf in all of the 5 hpfs identified Absolute change in endoscopic score as measured by Eosinophilic Gastritis Endoscopy Assessment. Absolute change in the total and each individual EG-SQ eDiary symptom score Absolute change in proportion of days with each individual symptom, multiple symptoms, and any (1 or more) symptom as measured by EG-SQ eDiary

	Absolute change in participant reported outcomes measured by additional PROs including the Severity of Dyspepsia Assessment as well as QOL instruments SF-12, PROMIS 29 and PROMIS 25 scores. We will also utilize clinician global impression of severity and clinician global impression of change. Induction of disease remission defined by the percentage of participants who achieve histological remission in the stomach as defined by peak eosinophil counts less than 30/hpf in 1, 2, 3 and 4 of the 5 hpfs identified for the primary endpoint. Absolute change in histologic score as measured by the EG Biopsy Evaluation Form. For those participants who also have esophageal involvement or duodenal involvement, we will assess changes in histology using the EoE-HSS and ED Biopsy Evaluation Form respectively. Absolute and relative change in blood biomarkers (primarily cytokine levels) and tissue biomarkers as well as gastric transcripts Absolute and relative change in blood eosinophil count, hemoglobin, hematocrit, total protein levels, albumin, IgE, iron storage panel (iron, ferritin, total iron-binding capacity) The association of blood and tissue biomarkers and transcripts with drug responsiveness. Assess histological changes in the esophagus and duodenum including peak eosinophil levels. Assess endoscopic changes in the esophagus and duodenum for those participants with involvement of these gastrointestinal segments using the EoE-EREFS and ED-EREFS, respectively
Accrual Objective	Approximately 40 participants
Study Duration	The duration of the study for a participant (excluding the screening period) is approximately 48 weeks. This includes participation in the double-blind and open-label treatment part, and the follow-up period.
Treatment Description	Qualifying participants will be blindly randomized 1:1 to either study drug (dupilumab) or placebo and will receive 600 mg once followed by 300 mg doses every two weeks of study treatment (for a total of 6 injections).
Eosinophilic Gastrointestinal (EGID) Definitions	• Eosinophilic Gastritis (EG): a peak gastric count of ≥ 30 eos/hpf in at least 5 hpfs in the gastric antrum and/or body. -Esophageal eosinophilia: ≥ 15 eosinophils/HPF in the distal and/or proximal esophagus -Duodenal eosinophilia: ≥ 30 eosinophils/HPF in at least 3 hpfs in the duodenum

Inclusion Criteria for Double Blind Phase	1. Participant and/or parent guardian must be able to understand and provide informed consent and/or assent prior to study procedures being performed. 2. Willing and able to comply with study visits and activities 3. Age ≥ 12 and < 71 years at study enrollment 4. Histologically active EG at time of screening, with a peak gastric count of ≥ 30 eos/hpf in at least 5 hpfs in the gastric antrum and/or body, with no other known cause for gastric eosinophilia; involvement of eosinophilic inflammation in other gastrointestinal segments will be allowed but not required or sufficient. 5. History (by patient report) of moderate to severe EG symptoms (stomach pain, stomach cramping, nausea, bloating, burning feeling in the chest, starting to eat and feeling full too quickly, loss of appetite, vomiting, or diarrhea) at least 2 days per week in the 2 weeks prior to screening. 6. EG symptoms (stomach pain, stomach cramping, nausea, bloating, burning feeling in the chest, starting to eat and feeling full too quickly, loss of appetite, diarrhea, or vomiting) at least 2 days per week in the two weeks leading up to V1 (randomization) documented via the EG-SQ eDiary. At least 8 of 14 days must be entered in the EG-SQ eDiary in the 2 weeks prior to V1 (randomization). 7. Stable medical management of EG (and other eosinophilic disorders, if applicable) including stable dosage of medications in the 8 weeks prior to study enrollment, if applicable. Participants may be on baseline anti-EG therapy (such as elimination diet, elemental diet, proton pump inhibitors, topical swallowed or systemic glucocorticoids (≤10 mg daily), immunosuppressive agents, cromolyn, and H1 and H2 anti-histamines) as long as there is agreement not to change their dosage unless medically indicated. See Section 7.1 (Concomitant and other Treatments) for additional details. 8. Willing to maintain current dietary regimen throughout the course of the study. Diet must have been stable for 8 weeks prior to baseline endoscopy. 9. If have asthma and/or any other chronic allergic conditions (e.g., chronic rhinosinusitis with nasal polyposis), they must be willing to maintain their pretrial medications until the end of study. Medication dose can be increased if there is a deterioration in the condition. 10. Score on Asthma Control Test (ACT™) ≥ 20
Exclusion Criteria for Double Blind Phase	1. Inability or unwillingness of a participant to give written informed consent or comply with study protocol. 2. Current active H. pylori infection. A history of H. pylori infection needs to have medical documentation of one of the three acceptable eradication tests: antigen, breath or histology. 3. Systemic gastrointestinal disorders such as Crohn's disease, inflammatory bowel disease, or Celiac disease.

	4. Known or suspected active colitis (e.g., Eosinophilic colitis) in the Principal Investigator's opinion or by biopsy. 5. Hypereosinophilic syndrome, defined by multiple organ involvement (with the exception of atopic disease or eosinophilic gastrointestinal disorder (EGID)) and persistent blood absolute eosinophil count ≥1500/mcL. 6. History of cancer: Individuals who have had basal cell carcinoma, localized squamous cell carcinoma of the skin, or in situ carcinoma of the cervix are eligible provided that the subject is in remission and curative therapy was completed at least 12 months prior to the date informed consent was obtained. Individuals who have had other malignancies are eligible provided that the individual is in remission and curative therapy was completed at least 5 years prior to the date informed consent was obtained. 7. Current or recent use of biological agents (within 4 months or 5 half-lives whichever is longer prior to screening). 8. Leukocyte count has not returned to the relevant lower limit of normal after discontinuing cell depleting biological agents. 9. Current or recent use of any investigational drug (within 3 months or 5 half-lives, whichever is longer, prior to screening). 10. Current use of systemic steroids with daily dose > 10 mg for any reason or steroid burst for > 3 days within 1 month of screening. 11. Prior exposure to dupilumab. 12. History of anaphylaxis to any biologic therapy. 13. Current pregnancy or breastfeeding. 14. Ocular disorder that, in the opinion of the investigator, could adversely affect the individual's risk for study participation. Examples include, but are not limited to, individuals with a history of or active case of herpes keratitis, Sjogren's Syndrome, keratoconjunctivitis sicca or dry eye syndrome that require daily use of supplemental lubrication; or individuals with ocular conditions that require the regular use of ocular corticosteroids or cyclosporine. 15. Individuals who have required use of a systemic corticosteroid for asthma within 3 months prior to the Treatment Initiation Visit or who require a dose greater than 880 mcg/day of fluticasone propionate or equivalent inhaled corticosteroid to maintain asthma control. 16. Received live vaccine 30 days prior to screening or planning on receiving a live vaccine during the time period that he/she is participating in the study. Study participants are allowed to receive non-live vaccines during study participation. 17. Any esophageal stricture unable to be passed with a standard, diagnostic upper endoscope.

	18. History of bleeding disorders or esophageal varices that, in the opinion of the investigator, would put the participant at undue risk for significant complications from an endoscopy procedure. 19. Active parasitic infection or suspected parasitic infection, unless clinical and/or laboratory assessments have ruled out active infection before randomization. 20. History of alcohol or drug abuse within 6 months prior to screening. 21. Participant or his/her immediate family is a member of the investigational team. 22. Any of the following abnormal lab values at screening: • Platelets < 100 x 10^3/ µl • Neutrophils <1.5 x 10^3/µl • Estimated glomerular filtration rate (eGFR) <30 Ml/min/1.73 m^2 • Absolute Eosinophil Count (AEC) >5,000 cells/mcl NOTE: if an abnormal value is detected at screening, a repeat test should be performed to confirm the abnormality. Only if the repeat test confirms the abnormality would the participant be categorized as a screen failure. 23. Planned or anticipated major surgical procedure during the study. 24. Any of the following subcutaneous immunotherapy (SCIT): • Treatment with subcutaneous immunotherapy (SCIT) unless on a stable maintenance dose, which must be maintained throughout the study. • If build-up SCIT is stopped prior to enrollment, discontinuation of build-up SCIT must occur at least 10 weeks prior to screening. • If maintenance SCIT is stopped prior to enrollment, discontinuation of maintenance SCIT must occur at least 6 months prior to screening. 25. Treatment with sublingual immunotherapy (SLIT) within 6 months prior to screening. 26. Treatment with oral immunotherapy (OIT) within 6 months prior to screening. 27. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals or antifungals within 2 weeks before the baseline visit Note: participant may be re-screened after the infection resolves. 28. Known or suspected immunodeficiency disorder, including human immunodeficiency disorder (HIV) or a history of invasive opportunistic infections (e.g., tuberculosis [TB], non-tuberculous mycobacterial infections, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution or otherwise recurrent infections of abnormal frequency or prolonged infections suggesting an immune-compromised status as judged by the investigator.

29. Planned or anticipated use of any prohibited medications and procedures during the study.
30. Initiation, discontinuation or change in the dosage regimen of the following medications within 8 weeks prior to the baseline endoscopy:
    Proton pump inhibitors (PPIs)
    Leukotriene inhibitors
    Nasal and/or inhaled corticosteroids
    Participants on a stable dose of these medications for at least 8 weeks prior to the baseline endoscopy may be included in the study. PPI and leukotriene inhibitor dosing must not change during the study, but nasal and/or inhaled corticosteroids can be increased if there is a deterioration in the condition for which the medications are prescribed.
31. Women of childbearing potential who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 12 weeks after the last dose. Highly effective contraceptive measures include:

    a. Stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) for one month prior to screening
    b. Intrauterine device; intrauterine hormone-releasing system
    c. Bilateral tubal ligation
    d. Vasectomized partner
    e. And/or sexual abstinence †‡

    *Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

    †Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

    ‡Periodic abstinence (calendar, symptothermal, and post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female and male condom should not be used together
32. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability

	to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.
Exclusion Criteria for Open Label Extension	A participant who meets any of the following criteria will not be permitted to enter the Open Label Extension portion of the study: 1. Participants who, during the double-blind treatment period, developed a serious adverse event (SAE) and/or adverse event (AE) deemed related to study drug 2. Participant who, during the double-blind treatment period, developed an adverse event (AE) deemed related to study drug which in the opinion of the investigator could indicate that continued treatment with study drug may present an unreasonable risk for the participant. 3. Participants who, during the double-blind treatment period, were prematurely withdrawn because of a protocol violation, poor compliance or inability to complete required study assessments. 4. Participants who became pregnant during the double-blind treatment period. 5. Participants who are prematurely discontinued from study drug due to an AE 6. Participants who did not undergo endoscopy with biopsies at the EOT (visit 5). 7. Systemic hypersensitivity to dupilumab or the excipients of the drug product based on participation in the double-blind phase of the trial. 8. Participants who are unable or unwilling to administer doses of dupilumab during the open label.
Safety Assessment	We will monitor the safety and tolerability of dupilumab in participants via AE's/SAE's
Study Stopping Rules	Study enrollment will be suspended pending Study Sponsor, Division of Allergy, Immunology and Transplantation and the National Institute of Allergy and Infectious Diseases (DAIT) (NIAID), and NIAID Allergy and Asthma Data Safety and Monitoring Board (DSMB) expedited review of all pertinent data if any of the following occur: • One death that is possibly related/related to dupilumab • One Grade 4 adverse event based on CTCAE 5.0 grading that is possibly related/related to dupilumab • Grade 3 adverse events based on CTCAE 5.0 grading that are possibly related/related to dupilumab in two or more participants • Grade 4 adverse events based on AEC grading (Table B) that are possibly related/related to dupilumab in two or more participants The study may not be resumed until all pertinent information is discussed with the Study Sponsor, DAIT NIAID, NIAID Allergy and Asthma DSMB, and the central Institutional Review Board (IRB), and all parties concur

	with the resumption of the study. Local IRBs will be informed of the study stoppage and the DSMB/Central IRB's decision on resumption of the study. The study may be terminated by DAIT/NIAID or the NIAID Allergy and Asthma DSMB upon review of any observations, events, or new information that merits such action.

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Glossary of Abbreviations

ACT	Asthma Control Test
ADL	Activities of Daily Living
AE	Adverse Event
AEC	Absolute Eosinophil Count
ALT	Alanine Aminotransferase
APGAR	Appearance Pulse Grimace Activity Respiration
AST	Aspartate Aminotransferase
BP	Blood Pressure
CBC	Complete Blood Count
CCHMC	Cincinnati Children's Hospital Medical Center
CEGIR	Consortium of Eosinophilic Gastrointestinal Disease Researchers
CFR	Code of Federal Regulations
CGI-C	Clinician Global Impression of Change
CGI-S	Clinician Global Impression of Severity
CRF	Case Report Form
COVID	Coronavirus Disease
CTCAE	Common Terminology Criteria for Adverse Events
DAIT	Division of Allergy, Immunology, and Transplantation
DBP	Double Blind Phase
DEGAS	Dupilumab Eosinophilic Gastritis Study
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
ED	Eosinophilic Duodenitis
EoE	Eosinophilic Esophagitis
EG	Eosinophilic Gastritis
EGD	Esophagogastroduodenoscopy
eGFR	Estimated Glomerular Filtration Rate
EGID	Eosinophilic Gastrointestinal Disorder
EG-QOL	Eosinophilic Gastritis Quality of Life
EG-REFS	Eosinophilic Gastritis Endoscopy Assessment
EG-SQ	Eosinophilic Gastritis Symptom Questionnaire
EOS	End of Study (Completion of telephone contact 12-weeks following the last dose of study drug)
EOT	End of Treatment
EREFS	Endoscopic Reference Score
FDA	Food and Drug Administration
FEV	Forced Expiratory Volume
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
hpf	High Power Field

HRQOL	Health-Related Quality of Life
HSS	Histology Scoring System
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IgE	Immunoglobulin E
IL	Interleukin
IND	Investigational New Drug
IPM	Independent Protocol Monitor
IRB	Institutional Review Board
mAb	Monoclonal Antibody
MCAR	Missing at Completely Random
MO	Medical Officer
MOP	Manual of Procedures
NIAID	National Institute of Allergy and Infectious Diseases
OHRP	Office for Human Research Protections
OIT	Oral Immunotherapy
OLE	Open Label Extension
PEF	Peak Expiratory Flow
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PHI	Protected Health Information
PI	[Site] Principal Investigator
PM	Project Manager
PoR	Pharmacist of Record
PRO	Patient Reported Outcome
PROMIS	Patient Reported Outcomes Measurement Information System
QC	Quality Control
QOL	Quality of Life
RDCRN	Rare Diseases Clinical Research Network
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SC	Subcutaneous
SCIT	Subcutaneous Immunotherapy
SF-12	Short Form 12 Health Survey
SLIT	Sublingual Immunotherapy
SOA	Schedule of Activities
SODA	Severity of Dyspepsia Assessment
SOP	Standard Operating Procedure
SUSAR	Serious Unexpected Suspected Adverse Reaction
TB	Tuberculosis

TCS	Topical Corticosteroids
TEAE	Treatment-Emergent Adverse Event
Th2	Type 2 Helper
TNF	Tumor Necrosis Factor
TPN	Total Parenteral Nutrition

1. Background and Rationale

1.1. Background and Scientific Rationale

Eosinophilic gastritis (EG) is an understudied rare disease characterized by eosinophil accumulation in the stomach and associated with a variety of symptoms including pain, vomiting, weight loss, and anemia. Currently, the prevalence of EG is estimated at 6.4/100,000 and extrapolated to be approximately 17,000 cases in the US [1,2]. There are no US Food and Drug Administration (FDA)-approved drugs for EG or any other eosinophilic gastrointestinal disease (EGID). At present, the treatment of EG has focused upon diet elimination therapy, systemic corticosteroids, swallowed topical corticosteroids, or a combination of therapies. Though these treatments can be efficacious, there are substantial rates of non-responsiveness. Moreover, these therapies require continuous use, as a majority of patients relapse if treatment is not maintained. Dietary elimination adversely impacts personal and social aspects of life owing to the need to avoid multiple common food groups. Moreover, concerns about the long-term risks of chronic steroid use, as well as a desire to find more tolerable and/or convenient methods of treatment, have driven the search for other potential targeted therapies. In EG, there are increased levels of gastric inflammatory infiltrates, including T cells, eosinophils, and mast cells, and increased levels of chemokines and cytokines, including CCL26 (eotaxin-3), interleukin (IL)-4, IL-5, and IL-13 [3]. IL-5 is a direct eosinophil growth and activating factor, whereas IL-4 and IL-13 mediate several cardinal aspects of allergic inflammation including immunoglobulin E (IgE) production, T cell polarization to type 2 helper (Th2) cells, chemokine induction and subsequent leukocyte infiltration and activation, mucus production, barrier impairment, and end-organ dysfunction. IL-4 and IL-13 signal through a common receptor subunit, designated the IL-4Rα that is required for signal transduction.

1.2. Rationale for Selection of Investigational Product or Intervention

Dupilumab is a fully human monoclonal antibody, directed against IL-4Rα, that inhibits signaling of IL-4 and IL-13 [4,5]. Dupilumab binds to the IL-4Rα and blocks the signaling of the cytokines IL-4 and IL-13, which are key components of type 2 immune responses involved in allergy. In EG, there are increased levels of gastric inflammatory infiltrates, including T cells, eosinophils, and mast cells, and increased levels of chemokines and cytokines, including CCL26 (eotaxin-3), interleukin (IL)-4, IL-5, and IL-13. IL-5 is a direct eosinophil growth and activating factor, whereas IL-4 and IL-13 mediate several cardinal aspects of allergic inflammation including immunoglobulin E (IgE) production, T cell polarization to type 2 helper (Th2) cells, chemokine induction and subsequent leukocyte infiltration and activation, mucus production, barrier impairment, and end-organ dysfunction.

The central hypothesis of this study is that dupilumab is safe and efficacious for reducing eosinophilia, improving clinical parameters and a Th2 gene profile in EG. To this end, the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) will conduct a proof-of-principle, randomized, placebo-controlled trial in adolescents and adults with EG. *We will test the primary hypothesis that dupilumab will decrease gastric eosinophil levels in participants with EG compared with placebo-treated participants.* We will also test several secondary hypotheses concerning the clinical benefit of dupilumab, as well as the hypothesis that dupilumab will reverse IL-13 signature genes expressed in the gastric mucosa of EG patients, including *CDH26* and *CCL26* and genes of type 2 cytokines (*IL4*, *IL5*, and *IL13*). It is anticipated

that this study will provide proof-of-concept that EG is a type 2 allergic, immune-mediated disease and set the stage for the further development and eventual approval of a therapy for EG.

1.3. Preclinical Experience

None relevant to EG

1.4. Clinical Studies

Dupilumab has demonstrated efficacy and a favorable safety profile in adult participants with moderate-to-severe atopic dermatitis as well as asthma, and has been recently approved by the FDA and European Medicine Agency for individuals 12 years and older with atopic dermatitis, asthma and chronic rhinosinusitis with nasal polyps[6-9]. In patients with atopic dermatitis, dupilumab treatment reverses overexpression of genes common to type 2 atopic/allergic inflammation, including those observed in EG [10]. In participants with asthma, dupilumab improves the rates of severe exacerbations and lung function (e.g. as measured by increased forced expiratory volume (FEV1)), reduces the dosages of oral glucocorticoids, particularly in patients with relatively higher levels of blood eosinophils (>300 cells/mcl) [11]. In participants with chronic rhinosinusitis with nasal polyps, dupilumab (Dupixent®) reduces nasal polyp size, nasal congestion, the need for nasal polyp surgery and oral steroid usage and increases ability to smell [12]. In studies conducted by investigators associated with CEGIR, dupilumab has recently demonstrated clinical, endoscopic, and histologic efficacy in a phase II trial in EoE [13].

2. Study Hypotheses/Objectives

2.1. Hypotheses

The central hypothesis of this study is that dupilumab is safe and efficacious for reducing eosinophilia and a Th2 gene profile in EG.

2.2. Primary Objective for the Double-Blind Phase (DBP) Population

- To assess the efficacy of repeat subcutaneous (SC) doses of dupilumab, compared with placebo, to reduce eosinophilic inflammation in the gastrointestinal tract of participants with EG with or without concurrent esophageal and/or duodenal eosinophilia involvement.

2.3. Secondary Objectives for the DBP Population

- To assess the efficacy of dupilumab compared to placebo as measured by:
  - Patient global impression of severity (PGI-S)
  - Patient global impression of change (PGI-C)
  - Proportion of participants achieving threshold response < 30 eos/hpf in 5 hpfs
  - Eosinophilic Gastritis Endoscopy Assessment (EG-REFS)
  - Eosinophilic Gastritis Symptom Questionnaire (EG-SQ)

2.4. Exploratory Objectives for the DBP Population

- To assess the efficacy of dupilumab compared to placebo as measured by:
  - Severity of Dyspepsia Assessment tool (SODA)
  - Clinician global impression of severity (CGI-S)
  - Clinician global impression of change (CGI-C)

- Quality of Life Questionnaire (SF12, PROMIS 29, PROMIS 25)
- EoE Endoscopic Reference Score (EREFS) (participants with esophageal involvement)
- Comprehensive assessment of histologic features
- Blood and tissue biomarkers and gastric transcripts
- Peripheral eosinophil counts, hemoglobin & hematocrit, total protein and albumin, total IgE, iron storage panel (iron, ferritin, total iron-binding capacity)
- EG-QOL
- Eosinophilic Duodenitis- Endoscopic Reference Score (ED-EREFS)

2.5. Exploratory Objectives for the Open Label Extension (OLE) Population

- **Key objective:** To assess the efficacy of repeat SC doses of dupilumab to reduce eosinophilic inflammation in the gastrointestinal tract of participants with EG with or without concurrent esophageal and/or duodenal eosinophilia involvement.

- To assess the efficacy of dupilumab as measured by:
  - Patient global impression of severity (PGI-S)
  - Patient global impression of change (PGI-C)
  - Proportion of participants achieving threshold response < 30 eos/hpf in 5 hpfs
  - Eosinophilic Gastritis Endoscopy Assessment (EG-REFS)
  - Eosinophilic Gastritis Symptom Questionnaire (EG-SQ)

- To assess the efficacy of dupilumab as measured by:
  - Severity of Dyspepsia Assessment (SODA)
  - Clinician global impression of severity (CGI-S)
  - Clinician global impression of change (CGI-C)
  - Quality of Life Questionnaire (SF12, PROMIS 29, PROMIS 25)
  - EoE Endoscopic Reference Score (EREFS) (participants with esophageal involvement)
  - Comprehensive assessment of histologic features
  - Blood and tissue biomarkers and gastric transcripts
  - Peripheral eosinophil counts, hemoglobin & hematocrit, total protein and albumin, total IgE, iron storage panel (iron, ferritin, total iron-binding capacity)
  - EG-QOL
  - Eosinophilic Duodenitis- Endoscopic Reference Score (ED-EREFS)

3. Study Design

3.1. Description of Study Design

Potential participants will be screened during an 8-week screening period. An esophagogastroduodenoscopy (EGD) with biopsies will be performed to determine study eligibility, and participants will be enrolled based on the presence of active disease and their ability to meet the study inclusion and exclusion criteria. Qualifying participants will be blindly randomized 1:1 to either study drug

(dupilumab) or placebo and will receive 600 mg once followed by 300 mg doses every two weeks of study treatment (for a total of 6 injections). During the treatment period, participants will be monitored for adverse events/reactions and will complete patient reported outcome metrics to track their symptoms and general wellbeing. At the end of the 12-week randomized treatment period (EOT), a repeat endoscopy with biopsies will be performed to assess the change in gastric eosinophil count from pre-to-post treatment. Participants and site study staff will remain blinded to the endoscopy biopsy results until all participants have completed the DBP EOT visit. Study participants who complete the 12-week treatment phase (whether on drug or placebo) will have the option to continue into an open-label extension (OLE) and laboratory studies and patient reported outcomes will be completed as indicated in the schedule of activities (SOA). The OLE ensures that every participant gets access to the drug and will provide data on the effect of a longer treatment period in comparison to the initial 12 weeks in the double-blind phase. A final study EGD will be performed two weeks after the last dose of the study drug. All participants will be followed for an additional 12 weeks after the last dose of study drug regardless of whether they participate in the OLE. A summary of the protocol is depicted in Figure 1.

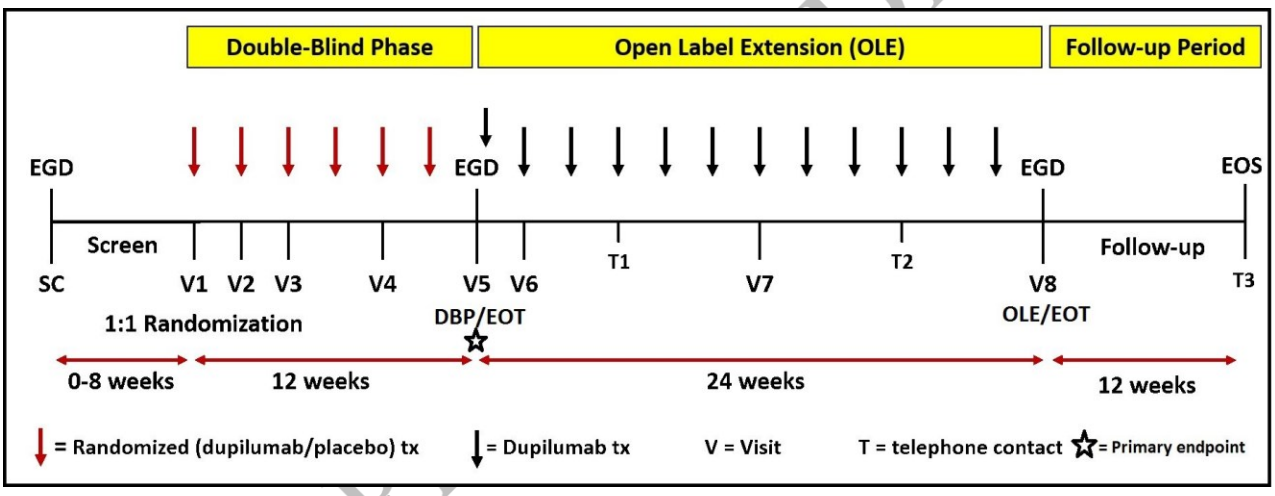

Figure 1. Schematic summary of clinical trial.

3.2. Primary Endpoint/Outcome for the DBP Population

- Relative change from baseline of the peak eosinophil counts in the 5 most eosinophil dense HPFs in the gastric antrum and/or body between drug vs placebo at 12 weeks. Relative change is defined as (week 12 – baseline)/baseline.

3.3. Secondary Endpoints/Outcomes for the DBP Population

- Absolute change in the mean of the peak eosinophil counts in the 5 most eosinophil dense HPFs in the gastric antrum and/or body between drug vs placebo at 12 weeks.
- Absolute change in the patient global impression of severity (PGI-S) score between baseline and post-treatment in dupilumab vs placebo at 12 weeks.
- Patient global impression of change (PGI-C) score between baseline and post-treatment in dupilumab vs. placebo at 12 weeks.
- Proportion of participants in dupilumab vs placebo achieving threshold response < 30 eos/hpf in all of the 5 hpfs identified for the primary endpoint

- Absolute change in endoscopic score from pre- to post-treatment with dupilumab or placebo as measured by Eosinophilic Gastritis Endoscopy Assessment at 12 weeks.
- Absolute change in the total EG-SQ eDiary score between baseline and post-treatment in dupilumab vs placebo at 12 weeks
- Absolute change in proportion of days with any (1 or more) symptom from pre- to post-treatment with dupilumab vs placebo as measured by the EG-SQ eDiary.

3.4. Exploratory Endpoints/Outcomes for the DBP Population

- Absolute change in participant reported outcomes from pre- to post-treatment with dupilumab or placebo as measured by additional PROs including the Severity of Dyspepsia Assessment tool as well as QOL instruments SF-12, PROMIS 29 and PROMIS 25 scores. We will also utilize clinician global impression of severity and clinician global impression of change.
- Absolute change in proportion of days with each individual symptom and multiple symptoms from pre- to post-treatment with dupilumab vs placebo as measured by the EG-SQ eDiary.
- Absolute change in each individual EG-SQ eDiary symptom score between baseline and post-treatment in dupilumab vs placebo at 12 weeks.
- Induction of disease remission defined by the percentage of participants who achieve histological remission in the stomach as defined by peak eosinophil counts less than 30/hpf in 1, 2, 3 and 4 of the 5 hpfs identified for the primary endpoint. Comparison between drug vs placebo at week 12 will be the measurement endpoint.
- Absolute change in histologic score from pre- to post-treatment with dupilumab or placebo as measured by the EG Biopsy Evaluation Form. For those participants with esophageal involvement or duodenal involvement, we will assess changes in histology using the EoE-HSS and ED Biopsy Evaluation Form respectively.
- Absolute and relative change in blood biomarkers (primarily cytokine levels) and tissue biomarkers as well as gastric transcripts from pre- to post- treatment.
- Absolute and relative change in blood eosinophil count, hemoglobin, hematocrit, total protein and albumin levels, total IgE, iron storage panel (iron, ferritin, total iron-binding capacity) from pre- to post- treatment with dupilumab or placebo.
- The association of blood and tissue biomarkers and transcripts with drug responsiveness.
- Assess histological changes in the esophagus and duodenum including peak eosinophil levels.
- Assess endoscopic changes in the esophagus and duodenum for those participants with involvement of these gastrointestinal segments using the EoE-EREFS and ED-EREFS, respectively.

3.5. Exploratory Endpoints/Outcomes for the OLE Population

There will be two key time points evaluated for the OLE. First, we will examine the overall change across the study (baseline to OLE/EOT (Week 24)). Second, we will examine change during the open label phase (DBP/EOT (Week 12) to OLE/EOT (Week 24)). These time points apply to all of the endpoints listed below.

- **Key Endpoint/Outcome:** Relative change of the peak eosinophil counts in the 5 most eosinophil dense HPFs in the gastric antrum and/or body

  Additional Endpoints

- Absolute change in the mean of the peak eosinophil counts in the 5 most eosinophil dense HPFs in the gastric antrum and/or body
- Absolute change in the patient global impression of severity (PGI-S) score
- Patient global impression of change (PGI-C) score
- Proportion of participants achieving threshold response < 30 eos/hpf in all of the 5 hpfs identified
- Absolute change in endoscopic score as measured by Eosinophilic Gastritis Endoscopy Assessment.
- Absolute change in the total and each individual EG-SQ eDiary symptom score
- Absolute change in proportion of days with each individual symptom, multiple symptoms, and any (1 or more) symptom as measured by EG-SQ eDiary
- Absolute change in participant reported outcomes as measured by additional PROs including the Severity of Dyspepsia Assessment as well as QOL (SF-12, PROMIS 29 and PROMIS 25) scores. We will also utilize clinician global impression of severity and clinician global impression of change.
- Induction of disease remission defined by the percentage of participants who achieve histological remission in the stomach as defined by peak eosinophil counts less than 30/hpf in 1, 2, 3 and 4 of the 5 hpfs identified for the primary endpoint.
- Absolute change in histologic score as measured by the EG Biopsy Evaluation Form. For those participants with esophageal involvement or duodenal involvement, we will assess changes in histology using the EoE-HSS and ED Biopsy Evaluation Form respectively.
- Absolute and relative change in blood biomarkers (primarily cytokine levels) and tissue biomarkers as well as gastric transcripts
- Absolute and relative change in blood eosinophil count, hemoglobin, hematocrit, protein levels, IgE, iron storage panel (iron, ferritin, total iron-binding capacity)
- The association of blood and tissue biomarkers and transcripts with drug responsiveness.
- Assess histological changes in the esophagus and duodenum including peak eosinophil levels.
- Assess endoscopic changes in the esophagus and duodenum for those participants with involvement of these gastrointestinal segments using the EoE-EREFS and ED-EREFS, respectively

3.6. Stratification, Randomization, and Blinding/Masking

Forty participants will be randomized in a 1:1 ratio to receive dupilumab or placebo. Randomization will be accomplished via a central variable block randomization scheme[14] provided by an independent statistician to the pharmacist of record (PoR). Block sizes will vary between 2 and 4. In addition, the randomization will be stratified based on age (≥ 12 and < 18 and ≥18) and whether the participant uses or does not use systemic corticosteroids (e.g. prednisone at daily dosage of 5 mg or higher), swallowed glucocorticosteroids for EG (Entocort), or systemic immunosuppression therapy at the time of randomization.

The investigators, pathologists, site staff other than the unblinded site pharmacist/pharmacy staff, and study participants will all remain blinded to treatment assignment until all participants complete the study. Blinded study drug kits coded with a medication numbering system will be used. In order to

maintain the blind, lists linking these codes with product lot numbers will not be accessible to blinded individuals involved in study conduct. Study site personnel will be blinded to the post-treatment endoscopy results until the completion of the double-blind phase of the study.

At the initiation of the OLE portion of the study, participants who were randomized to dupilumab for the double-blind phase will receive one 300 mg injection of dupilumab and one placebo injection, while participants who were randomized to placebo will receive two 300 mg injections of dupilumab. Clinical research staff and participants will be aware of the treatment being received during the OLE portion of the study, (except the first OLE dosage), as all participants will receive active treatment; neither the clinical research staff nor the participants will be told the original treatment assignment during the OLE portion of the study.

3.6.1. Masking of Investigational Product

To minimize the bias due to knowledge of the active and placebo treatment arms, the study will be double-blinded. Thus, the investigators and the participants, along with their caregivers if applicable, will be blinded to the assigned treatment regimens. As explained above, only unique code numbers for syringes assigned to each participant will be given to blinded clinical site staff for drug dispensation/administration purposes; treatment arm will not be divulged.

3.6.2. Procedure for Un-blinding/Unmasking

Un-blinding must be approved by the DAIT/NIAID medical officer (MO) unless an immediate life-threatening condition has developed and the MO is not accessible. In all cases of un-blinding, the MO will be notified immediately. The site investigator will notify the sponsor (Marc Rothenberg, MD, PhD) and the site Pharmacist of Record (PoR). The site PoR will provide the treatment assignment to the site investigator. The site investigator will notify the Data Management and Coordinating Center team of the un-blinding event by the next business day. The sponsor will notify the Independent Protocol Monitor by the next business day. The emergency un-blinding will also be reported to the Data and Safety Monitoring Board (DSMB).

A full account of the event will be recorded, including the date and time of the un-blinding, the reason for the decision to un-blind, and the name of the individual who made the decision and the names of the IPM and others who were notified. The reasons for un-blinding of a participant's treatment will be included in the final study report.

Un-blinding the study due to an approved interim analysis, final analysis, or study termination will require written approval from DAIT/NIAID.

4. Selection of Participants

4.1. Rationale for Study Population

We will enroll participants with EG that are active, defined by histological and clinical parameters. We will examine participants that are ≥ 12 and < 71 years of age. Dupilumab is currently FDA approved in this age range and is currently being studied even in children as young as 1 years old for other indications. We have included the adolescent population as evidence already exists that dupilumab is likely to be

efficacious in EG, based on positive phase 2 data in the related disease EoE. In addition, anecdotal off-label experience with dupilumab in select EG patients has shown preliminary positive effects.

Of note, we plan on including participants with EG who have involvement of eosinophilic inflammation in other gastrointestinal segments. Patients with EG may have eosinophilia in other parts of the gastrointestinal tract. Unpublished data from CEGIR suggests more than half of patients with EG also have esophageal and/or duodenal eosinophilia. Whether the pathophysiology of EG varies between patients with EG only and those with both EG and esophageal and/or duodenal eosinophilia is under research. In patients with active EG, the $EGDP_{18}$ score (a measure of disease severity derived from expression of 18 dysregulated genes linked to EG) showed consistency in patients with EG only compared to EG with esophageal involvement [15]. Further, EG patients with and without esophageal and/or duodenal eosinophilia universally responded to elimination diet therapy (Gonsalves et al, unpublished CEGIR data) suggesting similar EG pathology among these patients. Using sensitivity analysis this study will provide additional understanding as to whether the pathophysiology of EG is consistent in EG patients with and without esophageal and/or duodenal eosinophilia.

4.2. Inclusion Criteria for Double Blind Phase

Individuals who meet all of the following criteria are eligible for enrollment as study participants:

1. Participant and/or parent guardian must be able to understand and provide informed consent and/or assent prior to the study procedures being performed.

2. Willing and able to comply with study visits and activities.

3. Age ≥ 12 and < 71 years at study enrollment.

4. Histologically active EG at time of screening, with a peak gastric count of ≥ 30 eos/hpf in at least 5 hpfs in the gastric antrum and/or body with no other known cause for gastric eosinophilia; involvement of eosinophilic inflammation in other gastrointestinal segments will be allowed but not required or sufficient.

5. History (by patient report) of moderate to severe EG symptoms (stomach pain, stomach cramping, nausea, bloating, burning feeling in the chest, starting to eat and feeling full too quickly, loss of appetite, vomiting, or diarrhea) at least 2 days per week in the 2 weeks prior to screening.

6. EG symptoms (stomach pain, stomach cramping, nausea, bloating, burning feeling in the chest, starting to eat and feeling full too quickly, loss of appetite, diarrhea, or vomiting) at least 2 days per week in the two weeks leading up to V1 (randomization) documented via EG-SQ eDiary. At least 8 of 14 days must be entered in the EG-SQ eDiary in the 2 weeks prior to V1 (randomization).

7. Stable medical management of EG (and other eosinophilic disorders, if applicable) including stable dosage of medications in the 8 weeks prior to study enrollment. Participants may be on baseline anti-EG therapy (such as elimination diet, elemental diet, proton pump inhibitors, topical swallowed or systemic glucocorticoids (≤ 10 mg daily), immunosuppressive agents, cromolyn, and H1 and H2

anti-histamines) as long as there is agreement not to change their dosage unless medically indicated. See section 7.1 Concomitant and other Treatments for additional details.

8. Willing to maintain current dietary regimen throughout the course of the study. Diet must have been stable for 8 weeks prior to baseline endoscopy.

9. If have asthma and/or any other chronic allergic conditions (e.g., chronic rhinosinusitis with nasal polyposis), they must be willing to maintain their pretrial medications until the end of study. Medication dose can be increased if there is a deterioration in the condition.

10. Score on Asthma Control Test (ACT™) ≥ 20

4.3. Exclusion Criteria for Double Blind Phase

Individuals who meet any of these criteria are not eligible for enrollment as study participants:

1. Inability or unwillingness of a participant to give written informed consent or comply with study protocol.
2. Current active H. pylori infection. A history of H. pylori infection needs to have medical documentation of one of the three acceptable eradication tests: antigen, breath or histology.

3. Systemic gastrointestinal disorders such as Crohn's disease, inflammatory bowel disease, or Celiac disease.

4. Known or suspected active colitis (e.g., Eosinophilic colitis) in the Principal Investigator's opinion or by biopsy.

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

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

7. Current or recent use of biological agents (within 4 months or 5 half-lives, whichever is longer, prior to screening).

8. Leukocyte count has not returned to the relevant lower limit of normal per the reference range after discontinuing cell depleting biological agents.

9. Current or recent use of any investigational drug (within 3 months or 5 half-lives, whichever is longer, prior to screening).

10. Current use of systemic steroids with daily dose > 10 mg for any reason or steroid burst for > 3 days within 1 month of screening

11. Prior exposure to dupilumab.

12. History of anaphylaxis to any biologic therapy.

13. Current pregnancy or breastfeeding.

14. Ocular disorder that in the opinion of the investigator could adversely affect the individual's risk for study participation. Examples include, but are not limited to, individuals with a history of or active case of herpes keratitis; Sjogren's Syndrome, keratoconjunctivitis sicca or dry eye syndrome that require daily use of supplemental lubrication; or individuals with ocular conditions that require the regular use of ocular corticosteroids or cyclosporine.

15. Individuals who have required use of a systemic corticosteroid for asthma within 3 months prior to the Treatment Initiation Visit or who require a dose greater than 880 mcg/day of fluticasone propionate or equivalent inhaled corticosteroid to maintain asthma control.

16. Received live vaccine 30 days prior to screening or planning on receiving a live vaccine during the time period that he/she is participating in the study. Study participants are allowed to receive non-live vaccines during study participation.

17. Any esophageal stricture unable to be passed with a standard, diagnostic, 9 to 10 mm upper endoscope.

18. History of bleeding disorders or esophageal varices that, in the opinion of the investigator, would put the participant at undue risk for significant complications from an endoscopy procedure.

19. Active parasitic infection or suspected parasitic infection, unless clinical and/or) laboratory assessments have ruled out active infection before randomization or at high risk for contracting parasitic infections (e.g., living in or traveling to endemic areas).

20. History of alcohol or drug abuse within 6 months prior to screening.

21. Participant or his/her immediate family is a member of the investigational team.

22. Any of the following abnormal lab values at screening:
    - Platelets < 100 x 10^3/ µl
    - Neutrophils <1.5 x 10^3/µl
    - Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2
    - Absolute Eosinophil Count >5,000 cells/mcl

    NOTE: if an abnormal value is detected at screening, a repeat test should be performed to confirm the abnormality. Only if the repeat test confirms the abnormality would the participant be categorized as a screen failure.

23. Planned or anticipated major surgical procedure during the study.

24. Any of the following subcutaneous immunotherapy (SCIT):
    - Treatment with subcutaneous immunotherapy (SCIT) unless on a stable maintenance dose, which must be maintained throughout the study.
    - If build-up SCIT is stopped prior to enrollment, discontinuation of build-up SCIT must occur at least 10 weeks prior to screening.
    - If maintenance SCIT is stopped prior to enrollment, discontinuation of maintenance SCIT must occur at least 6 months prior to screening.

25. Treatment with sublingual immunotherapy (SLIT) within 6 months prior to screening.

26. Treatment with oral immunotherapy (OIT) within 6 months prior to screening.

27. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals or antifungals within 2 weeks before the baseline visit
    Note: participant may be re-screened after the infection resolves.

28. Known or suspected immunodeficiency disorder, including human immunodeficiency disorder (HIV) or a history of invasive opportunistic infections (e.g., tuberculosis [TB], non-tuberculous mycobacterial infections, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution or otherwise recurrent infections of abnormal frequency or prolonged infections suggesting an immune-compromised status as judged by the investigator.

29. Planned or anticipated use of any prohibited medications and procedures during the study.

30. Initiation, discontinuation or change in the dosage regimen of the following medications within 8 weeks prior to the baseline endoscopy:
    - Proton pump inhibitors (PPI)
    - Leukotriene inhibitors
    - Nasal and/or inhaled corticosteroids

    Participants on a stable dose of these medications for at least 8 weeks prior to the baseline endoscopy may be included in the study. PPI and leukotriene inhibitor dosing must not change during the study, but nasal and/or inhaled corticosteroids can be increased if there is a deterioration in the condition for which the medications are prescribed.

31. Women of childbearing potential who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 12 weeks after the last dose. Highly effective contraceptive measures include:

a. Stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) for at least one month prior to screening
b. Intrauterine device; intrauterine hormone-releasing system
c. Bilateral tubal ligation
d. Vasectomized partner
e. And/or sexual abstinence †‡

*Postmenopausal women must be amenorrhoeic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

†Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

‡Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female and male condom should not be used together

32. Past or current medical problems or findings from physical examination or laboratory testing that are not listed above, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.

4.4. Exclusion Criteria for Open Label Extension

A participant who meets any of the following criteria will not be permitted to enter the Open Label Extension portion of the study:

1. Participants who, during the double-blind treatment period, developed a serious adverse event (SAE) deemed related to study drug

2. Participants who, during the double-blind treatment period, developed an adverse event (AE) deemed related to study drug which in the opinion of the investigator could indicate that continued treatment with the study drug may present an unreasonable risk for the patient

3. Participants who, during the double-blind treatment period, were prematurely withdrawn because of a protocol violation, poor compliance or inability to complete required study assessments.

4. Participants who became pregnant during the double-blind treatment period.

5. Participants who are prematurely discontinued from study drug due to an AE. Participants who are prematurely discontinued from study drug, but not withdrawn from the study, due to lack of efficacy are eligible to enter the OLE.

6. Participants who did not undergo endoscopy with biopsies at the EOT (visit 5).

7. Systemic hypersensitivity to dupilumab or the excipients of the drug product based on participation in the double-blind phase of the trial.

8. Participants who are unable or unwilling to administer home doses of dupilumab during open label

5. Known and Potential Risks and Benefits to Participants

5.1. Risks of Investigational Product as cited in Investigator Brochure or Package Insert

There are no known serious side effects including infection risks in patients taking dupilumab based on existing data (see package insert [16] and investigator brochure). Based on trials to date, common adverse events (occurring in 10% or less of participants) include eye issues (e.g., conjunctivitis, blepharitis, keratitis, dry eyes), oral and other herpes simplex infections and injection site reactions. These were consistently mild-moderate and occurred with similar frequency between the treatment and placebo groups [16].

Conjunctivitis and keratitis occurred more frequently in atopic dermatitis participants who received dupilumab. Conjunctivitis was the most frequently reported eye disorder. Most participants with conjunctivitis recovered or were recovering during the treatment period. Keratitis was reported in <1% of the dupilumab group (1 per 100 subject-years) and in 0% of the placebo group (0 per 100 subject-years) in the 16-week monotherapy trials. In the 52-week dupilumab plus topical corticosteroids (TCS) trial, keratitis was reported in 4% of the dupilumab plus TCS group (12 per 100 subject-years) and in 0% of the placebo plus TCS group (0 per 100 subject-years). In the recent phase II EoE dupilumab study, conjunctivitis and keratitis were not seen. Study PIs should refer a participants to an ophthalmologist for any clinically significant ocular condition that develops during study participation. Based on post- marketing safety data, events of angioedema, arthralgia, keratitis and ulcerative keratitis are now considered adverse drug reactions (ADRs).

In recent asthma studies involving 2100 participants [11,17], dupilumab treatment was not associated with ocular side effects, but was associated with a small percentage of participants who developed transient hypereosinophilia (>3000 eosinophils/mcl) (e.g. 13% of participants on dupilumab vs 1% on placebo in study of oral glucocorticoid dependent participants and 1.2% vs 0.3% in the non-oral glucocorticoid dependent moderate-severe asthma participants). In the larger study involving 1902 moderate-severe asthma participants (not on oral glucocorticoids) studied over 52 weeks, blood eosinophilia was reported as an adverse event that emerged during the trial period in 52 participants (4.1%) who received dupilumab versus 4 participants (0.6%) who received placebo; in 0.2% of the total participant population, these adverse events were accompanied by clinical symptoms. Increased blood eosinophil levels were associated with symptoms in 4 participants who received dupilumab, and two of these events were reported as serious adverse events (worsening of hypereosinophilia and chronic eosinophilic pneumonia). A total of eight adverse events of eosinophilia (seven in participants who received dupilumab and one in

a participant who received placebo) resulted in permanent discontinuation of the assigned intervention. Per the trial protocol, all cases of an eosinophil count of more than 3000 per cubic millimeter during the 52-week intervention period were reported as adverse events. This event occurred in 1.2% of the participants in the combined dupilumab groups and 0.3% of those in the combined placebo groups.

In one study of patients with moderate to severe asthma, more patients on dupilumab reported serious adverse events involving the heart than patients on placebo. A similar imbalance has not been observed in other dupilumab clinical studies.

It is unknown if dupilumab will influence the immune response against helminth infections. But there is a theoretical risk of increased parasite infections; as such, participants with known helminth infections as well as those with increased risk will be excluded from participation in clinical studies.

Dupilumab can improve atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyposis symptoms, but medication changes should only be made in consultation with a physician. Participants will be made aware of this guidance. For those participants with asthma, a letter will be provided to alert the physician managing their asthma to contact the study physician if changes to the participant's asthma medication regimen will be made as a safety precaution.

5.1.1. Potential risk of hypersensitivity/allergic reactions

As with the administration of any foreign protein, acute allergic reactions and hypersensitivity reactions may occur, may be severe, and may result in death. Acute allergic reactions and hypersensitivity reactions may include hypotension, laryngeal edema, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, mental status changes, and unresponsiveness. There is a rare possibility of acute or late drug reaction (mild temporary abnormality of liver and renal function tests). Hypersensitivity reactions, including generalized urticaria, erythema nodosum, and serum sickness or serum sickness-like reactions have been reported in <1% of participants who received dupilumab in clinical trials. Two participants experienced serum sickness or serum sickness-like reactions that were associated with high titers of antibodies to dupilumab. Participants will be observed in the clinic for 30 minutes following their first 3 doses of study medication in double blind and first 2 doses during open label, in the event that anaphylaxis or a hypersensitivity reaction occurs. Based on the review of post-marketing data, signals of anaphylactic reaction and angioedema were confirmed and considered as ADRs.

5.1.2. Potential risks associated with immune reactivity

The administration of a monoclonal antibody (mAb) can result in the formation of anti-drug antibodies. The occurrence of anti-drug antibodies could result in immune complex disease or hypersensitivity type III (defined as disease resulting from immune-complex formation) with manifestations such as serum sickness, nephritis, and vasculitis, or altered dupilumab levels or activity. To date, no confirmed cases of immune complex disease have been observed and no appearance of a relationship between anti-drug antibodies and treatment-emergent adverse events (TEAEs) has been established.

5.1.3. Potential risk associated with malignancy

Since dupilumab targets the immune system, there is a theoretical risk of cancer, although this has not been observed in studies to date and mice with gene deletion of IL-4Rα do not develop spontaneous cancer but have an altered initiation and progression of cancer in at least one experimental model. To mitigate the potential risk of malignancies, the eligibility criteria excludes participants with a history of malignancy except in certain circumstances that are outlined (see Section 4.3, Exclusion Criteria 6).

5.1.4. Potential risks associated with vaccinations

Live Vaccines

Study participants should avoid the use of live vaccines during the study period since the possibility of an interaction exists, although this has not been reported to occur.

Non-Live Vaccines

Immune responses to vaccination were assessed in a study in which participants with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab (twice the recommended dosing frequency). After 12 weeks of dupilumab administration, participants were vaccinated with a Tdap vaccine (Adacel®) and a meningococcal polysaccharide vaccine (Menomune®). Antibody responses to tetanus toxoid and serogroup C meningococcal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated participants. Immune responses to the other active components of the Adacel and Menomune vaccines were not assessed. As such, there are no precautions with non-live vaccines.

5.2. Risks of Investigational Product cited in Medical Literature

Refer to Section 5.1 for reported risks.

5.3. Risks of Other Protocol Specified Medications

There are no other protocol specified medications.

5.4. Risks of Study Procedures

5.4.1. Esophagogastroduodenoscopy (EGD)

Endoscopy with biopsy is a well-established procedure, with few patients experiencing unexpected or serious complications. Biopsies are routinely collected from the esophagus, stomach, and duodenum during endoscopy, and collection of 24 biopsies or more is not uncommon (2-4 per site from sites of interest that may include including proximal esophagus, distal esophagus, gastric body, gastric antrum, gastric incisura, and duodenum).

The administration of anesthesia for medical procedures, such as EGDs, is generally very safe. The most common adverse effects include transient respiratory depression, anxiety, pruritus, nausea, vomiting and decreased blood pressure. The types of anesthesia used for procedures during this study will be participant-specific with decisions made by the treating provider. Prior to the use of any anesthesia, the licensed provider will discuss with the participant the potential risks and complications associated with the specific medications to be used. Throughout the administration of anesthesia, a licensed provider will be present, and procedures will be performed in accordance with the applicable standards at each of the

participating study site. At some sites this may include coronavirus disease (COVID-19) testing prior to the EGD.

5.4.2. Biopsies

The risks associated with collecting biopsies (up to a total of four obtained from each of the distal esophagus, gastric antrum, gastric body, as well as duodenum) for research at the time of the endoscopy include: bleeding at the site of tissue (biopsy) collection, and a small chance of perforation (hole) of the stomach, duodenum, or esophagus. Perforation is the most severe gastrointestinal complication, but generally it is self-resolving and poses no life-threatening risk. Transient bacteremia as a result of diagnostic EGD has been reported at rates as high as 8%, but the frequency of infectious endocarditis and other clinical sequelae is extremely low, such that current American Heart Association and American Society for Gastrointestinal Endoscopy guidelines do not recommend antibiotic prophylaxis with diagnostic EGD solely to prevent infectious endocarditis [18]. Using standard of care, pre-procedural instructions on fasting, the risk of aspiration during endoscopy is miniscule.

To minimize the risks of collecting biopsies during endoscopy, the procedure will be performed or supervised by a skilled endoscopist, and additional biopsies will only be collected if the endoscopist feels it is appropriate to do so.

5.4.3. Blood Draws

Risks associated with the collection of blood include bleeding, bruising, swelling, dizziness, fainting, and pain or infection at the site of blood draw. Blood draws will be performed by individuals with expert skills in phlebotomy. To minimize the additional risks associated with phlebotomy, blood will be obtained during the standard placement of intravenous lines when possible. Research centers may offer to apply a topical anesthetic (such as EMLA® or L.M.X) to the skin before blood draws to reduce the discomfort of the stick. Topical anesthetics are routinely used for venipunctures to minimize discomfort. The amount of blood drawn will adhere to institutional policy.

5.4.4. Patient Reported Outcomes (PRO)

There are no risks associated with patient-reported outcome measures, described in the Study Assessments section. However, some questions may be difficult or uncomfortable for participants to answer. All participants will be given ample time to complete the questionnaires, and participants may refuse to answer any questions that they are uncomfortable with.

5.4.5. Other Risks

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

It is possible that there are other unforeseen risks that we are not yet aware. There are no guaranteed benefits associated with study participation. Participants may experience reduced symptoms as a result

of treatment. Participants who complete the treatment period, whether on study drug or placebo, will be eligible to receive the drug during an open label extension.

Flexibility in the visit and dosing schedule has been added to this protocol in response to the COVID-19 pandemic. Allowing for this flexibility does not increase the risk of participating in this trial as there will be continued contact between the participants and study staff despite postponement of in-person clinic visits.

5.5. Potential Benefits

Dupilumab has demonstrated efficacy and a favorable safety profile in adult patients with moderate-to-severe atopic dermatitis, rhinosinusitis with nasal polyposis, as well as asthma, and has been recently approved for atopic dermatitis, asthma and chronic rhinosinusitis with polyps by the FDA and/or European Medicine Agency[6,8,9,12,19]. In patients with atopic dermatitis, dupilumab treatment reverses overexpression of genes common to type 2 atopic/allergic inflammation, including those observed in EG [10]. In studies conducted by investigators associated with CEGIR, dupilumab has recently demonstrated clinical, endoscopic, and histologic efficacy in a phase II trial in EoE [13]. Taken together, there is a potential benefit of treating EG patients with dupilumab.

Participants with comorbid atopic conditions (atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyposis) may experience improvement of those diseases.

6. Investigational Agent

6.1. Investigational Agents

6.1.1. Investigational Agent #1

The following information was taken from the dupilumab January 2021 package insert.

6.1.1.1. Formulation, Packaging, and Labelling

Dupilumab, an IL-4Rα antagonist, is a human monoclonal antibody of the IgG4 subclass that binds to the IL-4Rα subunit and inhibits IL-4 and IL-13 signalling. Dupilumab has an approximate molecular weight of 147 kDa. Dupilumab is produced by recombinant deoxyribonucleic acid (DNA) technology in Chinese Hamster Ovary cell suspension culture.

Clinical grade dupilumab is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for subcutaneous injection. Dupilumab is provided as a single-dose pre-filled syringe with needle shield in a 2.25 mL siliconized Type-1 clear glass syringe. Each pre-filled syringe delivers 300 mg dupilumab in 2 mL which also contains L-arginine hydrochloride (10.5 mg), L-histidine (6.2 mg), polysorbate 80 (4 mg), sodium acetate (2 mg), sucrose (100 mg), and water for injection, pH 5.9.

Dupilumab will be provided by Regeneron Pharmaceuticals, Inc. and will be shipped from Regeneron/Sanofi to DAIT/NIAID's drug distributor contractor for subsequent labelling and dissemination to the clinical sites' research pharmacies.

To allow for tracking each syringe will be assigned a unique code that is printed on labels attached to the syringe and syringe carton. Dupilumab should be stored in a refrigerator between 2°C - 8°C in its original carton to protect from light. Syringes should not be exposed to heat or direct sunlight. They should not be frozen or shaken and should be kept out of the reach of children. Additional packaging details should be followed.

6.1.1.2. Dosage, Preparation, and Administration

The dosing will be as described in the product label:

An initial dose of 600 mg (two 300 mg injections) will be administered at V1 and at V5 (for participants transitioning into open-label from placebo treatment to maintain blinding of double-blind treatment period) followed by 300 mg every other week.

At V5, participants transitioning from placebo will receive two 300 mg SC injections; participants transitioning from drug will receive one 300 mg SC injection and one placebo injection. Subsequent doses will continue at 300mg SC, every 2 weeks.

Before injection, the pre-filled syringe should be removed from the refrigerator and allowed to reach room temperature without removing the needle cap. The contents of the syringe should be inspected for particulate matter and/or discoloration prior to administration. If the liquid contents contain visible particular matter or are discolored or cloudy (other than clear to slightly opalescent, colorless to pale yellow), the syringe should not be administered.

Dupilumab should be administered by subcutaneous injection into the thigh or abdomen, except for the 2 inches (5 cm) around the navel. If a medical professional or caregiver is administering the injection, it may be given in the upper arm. Injection sites should be rotated with each injection, and different injection sites should be used for the two injections that make up the initial dose. Dupilumab should not be injected into skin that is tender, damaged, bruised or scarred. For adolescents, it is recommended that injections be administered by or under the supervision of a responsible adult.

If a dose is missed, it should be administered within 7 days of the ideal date and the original schedule should be resumed. If the missed dose is not administered within 7 days of the ideal date, the participant will be instructed to wait until the next dose on the original schedule. Doses should not be administered more frequently than once every 7 days.

Participants will be instructed by clinical staff on how to administer blinded home injections of dupilumab or placebo during visits 1, 2 and 3. The participant will be provided detailed written instructions for performing self-injections at home as well as the dosing schedule and a sharps bin. Injection administration technique and the dosing schedule will be reviewed at each clinic visit during the treatment period.

6.1.2. Investigational Agent #2 Placebo for Dupilumab

The composition of the placebo for dupilumab is the same as the active study drug without the dupilumab. The placebo for dupilumab is manufactured by Regeneron Industrial Operations and Product Supply Team in Rensselaer, New York. It will be packaged and labeled as described above for the dupilumab prefilled syringes.

6.1.2.1. Formulation, Packaging, and Labelling

The preparation and administration for the placebo dupilumab are the same as the active study drug.

6.1.2.2. Dosage, Preparation, and Administration

To maintain the blind, injection volumes will follow the initial and subsequent dosing instructions as per active dupilumab

6.2. Drug Accountability

Under Title 21 of the Code of Federal Regulations (21CFR §312.62) the investigator will maintain adequate records of the disposition of the investigational agent, including the date and quantity of the drug received, to whom the drug was dispensed (participant-by-participant accounting), returned from each participant (if applicable) and a detailed accounting of any drug accidentally or deliberately destroyed or returned to the manufacturer or designee.

Records for receipt, storage, use, and disposition will be maintained by the study site. A drug-dispensing log will be kept current for each participant. This log will contain the identification of each participant and the date and quantity of drug dispensed.

All records regarding the disposition of the investigational product will be available for inspection.

Any unused product will be returned to the Investigational pharmacy and destroyed according to facility guidelines after entering on accountability log.

6.3. Assessment of Participant Compliance with Investigational Agent

As explained above, dupilumab or its placebo will be tracked via unique box/syringe numbers that are printed on the box/syringe labels. Participants will be assigned specific syringe IDs through the randomization module. For doses administered subcutaneously (SQ) at clinic visits, box/syringe labels will be affixed to a case report form that indicates whether or not the full contents of the assigned syringe were administered. For doses administered SQ by participants at home, participants will record injection times and dates on a log provided by the study and used and unused syringes will be returned to the clinical site at the next clinical visit. Labels from these box/syringes will be affixed to case report forms that indicate whether or not the contents of the syringe were administered and the administration date, if applicable. Adherence will be determined by the number of injections received over the expected number of injections based on the protocol. The maximum number of doses that may be missed is one. If a participant misses more than one dose, the participant will be discontinued from study drug and will not be included in the per protocol analysis (see section 11.2). The participant will not be replaced.

6.4. Toxicity Management

Dose modification for an individual participant is not allowed. Study drug may be prematurely discontinued as delineated in Section 6.5.

Clinicians will be available 24/7/365 to respond to participant safety issues. Additional standard of care treatment will be administered as deemed necessary by the study physicians. Participants will be observed in the clinic for 30 minutes following their first 3 doses of study medication in double blind and first 2 doses during open label, in the event that anaphylaxis or a hypersensitivity reaction occurs.

Adverse Event listings will be reviewed at least monthly, as per Section 12.8.1, as a means of identifying potential safety signals associated with Dupixent® injections.

6.5. Premature Discontinuation of Investigational Agent

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

- Evidence of pregnancy.
- Suspected diagnosis of serum sickness related to the study drug (constellation of signs and symptoms that include arthritis/arthralgia, rash, fever, and lymphadenopathy).
- Clinical features of vasculitis.
- An infection that:
    - Requires parenteral treatment with an antibiotic, antifungal, antiviral, anti-parasitic, or antiprotozoal agent
    - Requires oral treatment with such agents for longer than 2 weeks
    - Is opportunistic, such as tuberculosis and other infections whose nature or course may suggest an immune-compromised status
- Anaphylaxis possibly related or related to investigational product according to the Sampson criteria (Appendix 1).
- A grade 3 injection site reaction.
- Evidence of non-compliance to study protocol such as missing more than one dose of study drug.
- The investigator feels that continuing use of the investigational product no longer in the best interest of the participant.
- Grade 3 or higher adverse event based on CTCAE 5.0 grading that is possibly related/related to the investigational product
- Grade 4 or higher adverse event based on AEC grading (Section 12.3.1, Table B) that is possibly related/related to the investigational product

7. Other Medications

7.1. Concomitant Medications and Other Treatments

There are no protocol mandated concomitant medications.

Throughout the study duration, all participants are expected to maintain the EG medication/diet regimen (including elimination diets) that was prescribed prior to study entry.

Other than the prohibited medicines listed in 7.3 concomitant medications are permitted.

Some examples of acceptable concomitant medications are:

- Proton Pump Inhibitors such as Esomeprazole (Nexium®), Lansoprazole (Prevacid®), Omeprazole (Prilosec®), Pantoprazole (Protonix®), and Rabeprazole Sodium
- Topical corticosteroids (including nasal, inhaled, swallowed, dermatologic). However, the dose of swallowed corticosteroids must not change during the course of the study. Nasal and/or inhaled corticosteroids may be increased if there is a deterioration in the condition for which the medications are prescribed but may not be decreased.
- Systemic corticosteroids if the dose is ≤ 10 mg daily. In the event a comorbid illness (e.g. asthma exacerbation) requires corticosteroids, a burst of 3 days or less is allowed as long as this treatment is not initiated 30 days prior to the end of treatment endoscopy. One-time use of a corticosteroid as a part of the anesthetic preparation used during each endoscopy procedure is allowed.
- Immunosuppressive Agents given for EG such as methotrexate, mercaptopurine and azathioprine.
- Cromolyn
- H1 and H2 Antihistamines (oral or nasal)
- If have asthma or any other chronic medical condition, they must be willing to maintain their pretrial medications until the end of study contact.

7.2. Prophylactic Medications

Research centers will offer to apply a topical anesthetic (such as EMLA® or L.M.X) to the skin before blood draws to reduce the discomfort of the stick. Topical anesthetics are routinely used for venipunctures to minimize discomfort.

7.3. Prohibited Classes of Drugs & Medications

Class of drug/Prohibited Medication Examples	**Washout Period Prior to Study Screening (i.e. Study Entry)**
Anti-immunoglobulin E [IgE] mAb/e.g., Omalizumab	4 months or 5 half-lives whichever is longer
Anti-tumor necrosis factor [TNF] mAb/e.g., Adalimumab, Certolizumab, Etanercept, Golimumab, Infliximab	4 months or 5 half-lives whichever is longer

AK002 (antolimab)	Return of baseline leukocyte counts and at least 4 months or 5 half-lives whichever is longer
Anti-IL-5 agents/e.g., benralizumab, mepolizumab, reslizumab	Return of baseline leukocyte counts and at least 4 months or 5 half-lives whichever is longer
Anti-IL-4 & Anti-IL-13 agents	4 months or 5 half-lives whichever is longer
Dupilumab	Absolute exclusion; no washout
Other investigative drugs or device	3 months or 5 half-lives, whichever is longer, prior to screening
Systemic steroids (daily dose > 10 mg or steroid burst for more than 3 days)	1 month
Live Vaccines	Should not receive 30 days prior to screening or throughout study participation.
Non-maintenance subcutaneous immunotherapy (SCIT)	10 weeks
Maintenance subcutaneous immunotherapy (SCIT)	6 months

7.4. Rescue Medications

Rescue/Supportive Medication/Class of drug:	**Usage:**
Study participants should continue their baseline medications and dietary therapy. Rescue medicines for EGID exacerbations are not allowed.	N/A

8. Study Procedures

8.1. Clinic Visit Procedures

8.1.1. Endoscopy (esophagogastroduodenoscopy) with Biopsies

Esophagogastroduodenoscopy (also known as upper endoscopy) is a well-established procedure, with few patients experiencing unexpected or serious complications. Biopsies are routinely collected from the esophagus, stomach, and duodenum during endoscopy, and collection of 24 biopsies or more is not uncommon (2-4 per site from sites of interest that may include including proximal esophagus, distal esophagus, gastric body, gastric antrum, and duodenum).

Endoscopy (esophagogastroduodenoscopy) with biopsies will be performed according to standard clinical procedures. Dilations will not be allowed until the last EGD associated with the OLE.

Biopsies will be collected from the following sites: three each from the proximal esophagus and distal esophagus, four from the duodenum (2 each from duodenal bulb and segment D2), four from the gastric body, and six from the gastric antrum, for a total of 20 biopsies.

8.1.2. Questionnaires

- **Severity of Dyspepsia Assessment (SODA): for both pediatric and adult participants**

This is a validated instrument to assess dyspepsia related health [20]. This patient questionnaire includes questions regarding abdominal pain and discomfort, burping, heartburn, bloating, passing gas, sour taste, nausea, and bad breath.

- **PROMIS: Patient Reported Outcomes Measurement Information System**

The PROMIS assessments[22] selected for this study are multi-purpose, short-form health surveys with 29 and 25 questions respectively. It yields a profile of general well-being. PROMIS 29 will be administered to adults (≥ 18 years old) and PROMIS 25 wil be administered to patients who are < 18 years old at consent.

- **Patient Global Impression of Severity (PGI-S)**

A single item which assesses the participant's impression of the overall EG severity in the past one week.

- **Patient Global Impression of Change (PGI-C)**

A single item which assesses the participant's impression of the overall change (improvement or worsening) in EG symptoms since initiation of the study injection.

- **Clinician Global Impression of Severity (CGI-S)**

A single item which assesses the physician's impression of the participant's overall EG severity.

- **Clinician Global Impression of Change (CGI-C)**

A single item which assesses the physician's impression of the participant's overall change (improvement or worsening) in EG since initiation of the study injection.

- **Short Form 12 Health Survey (SF-12 v2): for adult (≥ 18 years old) participants**

The SF-12 v2 is a validated questionnaire used to assess self-reported health-related quality of life. The survey has 12 questions that measure functional health and well-being from the patient's view.

- **EG-Quality of Life (EG-QOL): for adult (≥ 18 years old) participants**

The EG-QOL questionnaire was designed in a previous study by our group where participants with EG were interviewed about their experiences, as part of FDA requirements for PRO development.

- **EG-Symptom Questionnaire (EG-SQ): for all participants (both pediatric and adult)**

The EG-SQ is a patient-reported outcomes measure which assesses the frequency and severity of EG symptoms. This questionnaire will be administered daily using an electronic device (eDiary). Higher scores on the EG-SQ indicate greater symptom burden. The questionnaire assesses 9 symptoms associated with

EG (stomach pain, stomach cramping, nausea, bloating, burning feeling in the chest, starting to eat and feeling full too quickly, loss of appetite, vomiting, and diarrhea). Individual and total symptom scores can be calculated. Baseline scores will be calculated from the 14 days prior to V1 (week 0); end of double- blind treatment scores will be calculated from week 10 to week 12; and end of open label treatment scores will be calculated from week 22 to week 24.

- **Diet Assessment**

Information regarding the participants' current diet will be collected using a standardized form that captures any avoided foods, as well as the use of elemental formula and/or total parenteral nutrition (TPN) feeding. Although participants will be advised not to change their diet during the study, diet information will be reviewed at each visit to capture any changes.

- **Asthma Control Test™**

The Asthma Control Test™ questionnaire provides a numerical score to determine whether asthma symptoms are well controlled (ages 12 and older).

8.1.3. Physical examination

A physical examination will be performed at the time points indicated in Schedule of Activities (Table A). A full physical exam will be conducted at screening and brief targeted physical exams will be performed at other designated visits. A targeted physical exam by a licensed clinician will be performed when a participant reports an adverse event at any visit. A full physical exam will be performed on participants that withdraw from the study. Significant findings that are present prior to the start of the study must be included on the appropriate case report form (CRF) and will be assessed for exclusionary criteria. Significant findings that meet the definition of an adverse event (AE) must also be recorded on the AE form.

8.1.4. Vital signs

Vital signs, including height, weight, heart rate, blood pressure, and respiration rate, and body temperature will be measured per Schedule of Activities (Table A)

8.1.5. Laboratory testing

A venous blood sample will be obtained at multiple visits during the study (refer to Schedule of Activities (Table A)).

- **Complete Blood Count (CBC) with differential**

Repeat CBC with differential will be performed to measure changes in participants' blood eosinophil counts pre- and post-treatment and to monitor for anemia as per Schedule of Activities (Table A).

- **Iron Panel Tests**

Serum iron test, ferritin, and total iron binding capacity

- **Serum Chemistry**

Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, total bilirubin, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase will be measured as per Schedule of Activities (Table A).

- **Follicle Stimulating Hormone (FSH) Test**

A serum FSH test will be performed if there is a question regarding menopausal status.

- **Biomarker and genomic serum samples**

Blood for biomarker and DNA assays and Total IgE (description in Protocol Section 9.2) will be obtained as per Schedule of Activities (Table A).

- **Urinalysis-dipstick**

Specific gravity, pH, protein, glucose, ketones, blood, and leukocyte esterase (or nitrites) will be measured as per Schedule of Activities (Table A). Microscopic analysis will only be done at the discretion of the PI (see MOP) in the event of abnormal dipstick results.

- **Pregnancy Testing**

Pregnancy testing will be performed for all women of childbearing potential as per Schedule of Activities (Table A).

8.1.6. Schedule of Activities – Table A

Due to the public health emergency related to COVID-19, temporary alternative mechanisms to complete study procedures and drug administration may be required. All temporary mechanisms are described in section 8.4. If such mechanisms are utilized, they will be documented as related to COVID-19 and will only remain in effect during the public health emergency. Examples of such mechanisms include any of the following: phone contact, virtual visits, pick-up of study drug for home administration, use of local clinic or laboratory locations, and at-home pregnancy testing.

Schedule of Activities – Table A

Study Procedures	Screening	Double-blind Treatment							Open-label Extension													V8*	F/U**
Visit ID	SC	V1	V2	V3	V4		EOT/ V5* OLE		V6	T1			V7			T2						EOT	T3
Week (W)	W-8 to 0	0	2	4	6	8	10	12/0	2	4	6	8	10	12	14	16	18	20	22	24	36		
Window (days [d])	---	---	±3d	±3d	±2d	±3d	±2d	±3d	±3d	±2d	±3d	±2d	±2d	±3d	±2d	±2d	±3d	±2d	±2d	±3d	±3d		
Screening/Baseline																							
Informed Consent	x																						
Inclusion/Exclusion	x	x						x[1]															
Demographics, Med. History	x																						
Asthma Control Test (ACT)	x																						
Randomization		x[4]																					
Treatment																							
Training for self-injection		x	x	x																			
Administer study drug[3]		x	x	x	x[3]	x	x[3]	x[1]	x	x[3]	x[3]	x[3]	x[3]	x	x[3]	x[3]	x[3]	x[3]	x[3]				
Monitor 30 min post injection (including post dose vital signs)		x	x	x				x	x														
Dispense Take Home Drug				x		x			x					x									
Concomitant Medications	x	x	x	x		x		x	x		x			x			x			x			
Diet Assessment	x	x	x	x		x		x	x		x			x			x			x			
Efficacy																							
EGD with biopsies (histology, RNA, protein)	x							x												x			
Histologic features (HSS EG, EoE, ED form)	x							x												x			
Endoscopy assessments (EoE-EREFS, EG-REFS, ED-EREFS)	x							x												x			
EG-SQ (Electronic Diary)	Daily from Screening to End of Study ----------à																						
SODA§	x	x	x	x		x		x	x		x			x			x			x			
PROMIS 29‡		x						x												x			
PROMIS 25†		x						x												x			
EG-QOL‡		x						x												x			
SF12 Healthy Surveydo‡		x						x												x			
Patient global impression of severity (PGI-S)		x				x		x	x		x			x			x			x			

Schedule of Activities – Table A

Study Procedures	Screening	Double-blind Treatment							Open-label Extension												F/U**
Visit ID	SC	V1	V2	V3	V4		EOT/ V5* OLE		V6	T1			V7			T2				V8* EOT	T3
Week (W)	W-8 to 0	0	2	4	6	8	10	12/0	2	4	6	8	10	12	14	16	18	20	22	24	36
Window (days [d])	---	---	±3d	±3d	±2d	±3d	±2d	±3d	±3d	±2d	±3d	±2d	±2d	±3d	±2d	±2d	±3d	±2d	±2d	±3d	±3d
Patient global impression of change (PGI-C)						x		x	x		x			x			x			x	
Clinician global impression of severity (CGI-S)		x				x		x												x	
Clinician global impression of change (CGI-C)						x		x												x	
Safety																					
Vital Signs, Weight	x	x	x	x		x		x	x					x						x	
Height	x							x												x	
Physical Exam £	x	x		x				x												x	
Adverse Events	x	x	x	x		x		x	x		x			x			x			x	x
Laboratory Testing																					
Serum chemistry	x		x					x						x						x	
CBC with differential[2]	x	x	x	x		x		x	x	x[2]				x		x[2]				x	
Iron Panel		X						X												X	
Urinalysis	x		x					x						x						x	
Pregnancy test (or serum FSH)	Serum	Urine	Urine	Urine		Urine		Urine	Urine					Urine						Urine	
Biomarkers and Genomics																					
Biomarker blood and total IgE	x		x					x						x						x	
Blood DNA		x																			

[1]Only participants who elect to continue into OLE will have eligibility re-checked by investigator, and administration of study drug. [2]Will occur in local laboratory when not associated with visit. [3]Home administration [4]After confirming participant still meets inclusion/exclusion criteria, immediately contact the pharmacist to randomize the participant.

*End of treatment/early withdrawal visit (participants who withdraw will be asked to undergo end of treatment assessments).

**Follow-up should occur 12 weeks after the last injection (includes participants that withdraw prior to end of treatment).

‡Distribute to participates ≥18

†Distribute to participants ages 8-17.

§ Although technically validated for ≥18, distribute to participants of all ages.

£ A full physical exam will be conducted at screening and early withdrawal. Brief targeted physical exams will be performed at subsequent visits and when an AE is reported at any visit.

V, visit encounter. T, telephone encounter.

8.2. Enrollment/Recruitment

The research study will be explained in lay terms to each potential research participant. The potential participant or participant's parent or legal guardian will sign an informed consent form and the adolescent participant, if able to read and write, will sign assent, before undergoing any study procedures. Once the informed consent/assent is signed, the participant is considered enrolled in the study and will be assigned a unique participant identification number that will be used on CRFs and in all communications with external entities, such as the Data Center, centralized CEGIR pathology core, and central (CCHMC) lab.

Outreach to potential participants will occur through clinicaltrials.gov, patient advocacy groups, social media, and referrals from colleagues, through a review of local site medical records and clinical schedules. Potential participants may be contacted via phone, email, or in person once identified for initial discussions regarding the study. Interested participants will be provided with a copy of the IRB-approved consent document(s) and a detailed conversation about the study will take place. Any recruitment materials will be submitted to and receive IRB approval prior to implementation.

8.2.1. Screening Period (-8 to 0 weeks)

During the screening period (-8 to 0), informed consent will be obtained, and inclusion/exclusion criteria will be reviewed.

The following activities will occur:

- Consent
- Review eligibility criteria
- Demographics, Medical history
- Review of AE and concomitant medication
- Physical Examination
- Vital signs, and height, weight
- Blood draw (laboratory, biomarker (includes total IgE))
- Serum Pregnancy
- Diet assessment
- Questionnaires
- Screening endoscopy (biopsies, endoscopic features)
- ACT™ (Asthma Control Test) questionnaire

When the results of all screening activities are available, the PI will make a determination of study eligibility.

If it has been confirmed that a participant does not meet inclusion and/or exclusion criteria, the participant will be considered a screen failure. Screen failed participants may be re-screened up to two additional times at the discretion of the site investigator. If the screen failure was due to a concomitant medication that can be discontinued prior to rescreening, re-screening may be appropriate. Rescreening with repeat EGD (for failed eligibility scope) may occur at time points consistent with clinical care (every 2-3 months). The window during which a patient may rescreen for other entry criteria is the length of screening window

(8 weeks). Other potential reasons for rescreening (i.e. reasons unrelated to the inclusion/exclusion criteria) must be approved by the study principal investigator prior to rescreening the participant.

8.3. Baseline/Initiating Treatment

Visit 1 (Week 0)

- Review inclusion/exclusion criteria for final determination of study eligibility
- Urine pregnancy test
- Randomization
- Vital signs, and weight
- Physical Examination
- Review of AE and concomitant medication
- Blood draw (laboratory, genomic)
- Questionnaires
- Diet assessment
- Training of participant and/or caregiver on administration of injection
- Administer study medication (by clinic staff, patient, or caregiver)
- Post-treatment monitoring for 30 minutes

Participants or their caregivers are expected to complete supervised study product administration at a minimum of one clinic visit before the participant/caregiver administers injections at home.

8.4. Study Visits

8.4.1. Study Visits During Treatment Period

For visits 2 - 4, if COVID-19 restrictions prevent the staff or the participant from attending an in-clinic visit, participants may be dispensed study drug for pick-up for at-home dosing provided the participant/caregiver has completed at least one supervised study product administration and there are no specific safety concerns. A handout will be provided for guidance on identifying hypersensitivity reactions and what the participant should do in the event of a reaction. Research staff must assess adverse events, concomitant medications, and diet over the phone and provide at home monthly pregnancy test kit, if required. Vital signs pre- and post-dose may not be performed when COVID-19 restrictions prevent in-clinic visits. Questionnaires required at the visit should be administered over the phone. Participants will complete dosing diaries (paper CRFs) per the MOP.

Visit 2 (Week 2 ± 3 days)

- Urine pregnancy test

- Vital signs, and weight
- Blood draw (laboratory, biomarker (includes total IgE))
- Urinalysis
- Review of AE and concomitant medication
- Questionnaires
- Diet assessment
- Training of participant and/or caregiver on administration of injection
- Administer study medication (by clinic staff, patient, or caregiver)
- Post-treatment monitoring for 30 minutes

Participants or their caregivers are expected to complete supervised study product administration at a minimum of one clinic visit before the participant/caregiver administers injections at home.

Visit 3 (Week 4 ± 3 days)

- Urine pregnancy test
- Vital signs, and weight
- Physical exam
- Blood draw (laboratory)
- Review of AE and concomitant medication
- Questionnaires
- Diet assessment
- Training of participant and/or caregiver on administration of injection
- Administer study medication (by clinic staff, patient, or caregiver)
- Dispense take home drug
- Post-treatment monitoring for 30 minutes

Participants or their caregivers are expected to complete supervised study product administration at a minimum of one clinic visit before the participant/caregiver administers injections at home.

The investigator or other qualified staff must feel confident that participants or their caregiver can administer study product per the study protocol before they will be provided with study product for home administration. If needed, study drug administration may occur in-clinic at Week 6 and Week 10 with permission from the site PI.

~~Home self-administration of study drug~~ (Week 6 ± 2 days)

- Participants will self-administer study drug and complete the paper CRF's which they will bring to next clinic visit. If needed, study drug administration may occur in-clinic at Week 6 with permission from the site PI. A handout will also be provided for guidance on identifying hypersensitivity reactions and what the participant should do in the event of a reaction. Drug accountability will occur per the MOP.

Visit 4 (Week 8 ± 3 days)

- Urine pregnancy test
- Vital signs, and weight
- Blood draw (laboratory)
- Review of AE and concomitant medication
- Questionnaires
- Diet assessment
- Administer study medication (by clinic staff, patient, or caregiver)
- Dispense take home drug

Home self-administration of study drug (Week 10 ± 2 days)

- Participants will self-administer study drug at week 10 and complete the paper CRFs which they will bring to the next clinic visit. If needed, study drug administration may occur in-clinic at Week 10 with permission from the site PI. Drug accountability will occur per the MOP.

If visit 5/week 12 endoscopy with biopsies is delayed due to COVID-19 restrictions, extended blinded dosing of study drug is allowed for up to 8 weeks (4 doses) until the endoscopy can be performed. Accordingly, Visit 4 followed by home self-administration of study drug two weeks later can be repeated up to two times. If COVID-19 restrictions prevent the staff or the participant from attending the in-clinic visit (visit 4 or repeat visit 4), participants may be dispensed study drug for pick-up for at-home dosing provided there are no specific safety concerns. Research staff must assess adverse events, concomitant medications, diet, and provide at home monthly pregnancy test kit, if required, every 4 weeks. Questionnaires required at the visit should be administered over the phone. Participants will complete dosing diaries (paper CRFs) per the MOP.

Visit 5 DBP/EOT or Early Withdrawal (Week 12 ± 3 days, end of double-blind treatment)

- EGD with biopsies, endoscopic features
- Urine pregnancy test
- Physical Examination
- Vital signs, and height, weight
- Blood draw (laboratory, biomarker (includes Total IgE)
- Urinalysis
- Review of AE and concomitant medication
- Questionnaires
- Diet assessment

EOT assessments should occur within the 3 day visit window but do not have to be on the same day.

- For participants who wish to continue into the OLE, the investigator will assess and confirm their eligibility before they continue into the OLE.
- Participants who do not wish to continue into the OLE will discontinue treatment and be scheduled for their 12-week telephone contact.

8.4.2. Study Visits During Open-Label Extension Period (OLE)

Following the V5 EGD and EOT assessments, interested and eligible participants will begin the open-label extension, in which all participants will receive dupilumab every 2 weeks for an additional 12 doses (24 weeks). Participants who previously received placebo will have an initial dose of 600mg (2 syringes of dupilumab), whereas participants who previously received dupilumab will have an initial dose of 300mg (1 syringe of dupilumab and 1 syringe of placebo). All subsequent doses will be 300mg. Study drug dose will be determined by an unblinded pharmacist, and study blinding will be maintained for study participants and all other research staff. The open-label phase will last for 24 weeks and be followed by an EGD 2 weeks after the last dosage to assess endoscopic and histologic outcomes. All visit windows are calculated from the day of the first open-label drug administration (i.e. "Visit 5 OLE"). Home administration of dupilumab is expected starting at Week 4 of the OLE phase. The investigator or other qualified staff must feel confident that participants or their caregiver can administer study product per the study protocol before they will be provided with study product for home administration. Participants who are unable or unwilling to administer home doses of drug during open label will be withdrawn.

Visit 5 OLE (Week 12 ± 3 days)

- Review inclusion/exclusion criteria for determination of open label phase (OLE)
- Administer study medication (by clinic staff, patient, or caregiver)
- Post-treatment monitoring for 30 minutes

For visits 6 and 7, if COVID-19 restrictions prevent the staff or the participant from attending an in-clinic visit, participants may be dispensed study drug for pick-up for at-home dosing provided there are no specific safety concerns. A handout will be provided for guidance on identifying hypersensitivity reactions and what the participant should do in the event of a reaction. Research staff must assess AEs, concomitant medications, and diet, and provide at home monthly pregnancy test kit, if required. Questionnaires required at the visits should be administered over the phone. Participants will complete dosing diaries (paper CRFs) per the MOP.

Visit 6 (Week 2 ± 3 days)

- Urine pregnancy test
- Vital signs, and weight
- Blood draw (laboratory)
- Review of AE and concomitant medication
- Questionnaires
- Diet assessment
- Administer study medication (by clinic staff, patient, or caregiver)
- Dispense take home drug
- Post-treatment monitoring for 30 minutes

Home self-administration of study drug (Weeks 4 and 6 ± 2 days)

Participants will self-administer their next 2 doses of study drug and complete the paper CRFs which they will provide to the study staff per the MOP. A handout will also be provided for guidance on identifying hypersensitivity reactions and what the participant should do in the event of a reaction. Drug accountability will also occur per the MOP. Participants who are unable or unwilling to administer home doses of drug during open label will be withdrawn. Local lab CBC at Week 4 is required.

Telephone Visit 1 (Week 6 ± 3 days)

- Study staff will contact the participant by phone to check general updates, diet assessment, AEs, and medications.
- Participants will complete patient-reported assessments by phone or patient portal, as described in the SOA.

Home self-administration of study drug (Weeks 8 and 10, ± 2 days)

- Participants will self-administer their next 2 doses of study drug and complete the paper CRFs which they will provide to the study staff per the MOP. Drug accountability will also occur per the MOP. Participants who are unable or unwilling to administer home doses of drug during open label will be withdrawn.

Visit 7 (Week 12 ± 3 days)

- Urine pregnancy test
- Vital signs, and weight
- Blood draw (laboratory, biomarker (includes Total IgE))
- Urinalysis
- Review of AE and concomitant medication
- Questionnaires
- Diet assessment
- Administer study medication (by clinic staff, patient, or caregiver)
- Dispense take home drug

~~Home self-administration of study drug~~ (Weeks 14, 16 and 18, ± 2 days)

- Participants will self-administer their next 3 doses of study drug and complete the paper CRFs which they will provide to the study staff per the MOP. Drug accountability will also occur per the MOP. Participants who are unable or unwilling to administer home doses of drug during open label will be withdrawn. Local lab CBC at Week 16 is required.

~~Telephone Visit 2~~ (Week 18 ± 3 days)

- Study staff will contact the participant by phone to check general updates, diet assessment, AEs, and medications.
- Participants will complete patient-reported assessments by phone or patient portal, as described in the SOA.

Home self-administration of study drug (Weeks 20 and 22, ± 2 days)

Participants will self-administer their next 2 doses of study drug and complete the paper dosing diary which they will provide to the study staff per the MOP. Drug accountability will also occur per the MOP. Participants who are unable or unwilling to administer home doses of drug during open label will be withdrawn.

If visit 8 EOT/week 24 endoscopy with biopsies is delayed due to COVID-19 restrictions, extended open label dosing of study drug is allowed for up to 8 weeks (4 doses) until the endoscopy can be performed. Accordingly, participants may be dispensed study drug for pick-up for at-home dosing two times (2 doses may be picked up every 4 weeks) provided there are no specific safety concerns. Research staff must assess adverse events, concomitant medications, diet, and provide at-home monthly pregnancy test kit, if required, every 4 weeks. Questionnaires required at the visit should be administered over the phone. Participants will complete dosing diaries (paper CRFs) per the MOP.

Visit 8, EOT (Week 24 ± 3 days)

- EGD with biopsies, endoscopic features
- Urine pregnancy test
- Physical Examination
- Vital signs, and height, weight
- Blood draw (laboratory, biomarker (includes Total IgE))
- Urinalysis
- Review of AE and concomitant medication
- Questionnaires
- Diet assessment

8.4.3. Study Visit During Follow-up Period (12 weeks)

All participants will be followed for 12 weeks after the last dose of the study drug or placebo.

Telephone Visit 3 (Week 36 ± 3 days)

- AEs
- Pregnancy assessment
- End of study

8.4.4. Unscheduled Visits

An end of Treatment (EOT) visit, including EGD, will occur for participants who withdraw or are withdrawn early without withdrawing consent. In this circumstance, the EOT visit is considered 'unscheduled' since it will not occur during the time period specified in the 'Schedule of Activities'.

An unscheduled visit may also occur if a participant needs to be seen for a possible AE or a repeat blood draw needs to occur because of a possible laboratory abnormality, loss of a sample, or difficult obtaining the sample at the planned visit.

9. Mechanistic Assays & Tissue Evaluations

9.1. Tissue Biopsy Samples

In all participants, biopsies will be collected from the following sites: three each from the proximal esophagus and distal esophagus, four from the duodenum (2 each from duodenal bulb and segment D2), four from the gastric body, and six from the gastric antrum, for a total of 20 biopsies. . In general, all biopsies from each site (except for one) will be used for histological evaluations conducted in a blinded fashion by a centralized CEGIR pathology core using digital images of slides. The remaining block from one biopsy will be used for research. For mechanistic assays, ribonucleic acid (RNA) and protein isolation will also be performed from the remaining biopsy. The tissue blocks, RNA and protein samples will be entered into a DEGAS biorepository for long term storage at Cincinnati Children's Hospital.

If a patient must undergo an unplanned EGD (e.g., for a food impaction) as a clinical procedure, research biopsies are not mandatory but will be collected if feasible. The biopsies may be used for study mechanistic assays or for central pathology review. Medical records (including pathology reports) related to the procedure may be obtained for the purpose of obtaining data for statistical imputations in the event the participant withdraws from the study.

9.2. Blood Samples

Biomarker and genomic analyses will be performed including total IgE, cytokine protein array analysis, and next generation sequencing including RNA transcriptome profiling.

9.3. Evaluation of Eosinophilic Inflammation

All histological evaluations will be conducted in a blinded fashion by a centralized CEGIR pathology core using digital images of slides. Eosinophilic inflammation will be quantified by counting the number of eosinophils in biopsies from the stomach. In general, three of the four biopsies from each site will be evaluated for this purpose. The remaining biopsy will be retained for additional research evaluations. In the stomach, the mean peak eosinophil counts in the 5 most eosinophil-dense HPFs (in the body and antrum) will be used for comparison within participants and across groups. We will also compare the eosinophil levels pre/post treatment at each gastric biopsy location. We will also determine histological disease remission, defined as the percentage of participants who achieve peak eosinophil counts less than 30/hpf all hpfs in the antrum and body. We will also determine if all, 1, 2, 3, 4, or 5 sites have >30 eosinophils/hpf. If in a post-therapy biopsy all hpfs have < 30 eosinophils/hpf, then this will be considered a complete remission. If 1-4 hpfs have peak ≥30 eosinophils/hpf, then this will be considered a partial remission. If 5 or more HPFs have peak eosinophil >30 eosinophils/hpf, then this will be considered non-remission. In the esophagus, we will use ≥15 eosinophils/HPF in one field to define active disease. In the duodenum, we will we will use ≥30 eosinophils/HPF in 3 hpfs to define active disease.

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

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

9.5. Esophageal Histology Scoring System (HSS)

The HSS is a scale developed by Collins, et al. [24] to express the severity and extent of abnormalities in the esophagus. The HSS evaluates esophageal biopsies for various features (e.g. basal layer hyperplasia, dilated intercellular spaces, surface epithelial alteration, apoptotic epithelial cells), eosinophilic inflammation (peak count, eosinophil abscess, eosinophil surface layering), and lamina propria (fibrosis). The EoE-HSS will be completed on all participants.

9.6. Eosinophilic Gastritis Endoscopy Assessment (EG-REFS)

The Eosinophilic Gastritis Endoscopy Assessment is an endoscopic grading system that was specifically developed to evaluate eosinophilic gastritis and is completed by the endoscopist at the time of the EGD. It has been used in therapeutic trials and captures granularity (0-2 scale), erosion/ulceration (0-6), raised lesions (0-2), erythema (0-2), friability/bleeding (0-2), and pyloric stenosis (0-1) of the gastric fundus, body, and antrum.

9.7. Endoscopic Reference Score (EREFS)

The EREFS measures EoE esophageal mucosal inflammatory and remodeling features as identified during endoscopy. The score includes a total of 17 items related to the presence and severity of esophageal features. Specific esophageal features assessed include: rings (absent, mild, moderate, severe, not applicable); stricture (yes, no, not applicable); diameter of the stricture (if applicable); exudates (absent, mild, severe), furrows (absent, present); edema, (absent, present); crêpe paper esophagus (absent, present); overall general appearance incorporating all endoscopically identified EoE findings (i.e., fixed rings, strictures, whitish exudates, furrowing, edema, and crêpe paper mucosa). Mucosal changes associated with gastroesophageal reflux disease will also be recorded using the Los Angeles classification system for erosions (No Erosions or LA Classification A, B, C, D). The EREFS is a validated scoring system for the assessment of inflammatory and remodeling features of disease using both overall scores and scores for each individual characteristic [25]. The EoE-EREFS should be performed by the physician who performs the endoscopy procedure.

9.8. ED-Endoscopic Reference Score (ED-EREFS)

The ED-EREFS measures inflammatory and remodeling features in the duodenum identified during endoscopy.

10. Biospecimens

10.1. Storage

During the consent process, participants will be asked to give permission for long-term storage and future use of samples for tests that are not currently planned. The following deidentified bio-specimens will be securely stored at Cincinnati Children's Hospital Medical Center (CCHMC):

- Tissue biopsies

- DNA
- Blood (whole blood, plasma, serum)

Instructions for sample preparation, handling, storage and shipping are included in the MOP and lab manual. Principal Investigators (PIs) will be responsible for being aware of and observing all the regulations for classification, packaging and labeling, permits or authorizations and personnel training for shipment of biological and hazardous materials required for the conduct of this study.

11. Criteria for Participant and Study Completion and Premature Study Termination

11.1. Participant Completion

The primary outcome is reached when a participant completes the visit 5 EGD at the end of the double-blind phase. Participants complete study participation when they have completed the end of study (EOS) telephone check-in.

11.1.1. Participant Stopping Rules and Withdrawal Criteria

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

1. The participant elects to withdraw consent from all future study activities, including follow-up.
2. The participant is "lost to follow-up" (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).
3. The participant dies.
4. The Investigator no longer believes participation is in the best interest of the participant.
5. Participant develops severe complications from their EG or associated esophageal or duodenal eosinophilia that in the opinion of the investigator would preclude continuing in the trial (for instance acute anemia requiring transfusion, perforated ulcer, edema/refractory ascites, acute bleeding requiring hospitalization).
6. Participant has suspected serum sickness related to the study drug (constellation of signs and symptoms that include arthritis/arthralgia, rash, fever, and lymphadenopathy).
7. Participant requires EGID rescue medicines.
8. Participant requires prohibited medications, with the exception of 3 or less days of systemic corticosteroid for a comorbid illness within 30 days of the end of treatment endoscopy.
9. Participant becomes pregnant.
10. Participant develops a Grade 3 or higher adverse event based on CTCAE 5.0 grading that is possibly related/related to investigational product
11. Participant develops a Grade 4 or higher adverse event based on AEC grading (Section 12.3.1, Table B) that is possibly related/related to investigational product
12. Anaphylaxis possibly related or related to investigational product according to the Sampson criteria (Appendix 1).
13. Clinical features of vasculitis.
14. An infection that:

- Requires parenteral treatment with an antibiotic, antifungal, antiviral, anti-parasitic or antiprotozoal agent
- Requires oral treatment with such agents for longer than 2 weeks.
- Is opportunistic, such as tuberculosis, and other infections whose nature or course may suggest an immune-compromised status.

15. Participant misses more than one dose of study drug.
16. Participant is unable or unwilling to administer home doses of drug during the open label phase of the study.

11.1.2. Voluntary Participant Withdrawal

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

If a participant no longer wishes to receive injections, he/she will be given the option to withdraw from study treatment and continue to stay in the study to complete study assessments.

11.2. Participant Replacement

Participants will not be replaced. All participants who receive at least one dose of study drug will be included in the intent to treat analysis. Participants who miss more than 1 injection/dose will be discontinued from study drug and will not be included in the per protocol analysis. These participants will still undergo all assessments (they will not be withdrawn from the study). Participants who receive steroid medications for conditions unrelated to EG or associated esophageal or duodenal eosinophilia (e.g., steroids burst for asthma within 30 days of EOT endoscopy) will also not be included in the per protocol analysis. These participants will still undergo all assessments (they will not be withdrawn from the trial).

11.3. Follow-up after Early Study Withdrawal

Participants who withdraw will be asked to undergo End of Treatment (EOT) visit including EGD. Participants that withdraw early will not be entered into the OLE.

11.4. Study Stopping Rules

Study enrollment will be suspended pending Study Sponsor, DAIT NIAID, the central IRB and NIAID Allergy and Asthma DSMB expedited review of all pertinent data if any of the following occur:

- 1 death that is possible related/related to dupilumab
- One Grade 4 adverse event based on CTCAE 5.0 grading that is possibly related/related to dupilumab
- Two or more participants have a Grade 3 adverse event based on CTCAE 5.0 grading that is possibly related/related to dupilumab
- Two or more participants have a Grade 4 adverse events based on AEC grading (Section 12.3.1, Table B) that are possibly related/related to dupilumab.

The study may not be resumed until all pertinent information is discussed with the Study Sponsor, IPM, DAIT NIAID, NIAID Allergy and Asthma DSMB, and the central IRB, and all parties concur with the resumption of the study. Local IRBs will be informed of the study stoppage and the DSMB/Central IRB's decision on resumption of the study. The study may be terminated by DAIT/NIAID or the NIAID Allergy and Asthma DSMB upon review of any observations, events, or new information that merits such action. If the study is suspended or terminated, the Sponsor/principal investigator will notify the drug manufacturer, and regulatory agencies and the IRB will be notified as appropriate. Additionally, the study entry on clinicaltrials.gov will be updated to reflect that the study has been discontinued.

12. Safety Monitoring and Reporting

12.1. Overview

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of health authorities must be reported promptly (per Section 12.5, Reporting of Serious Adverse Events and Adverse Events) to Dr. Rothenberg, the study sponsor. Appropriate notifications will also be made to IPM, DAIT MO, DAIT PM, site Principal Investigators, Institutional Review Boards (IRBs), and health authorities.

Information in this section complies with International Conference on Harmonization (ICH) Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice, 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version5 : http://ctep.cancer.gov/reporting/ctc.html.

12.2. Definitions

12.2.1. Adverse Event (AE)

Any untoward or unfavorable medical occurrence associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from the office for human research protection (OHRP)) "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events(1/15/07)" http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2).

The investigator must report adverse events regardless of relationship to study therapy regimen or study mandated procedures. Preexisting diseases, conditions, or laboratory abnormalities present or detected before visit 1 (Treatment Initiation) will be considered AEs if they change in severity of grade from Visit 1.

For the study-mandated procedures below, only the signs and symptoms listed under each procedure will be considered outside normal range and will be recorded as an AE. These situations do not limit the Principal Investigator from reporting to the Study Sponsor any other events, associated or not with these procedures, as AEs. For all other study-mandated procedures, all AEs will be recorded:

Blood Draws

The following events related to the blood draw procedure will be considered AEs if they occur within 48 hours of the blood draw:

- Fainting/vasovagal events
- Bruising at puncture site larger than 2 cm diameter
- Bleeding from puncture site lasting more than 30 minutes
- Swelling at puncture site larger than 2 cm
- Allergic reaction to topical anesthetic that requires use of steroid medications

Endoscopy with Biopsy Collection

The following events related to the biopsy collection procedure will be considered AE's if they occur within 72 hours after the procedure:

- Bleeding that requires medical attention
- Infection
- Perforation

In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Definition of adverse events. Throughout the study, the investigator will record adverse events and serious adverse events on the appropriate AE/SAE paper CRF.

12.2.2. Suspected Adverse Reaction (SAR)

Any adverse event for which there is a reasonable possibility that the investigational drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

12.2.3. Unexpected Adverse Event

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator Brochure or package insert or is not listed at the specificity, severity or rate of occurrence that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the Investigational New Drug (IND) application.

"Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the Investigator Brochure or package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation (21 CFR 312.32(a).

12.2.4. Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Sponsor (Marc Rothenberg, MD, PhD) it results in any of the following outcomes (21 CFR 312.32(a)):

1. Death.
2. A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the investigator or Sponsor Dr. Rothenberg, its occurrence places the participant at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly or birth defect.
6. 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 above.

Elective hospitalizations will not be reported as an SAE unless hospitalization is prolonged due to complications.

12.3. Grading and Attribution of Adverse Events

12.3.1. Grading Criteria

The study site will grade the severity of adverse events experienced by the study participants, with the exception of peripheral eosinophilia, according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE; version 5.0; November 27, 2017). This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE has been reviewed by the study sponsor study sponsor (Marc Rothenberg, MD, PhD) and has been deemed appropriate for the participant population to be studied in this protocol.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual. A semicolon indicates 'or' within the description of the grade.

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) (e.g., shopping, preparing meals, using the phone, etc.)

Grade 3 = severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (e.g., bathing, dressing, feeding self, etc.)

Grade 4 = life-threatening consequences; urgent intervention indicated

Grade 5 = death related to AE.

AE's will be recorded on the appropriate AE paper case report for this study.

For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, an electrocardiogram etc.), a treatment-emergent adverse event is defined

as an increase in grade from baseline. Changes in grade from screening to baseline will also be recorded as adverse events but are not treatment-emergent. If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented as a result of the event/result.

The Principal Investigator will report elevated peripheral eosinophilia as an AE based on the following table indicating baseline absolute eosinophil count (AEC), absolute increases in eosinophil count and a corresponding AE grading scale. Participants with Grade 4 assessments of eosinophilia (after repeat determination over the period of one week) will be withdrawn. Participants with Grade 3 assessments will be evaluated by the investigator for continuation of the study therapy.

Table B: Absolute Eosinophil Count Adverse Event Grading Table V1.0

Grade	Screening AEC <500	Screening AEC 500-1000	Screening AEC 1000-1500	Screening AEC >1500
1	AEC >1000	AEC >1500	AEC >2000	Absolute increase >1000*
2	AEC>1500	AEC>3000	AEC>3000	Absolute increase >3000*
3	AEC>5000	AEC>5000	AEC>5000	Absolute increase >5000*
4	Hyper-eosinophilic disease requiring treatment	Hyper-eosinophilic disease requiring treatment	Hyper-eosinophilic disease requiring treatment	Hyper-eosinophilic disease requiring treatment
5	Death	Death	Death	Death

* compared with screening

12.3.2. Attribution Definitions

The relationship, or attribution, of an adverse event to the study therapy regimen or study procedure(s) will initially be determined by the site investigator and recorded on the appropriate AE/SAE paper CRF. Final determination of attribution for safety reporting will be determined by, sponsor (Marc Rothenberg, MD, PhD) after consultation with IPM and DAIT/NIAID. The relationship of an adverse event to study therapy regimen or procedures will be determined using the descriptors and definitions provided in Table 12.3.2.

For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site: http://ctep.cancer.gov/reporting/ctc.html.

Table 12.3.2 Attribution of Adverse Events

Code	Descriptor	Relationship (to primary investigational product and/or other concurrent mandated study therapy or study procedure)
UNRELATED CATEGORY		
1	Not Related	The adverse event is clearly not related: there is insufficient evidence to suggest a causal relationship.

RELATED CATEGORIES		
2	Possibly Related	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Related	The adverse event is clearly related.

Additional Considerations for Causality of Adverse Events

Exposure:

- Is there evidence that the participant was actually exposed to the investigational product such as: reliable history, acceptable compliance assessment, expected pharmacological effect or measurement of drug/metabolite in bodily specimen?

Time Course:

- Did the AE follow in a reasonable temporal sequence from administration of the investigational product?
- Is the AE onset compatible with a drug-induced effect?

Likely Cause:

- Is the AE not reasonably explained by another etiology such as an underlying disease, other drug(s)/vaccine(s) or other host or environmental factors?

12.4. Collection and Recording of Adverse Events

12.4.1. Collection Period

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

12.4.2. Collecting Adverse Events

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

- Observing the participant.
- Interviewing the participant [e.g., using a checklist, structured questioning, diary, etc.] .
- Receiving an unsolicited complaint from the participant.
- Reviewing the participant's electronic medical record during study participation.
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 12.3, *Grading and Attribution of Adverse Events.*

12.4.3. Recording Adverse Events

Throughout the study, the investigator will record adverse events and serious adverse events as described previously (Section 12.2, *Definitions)* on the appropriate paper AE/SAE CRF regardless of the relationship to study therapy regimen or study procedure.

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the participant prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

12.5. Reporting of Serious Adverse Events and Adverse Events

12.5.1. Reporting of Serious Adverse Events to Sponsor (Dr. Marc Rothenberg)

This section describes the responsibilities of the site investigator to report serious adverse events to the sponsor (Marc Rothenberg, MD, PhD) via paper CRFs, facsimile, electronically, or by phone. Timely reporting of adverse events is required by 21 CFR and ICH E6 guidelines.

Site investigators will report to the sponsor (Marc Rothenberg, MD, PhD) and the IPM all serious adverse events (see Section 12.2.4, *Serious Adverse Event*), regardless of relationship or expectedness within 24 hours of discovering the event.

For serious adverse events, all requested information on the AE/SAE paper CRF will be provided. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the paper AE/SAE CRF will be updated and submitted.

Additionally, All SAEs, regardless of assessment of causal relationship to study drug, must be reported to Regeneron within 24 hours.

Fax SAE/CIOMS or MedWatch Reports to 914-345-7476

Email Form: **medical.safety@regeneron.com**

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

12.5.2. Reporting of Unexpected and Study-Related Non-Serious Adverse Events

An unexpected, non-serious adverse event that is of Grade 2 severity or higher and study related will be recorded and reported to the sponsor and IPM under the serious adverse event reporting procedure above (i.e., within 24 hours).

12.5.3. Reporting to the U.S. Food and Drug Administration (FDA)

After an adverse event requiring 24 hour reporting (per Section 12.5.1, Reporting of Serious Adverse Events to Sponsor) is submitted by the site investigator and assessed by the sponsor and IPM there are two options for the sponsor to report the adverse event to the appropriate health authorities:

12.5.3.1 Annual Reporting

The sponsor will include in the annual study report to the FDA, IRB, DSMB, and Sanofi/Regeneron all adverse events classified as:

- Serious, expected, suspected adverse reactions (see Section 12.2.2, *Suspected Adverse Reaction,* and Section 12.2.3, *Unexpected Adverse Event*).
- Serious and not a suspected adverse reaction (see Section 12.2.2, *Suspected Adverse Reaction*).
- Pregnancies.

12.5.3.2 Expedited Safety Reporting

This option, with two possible categories, applies if the adverse event is classified as one of the following:

Category 1: **Serious and unexpected suspected adverse reaction** [**SUSAR]** (see Section 12.2.2, *Suspected Adverse Reaction (SAR)* and Section 12.2.3, *Unexpected Adverse Event* and 21 CFR 312.32(c)(1)i).

The sponsor shall report any suspected adverse reaction that is both serious and unexpected. The sponsor shall report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study drug and the adverse event, such as:

1. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure;
2. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug;
3. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Certain SAEs occur commonly in this study population and will not be considered as a SUSAR unless there is evidence to suggest a causal relationship to the study drug, dupilumab. These events will be captured in the study database but will not be reported as expedited Safety Reports.

Category 2: **Any findings from studies that suggests a significant human risk**

The sponsor shall report any findings from other epidemiological studies, analyses of adverse events within the current study or pooled analysis across clinical studies or animal or in vitro testing (e.g. mutagenicity, teratogenicity, carcinogenicity) that suggest a significant risk in humans exposed to the drug that would result in a safety-related change in the protocol, informed consent, investigator brochure or package insert or other aspects of the overall conduct of the study.

The IND Sponsor, Marc Rothenberg, MD, PhD, shall notify the FDA of the fatal or life-threatening SUSAR(s) and IND Safety Reports within 7 and 15 calendar days of IND Sponsor awareness, respectively. The IND Sponsor will provide the IND Safety Reports to the Investigational Drug Product Manufacturers and all participating PIs.

12.5.4. Standard Reporting (report in the IND Annual Report)

All AEs as per 21 CFR 312.33, as well as all pregnancies, will be recorded by the study sites, reported to the IND Sponsor, and included in the IND Annual Report submitted to the FDA by the IND Sponsor.

12.5.5. Reporting of Adverse Events to IRBs/IECs

All investigators shall report AEs and SAEs in a timely fashion to their local and central IRB in accordance with applicable regulations and guidelines.

12.5.6. Reporting of Other Safety Information

A PI shall promptly notify the IND Sponsor, the IPM, and the DAIT/NIAID Medical Monitor and DAIT Project Manager (PM) when an "unanticipated problem involving risks to participants or others" is identified, which is not otherwise reportable as an AE.

12.6. Pregnancy Reporting

The investigator shall be informed of any pregnancy in a female study participant immediately upon becoming aware of the event. Study treatment will be discontinued for the pregnant participant. The investigator shall counsel the female participant and discuss the risks of continuing the drug during pregnancy and the possible effects on the fetus. Monitoring of the pregnant participant shall continue until the conclusion of the pregnancy. The investigator shall report to the IND Sponsor and IPM all pregnancies within 24 hours of becoming aware of the event. All pregnancies in female participants identified during the study shall be followed to conclusion, and the outcome of each must be reported. The Pregnancy paper CRF shall be updated when details about the outcome are available.

Information requested about the delivery shall include:

- Gestational age at delivery
- Birth weight, length, and head circumference
- Gender
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, 5 minutes, and 24 hours after birth, if available
- Any abnormalities.
    - Any complication to pregnancy such as a congenital abnormality or birth defect shall be submitted as an SAE to the sponsor, IPM, DAIT MO and DAIT PM using the SAE reporting procedures described above.
    - The investigator shall report to the sponsor (Marc Rothenberg, MD, PhD) and IPM all pregnancies within 24 hours of becoming aware of the event.

Female participants that become pregnant during the study will be referred to the *Pregnancy Exposure Registry per the Dupixent package insert.*

12.7. Reporting of Other Safety Information

An investigator shall promptly notify the sponsor (Marc Rothenberg, MD, PhD), IPM, DAIT MO and DAIT PM when an "unanticipated problem involving risks to participants or others" is identified, which is not otherwise reportable as an adverse event.

12.8. Review of Safety Information

12.8.1. Independent Protocol Monitor (IPM) Review

The IPM will receive notification of all SAEs within 24 hours of notification by the Investigator and will make decisions on expedited safety reporting. The DAIT/NIAID medical officer will be notified about the event and the decision on expedited safety reporting within 24 hours of the IPM decision.

The IPM will receive monthly reports from the Data Center compiling new and accumulating information on AEs. The Sponsor, Medical Vigilance Solutions and DAIT/NIAID medical officer will also receive these monthly reports.

12.8.2. DSMB Review

12.8.2.1 Planned DSMB Reviews

The DAIT/NIAID Data and Safety Monitoring Board (DSMB) shall review safety data annually from the first participant randomized. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs.

12.8.2.2 *Ad hoc* DSMB Reviews

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for ad hoc reviews. The DSMB will review any event that potentially impacts safety at the request of the Sponsor/protocol chair, IPM, or DAIT/NIAID medical officer. In addition, the events described in Section 11.4 (Study Stopping Rules) will trigger an ad hoc comprehensive DSMB Safety Review. After review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

12.8.2.2.1 Temporary Suspension of *Enrollment* for *ad hoc* DSMB Safety Review

A temporary halt in enrollment will be implemented if an ad hoc DSMB safety review is required. New participants will not be consented for study participation during the enrollment halt. Participants already on therapy will continue dupilumab or placebo treatment. Participants screened but not yet randomized will not be allowed to continue with the Day 0 Treatment Initiation Visit. All participants not randomized within 12 days of the Screening Visit must rescreen.

13. Statistical Considerations and Analytical Plan

13.1. Overview

To assess the efficacy of repeat subcutaneous (SC) doses of dupilumab, compared with placebo, to reduce eosinophilic inflammation in the stomach of EG participants in a phase 2, multi-center, randomized, double-blind, placebo-controlled trial. The participants will have histologically active EG, ongoing clinical symptoms prior to enrollment and are between 18-70 years old at the time of enrollment.

This section describes the statistical methods to be used for the analysis of the data from the study. A separate Statistical Analysis Plan (SAP), which will be documented as completed prior to unblinding the study, will describe data handling and statistical analysis approaches in detail and will augment the

statistical methods described in the protocol. The SAP will detail any modifications to the analysis plan described below.

13.2. Endpoints

Refer to sections 3.2 – 3.5 outlined in protocol above.

Primary Endpoint:

Relative change from baseline of the peak eosinophil counts in the 5 most eosinophil dense HPFs in the gastric antrum and/or body between drug vs placebo at 12 weeks in the intent to treat population. This information will be gathered by collecting biopsies at the 12-week visit, which are converted into slides, and then evaluated on Histology Scoring Sheets by the central pathology core.

Secondary Endpoints:

Additional endpoints will be evaluated in both the intent to treat and the per protocol population. The per protocol population analyses will be secondary (sensitivity) analyses. Participants who complete the blinded phase and who do not have any major protocol deviations will be considered in the per protocol set. Examples (not all inclusive) of major protocol deviations include missing more than one dose of IP or steroid use within 30 days of endoscopy.

Change in the absolute mean of the peak eosinophil counts in the 5 most eosinophil dense HPFs in the gastric antrum and/or body between drug vs placebo at 12 weeks.

Absolute change in the patient global impression of severity (PGI-S) score between baseline and post-treatment in dupilumab versus placebo at 12 weeks.

Patient global impression of change (PGI-C) score between baseline and post-treatment in dupilumab vs placebo at 12 weeks.

Proportion of participants in dupilumab vs placebo achieving threshold response < 30 eos/hpf in all 5 hpfs identified for the primary endpoint.

Absolute change in endoscopic score from pre- to post-treatment with dupilumab or placebo as measured by Eosinophilic Gastritis Endoscopy Assessment at 12 weeks. The Endoscopy Assessments will be gathered at the screening visit and the visit 5 end of treatment visit at the end of the double-blind treatment period. For those participants with esophageal and duodenal involvement, we will also assess the EoE-EREFS and ED-EREFS.

Absolute change in the total EG-SQ eDiary score between baseline and post-treatment in dupilumab vs placebo at 12 weeks.

Absolute change in proportion of days with any (1 or more) symptom from pre- to post-treatment with dupilumab vs placebo as measured by the EG-SQ eDiary.

Exploratory Endpoints:

We will evaluate the absolute change in PROs during the double blind period and the OLE treatment period. Exploratory PROs will include the Severity of Dyspepsia Assessment tool as well as a QOL (SF-12, PROMIS 29 and PROMIS 25) scores. We will also utilize clinician global impression of severity and clinician global impression of change. The SODA will be collected at the screening visits and all study visits (visits 1, 2, 3, 4 & 5) during the double-blind and OLE treatment periods.

The induction of disease remission defined by the percentage of participants who achieve histological remission in the stomach as defined by peak eosinophil counts less than 30/hpf in 1, 2, 3 and 4 of the 5 hpfs identified for the primary endpoint. Comparison between drug vs placebo at week 12 will be the measurement endpoint. This information will be gathered by collecting biopsies at the 12-week visit, which are converted into slides, and then evaluated on Histology Scoring Sheets by the central pathology core.

The absolute change in histologic score from pre- to post-treatment with dupilumab or placebo as measured by the EG Biopsy Evaluation Form. For those participants with esophageal involvement or duodenal involvement, we will assess absolute changes in histology using the EoE-HSS and ED Biopsy Evaluation Form respectively. The biopsy evaluation forms will be gathered at the screening visit and the visit 5 end of treatment visit at the end of the double-blind treatment period.

The absolute and relative change in blood biomarkers (primarily cytokine levels) and tissue biomarkers as well as gastric transcripts before and after treatment. The blood biomarkers will be evaluated at the screening visit and visits 1 and 5 of the double-blind treatment period.

The absolute and relative change in blood eosinophil count, hemoglobin, hematocrit, protein levels, IgE, iron storage panel (iron, ferritin, total iron-binding capacity) before and after treatment with dupilumab or placebo (total protein and albumin levels). The CBC with differential will be gathered at the screening visit and all visits (visits 1, 2, 3, 4 & 5) during the double-blind treatment period. The serum chemistry will be evaluated at the screening visit and visits 2 and 5 of the double-blind treatment period.

The association of blood and tissue biomarkers and transcripts with drug responsiveness.

Assess histological changes in the esophagus and duodenum including peak eosinophil levels. This information will be gathered on the EoE Histological Scoring System and ED Biopsy Evaluation Forms respectively at the EOT visit at the end of the double-blind treatment period.

Assess endoscopic changes in the esophagus and duodenum for those participants with involvement of these gastrointestinal segments, using the EoE-EREFS and ED-EREFS, respectively.

The absolute change in proportion of days with each individual symptom and multiple symptoms from pre- to post-treatment with dupilumab vs placebo as measured by the EG-SQ ediary.

The absolute change in each individual EG-SQ eDiary symptom score between baseline and post-treatment in dupilumab vs placebo at 12 weeks.

13.3. Safety Assessment:

A list of AE's/SAE's based on data collected in the study will be recorded and tabulated for the drug and placebo cohorts.

13.4. Measures to Minimize Bias

Randomization will be accomplished via a central variable block randomization scheme [14] provided by an independent statistician to the study pharmacist (or qualified designee). Block sizes will vary between 2 and 4. In addition, the randomization will be stratified based on age (≥ 12 to < 18 and ≥18 years) and whether the patient uses or does not use systemic corticosteroids, (e.g. prednisone at daily dosage of 5 mg or higher), swallowed glucocorticosteroids for EG (Entocort), or other systemic immunosuppression therapy at the time of randomization. The randomization schema will ensure that potential confounding factors are equally distributed among the placebo and drug treatment groups and will eliminate 'researcher selection bias'.

The investigators, site staff other than the unblinded site pharmacist/pharmacy staff, pathologists, and study participants will all remain blinded to treatment assignment and IgE levels throughout the trial (IgE will be analyzed after participants have completed the study). The IPM, DAIT/NIAID MO, DAIT/NIAID PM, and any other personnel designated by the sponsor (Dr. Rothenberg as PI of the study) who have regular contact with the study site will remain blinded to all treatment assignments.

13.5. Analysis Plan

13.5.1. Analysis Populations

Patient drop out is always a concern for clinical trials as if the participants who drop out are not missing at completely random (MCAR), the results may be biased. Based on our prior study of diet and eosinophilic esophagitis, a related eosinophilic condition of the gastrointestinal tract, we expect a low rate of participant drop out (3.9%). Missing data below 5% is considered negligible, and many studies use only the complete data [26]. However, our analytic strategy will be to include all randomized participants who receive study drug (complete V1; intent to treat sample) in the primary analyses. The per protocol population analyses will be conducted as secondary (sensitivity) analyses for all outcomes. Participants who complete the blinded phase and who do not have any major protocol deviations will be considered in the per protocol set. Examples (not all inclusive) of major protocol deviations include missing more than one dose of IP or steroid use within 30 days of endoscopy.

13.5.2. Primary Analysis of Primary Endpoint

The primary outcome measure will be the relative change from baseline from week 0 to week 12 in the mean of the eosinophil counts from the 5 worst microscopic fields in the gastric antrum and/or body in the intent to treat population. Relative change is defined as (week 12 – baseline)/baseline. Regression analyses will be performed with the primary outcome measure as the dependent variable and treatment group as the independent variable. Appropriate transformations, such as a log-transformation, may be used to satisfy the distributional assumptions prior to model fitting. If there are continued concerns about data distributions, equivalent nonparametric tests will be employed. To ensure that immunosuppression (e.g. corticosteroid, swallowed glucocorticosteroids for EG (Entocort), or immunosuppressive agents) use does not influence results, we will also perform regression analyses with corticosteroid/immunosuppression therapy as a covariate (including considering binary (y/n), and dose (none, low, high). Statistical testing will be performed at the two-sided 5% level of significance.

Because we will be using an intent to treat model, all individuals completing study visit 1 will be included in the analysis of the primary outcome including participants receiving steroids within the last 30 days before endoscopy. Because early termination/withdrawal of the study is possible, missing outcome data must be imputed. First, we will evaluate the patterns of missing data to help us understand whether the data may be missing at random. Specifically, we will review patient drop out reasons and baseline patient characteristics. We will then use multiple imputation which will allow us to handle the data whether missing at random or missing not at random, leveraging the longitudinal data collected. Factors to be considered in the multiple imputation are the prior eosinophil counts, participant clinical characteristics and longitudinal secondary outcomes.

To ensure the robustness of our missing data approach, analyses will also be conducted among participants that completed the study at 12 weeks (per protocol) as sensitivity analysis. If differences occur between the results of the two analyses, we will explore the data to understand the pattern of missingness, using tipping point analysis to understand the impact of the missing data on inference, and consider additional imputation or utilize longitudinal data analyses.

For the intent to treat model, it is also possible that some participants may be exposed to extended dosing due to an inability to perform the endoscopy as scheduled due to a public health emergency. If a subset of participants undergo extended dosing, we will compare individuals on study drug who had extended dosing to those who did not (sensitivity analysis) to see if the primary study outcome was substantially different based on extended dosing and will perform analyses only on those who did not undergo extended dosing to ensure results are consistent.

13.5.3. Supportive Analyses of the Primary & Secondary

For the primary and secondary outcome measures, sensitivity analyses may be done by including the following covariates in the models described above: sex, age group, baseline eosinophil counts, missing last injection before EGD, and baseline disease severity. Given the sample size, covariates will be tested individually in the models.

13.5.4. Analyses of Secondary and Other Endpoints

For the secondary and exploratory outcome measures related to differences between the arms of the study, generalized linear mixed effects models will be used with the appropriate distribution function and link function (e.g. binomial distribution and logit link for binary outcomes, normal distribution and identity link for normally distributed continuous outcomes). Appropriate transformations may be used to satisfy the normality assumptions of the model, if needed. Baseline corticosteroid/immunosuppressive therapy use will be included as a covariate in the models. Study site will be included as a random effect in the models. To evaluate factors associated with drug responsiveness, we will use generalized linear mixed models as described above but restrict the analyses to those in the medication arm of the study. Statistical testing will be performed at the two-sided 5% level of significance.

13.5.5. Safety outcomes

Adverse events will be summarized for each treatment group. The number and percentage of participants experiencing each adverse event category and the number of adverse events that occurred will be presented. Relative risk and exact 95% confidence intervals will be reported for each treatment group and each adverse event category. Serious adverse events will be summarized using the same approach. The following descriptive data displays and summaries will be provided for vital sign, urinalysis, blood chemistry and hematology measures. For continuous measures, scatter plots of each measure for each treatment group will be presented with the baseline measure on the x-axis and the week 12 measure on the y-axis. A 45-degree reference line will be included in each plot. For categorical measures, two-way frequency tables will be provided for each treatment group that include baseline result versus week 12 result. Any clinically relevant changes in physical exam data will be described for each treatment group.

13.5.6. Descriptive Analyses

Demographic and baseline characteristics will be summarized within each treatment group using frequency and percentages for categorical variables and mean and standard deviation or median and interquartile range for continuous variables. The two treatment groups will be compared using Fisher's Exact Test for categorical variables and the nonparametric Wilcoxon Ranks Sum Test for the continuous variables.

13.5.7. Analysis for OLE Phase of the Study

For participants that continue into the open label phase of the study, we will evaluate change for two time ranges. We will examine the overall change across the study (baseline to OLE/EOT (Week 24)). Then, we will examine change during the open label phase (DBP/EOT (Week 12) to OLE/EOT (Week 24)). When evaluating the across study change, analyses will be stratified by treatment status during the blinded phase of the study. Mean relative change and two-sided 95% confidence intervals will be presented for the key OLE endpoint.

13.6. Interim Analyses

There is no interim analysis planned.

13.7. Statistical Hypotheses

Primary Endpoint: the percent change from baseline from week 0 to week 12 in the mean of the eosinophil counts from the 5 worst microscopic fields in the gastric antrum and/or body

$H_{0:}\ b_1 = b_{1,0}$

$H_{A:}\ b_1 \neq b_{1,0}$

Where b_1 is the coefficient for treatment status from the linear model and $b_{1,0}$ is zero.

Key secondary endpoint: We have secondary endpoints (Patient global impression of severity (PGI-S), Patient global impression of change (PGI-C), Proportion of participants achieving threshold response < 30 eos/hpf in 5 hpfs, Eosinophilic Gastritis Endoscopy Assessment (EG-REFS), Eosinophilic Gastritis Symptom Questionnaire (EG-SQ).

$H_{0:}\ b_1 = b_{1,0}$

$H_{A:}\ b_1 \neq b_{1,0}$

Where b_1 is the coefficient for treatment status from the linear model and $b_{1,0}$ is zero.

For both primary and secondary endpoints, the type of comparison is superiority.

13.8. Sample Size Considerations

As we recognize that not all participants may complete the study, a dropout rate of 10% is assumed for all sample size calculations provided below.

It is assumed that the true mean percent reduction from baseline in mean gastric eosinophil counts when treated with dupilumab will be at least 50%. This is a conservative estimate based on the efficacy of dupilumab in EoE patients; dupilumab reduced the mean (least square) peak esophageal eosinophil count by -94/HPF (9.5 standard error; n=23) and -7.4 (9.6 standard error; n=24) in the placebo group in a recent study of EoE[13]. At Week 12, dupilumab versus placebo significantly reduced peak eosinophil counts from baseline (−92.9% vs +14.2%; P<0.0001). It is also assumed that the true mean percent reduction from baseline in mean eosinophil counts for the placebo group will be at most 25% and we expect it to be much less as the placebo effect in EoE was 14% increase in eosinophil levels as noted above. Assuming a standard deviation of 25 percentage units, a sample size of 20 participants per treatment group will provide at least 80% power to detect a true absolute difference in percent reduction from baseline in mean eosinophil counts of 23% at alpha = 0.05. If we assume that the dropouts from the dupilumab arm have a mean reduction in eosinophil counts similar to those on placebo (25%) then we would expect 48% decline in eosinophil count among those in the dupilumab arm, thus we are sufficiently powered even with dropouts. A sample size of 20 per treatment group will also provide at least 80% power to detect a difference in the proportions of participants with induction of disease remission of 42 percentile points (e.g. 62% vs. 20%) at the two-sided 5% level of significance. Notably, if 2 individuals in the dupilumab arm drop out then the effective disease remission rate would be 67% among those completing the study in order to obtain a 62% overall remission rate for the dupilumab arm.

14. Identification and Access to Source Data

14.1. Source Data

Source documents and source data are considered to be the original documentation where participant information, visits consultations, examinations and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation and validation of clinical findings, observations and other activities during a clinical trial. All source documents must be kept on file with the CRFs (CRFs may be either paper or electronic [eCRF]). Data will be entered into a database that complies with all applicable guidelines.

14.2. Access to Source Data

The site investigators and site staff will make all source data available to the DAIT/NIAID, IPM, study sponsor (Dr. Rothenberg) as well as to relevant health authorities such as the FDA. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals.

14.3 Data Collection and Management Responsibilities

Data collection is the responsibility of the study staff at the site under the supervision of the site principle 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.

The DMCC will develop, test, and maintain the data capture system using a web-based data collection system, REDCap, as the primary source of data entry and storage. REDCap is a software toolset and workflow methodology for electronic collection and management of research and clinical trial data developed by Vanderbilt University. The REDCap system provides a secure, web-based application that is flexible and provides: 1) an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry; 2) HIPAA-compliant and 21 CFR Part 11-ready audit trails for tracking page views, data manipulation and export procedures; 3) record locking and electronic signature functions; 4) fine grained control of user rights to view and manipulate data, and tool to sequester data access for multiple sites; 5) a report builder for reporting, monitoring and querying patient records; and 6) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R/S-Plus).Study data will be entered into REDCap, supported by the DMCC. The REDCap system complies with all applicable guidelines to ensure patient confidentiality, data integrity, and reliability. All data management best practices including quality controls and data validation procedures will be applied to ensure the validity and accuracy of the clinical database. A data management plan will be developed which will describe the data collection process, database development, quality control processes and reporting.

15. Quality Assurance and Quality Control

15.1. Training of study site personnel

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

15.2. Monitoring of the study

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

15.3. Audits and inspections

The study PI, funding agency or Cincinnati Children's Hospital Medical Center (CCHMC) representative may subject this trial to quality assurance audits or inspections at any time. In the case of an audit or inspection, the investigator is responsible for the following:

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

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

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

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

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.

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.

16. Protocol Deviations

16.1. Protocol Deviation Definitions

Protocol Deviation – The investigators and site staff will conduct the study in accordance to the protocol; no deviations from the protocol are permitted. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions will be developed by the site and implemented promptly.

Major Protocol Deviation (Protocol Violation) - A Protocol Violation is a deviation from the IRB approved protocol that may affect the participant's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human subject protection regulations, or policies, any action that is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.

Non-Major Protocol Deviation - A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

16.2. Reporting and Managing Protocol Deviations

The study site principal investigator has the responsibility to identify, document and report protocol deviations as directed by the study Sponsor. However, protocol deviations may also be identified during site monitoring visits or during other forms of study conduct review, including processing of data at the Data Center. Upon determination that a protocol deviation has occurred, the study staff will a) notify the site Principal Investigator, b) notify the NIAID Project Manager, and c) will complete a Protocol Deviation form. The DAIT Project Manager will review and approve the correction action plan that is to be implemented as a result of the protocol deviation will make the final decision as to whether the Deviation is major or not. The study sponsor (Marc Rothenberg, MD, PhD will submit the Protocol Deviation reports to the appropriate review bodies (IRB, DSMB, FDA etc.). Ethical Considerations and Compliance with Good Clinical Practice.

17. Ethics and regulatory review

Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the Cincinnati Children's Hospital Medical Center IRB (CCHMC IRB) which will work as a central IRB (following reliance agreements from each site).

17.1. Statement of Compliance

This clinical study will be conducted using good clinical practice (GCP), as delineated in Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the IRB. Any amendments to the protocol or to the consent materials will also be approved by the IRB before they are implemented.

17.2. Informed Consent Process

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

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

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

17.3. Privacy and Confidentiality

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information. Site personnel will not transmit documents containing protected health information (PHI) to the study sponsor or their representatives.

18. Additional Regulatory Items

18.1. Transfer of Study Materials and Data

Some samples that are collected during research activities may be frozen and shipped to other hospitals, institutions, and testing companies for analysis. Data may also be shared. The data and/or samples will be de-identified per the Health Insurance Portability and Accountability Act (HIPAA) and have no protected health information (PHI) associated with them. The data and/or samples will be used in a collaborative relationship between institutions, or testing companies receiving the data and/or samples. All of these samples will be shared under a Material Transfer Agreement (MTA), or other applicable agreement.

18.2. Closure of Study Sites

If the PI in coordination with DAIT/NIH chooses to close out the study site (for example, due to lack of participant enrollment within a reasonable period of time, violation of the study agreement, breach of protocol, early attainment of study enrollment targets, etc.), the PI will notify involved individuals in writing. The appropriate regulatory agencies must be informed according to applicable requirements, and adequate consideration must be given to the protection of the participants' interests.

18.3. Archiving of study documents

All essential study documents must be retained by the investigator for at least 3 years after the conclusion or discontinuation of the trial. Prior to destroying any essential documents, the investigator must consult with the study sponsor (Marc Rothenberg, MD, PhD). If, and when, destruction is authorized, records must be destroyed in a manner that ensures confidentiality. If an investigator can no longer ensure archiving, the sponsor and the investigator will agree upon a suitable designation for transferring the essential records.

18.4. Changes to the protocol and informed consent form

Any amendments to the protocol or consent materials will be approved by the study sponsor, CCHMC, cIRB and NIAID before they are implemented.

19. Publication Policy

The CEGIR policy on the publication of study results will apply to this trial.

20 References

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Appendix 1.0

Anaphylaxis

Clinical criteria for diagnosing anaphylaxis will be as follows [27]:
Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING:

   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced Peak expiratory flow (PEF), hypoxemia)
   b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

*Low Systolic BP is defined as less than (70 + [2 x age]) mm Hg