IND: 107969 Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A Randomized, Double-Blind, Parallel, Placebo-Controlled Study of the Efficacy, Safety and Tolerability of Dupilumab in Adult Patients with Active Eosinophilic Esophagitis

Compound:	Dupilumab
Clinical Phase:	2
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Amendment 3 Date of Issue:	04 May 2016
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Scientific/Medical Monitor: [redacted]
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AMENDMENT HISTORY

Amendment 4

The following table outlines the changes made to the protocol and the affected sections:

Change	Section Changed
Due to failure with electronic diaries, data from many patients are missing for the week 12 analysis. Therefore, the primary endpoint is modified to have change from baseline to week 10 instead of to week 12 to ensure an adequate amount of data for analysis.	Synopsis: Endpoints Section 8.2.1 Primary Endpoints
The list of secondary endpoints has been modified as a result of changing the primary endpoint to week 10. The list now includes endpoints of both percent change and change in Eosinophilc Esophagitis Activity Index (EEsAI) patient-reported outcome (PRO) at both week 10 and week 12, and change and percent change in Straumann Dysphagia Instrument (SDI) PRO at week 12 and percent change in SDI PRO at week 10. The end point: "Change in SDI PRO and EEsAI PRO scores from baseline during the follow-up period (weeks 16, 20, 24, 28) has been removed" as a result of the modification to the analyses. The endpoint "Change in EoE-EREFS (endoscopy visual anatomical score) from baseline to week 12" has been moved from exploratory to secondary to be consistent with completed competitor studies.	Synopsis: Endpoints Section 8.2.2 Secondary Endpoints Section 8.2.3 Exploratory Endpoints
The text for some of the endpoints has been modified for clarification purposes only eg, "weekly" EEsAI, "percent" in "overall" peak eos/hpf, and specifying "baseline" to week 12 for some endpoints.	Synopsis: Endpoints Section 8.2.2 Secondary Endpoints Section 8.2.3 Exploratory Endpoints
In a secondary objective inflammation was changes to infiltration for accuracy.	Synopsis Section 2.2

Change	Section Changed
Updated statistical plan to: Specify that the analysis of the primary and secondary endpoints at the first database lock is considered the final analysis for the primary and secondary endpoints. Clarify that the full analysis set (FAS), the safety analysis set (SAF), and the pharmacokinetic (PK) analysis set includes all randomized patients. Revise the statistical methods for analysis of the primary and secondary endpoints. Due to the substantial imbalance in the number of patients in the 2 randomization strata, the randomization strata will not be included in the statistical models. Instead, baseline SDI score will be included as a continuous covariate in the statistical models. Update justification for sample size. Clarify study periods for adverse events (AEs)	Synopsis: Statistical Plan Section 9 Statistical Plan Section 9.2 Justification of Sample Size Section 9.3.1 Efficacy Analysis Set Section 9.3.3 Pharmacokinetic Analysis Set Section 9.5.2 Efficacy Analyses Section 9.5.2.1 Analysis of the Primary Efficacy Endpoints Section 9.5.2.2 Analysis of Secondary Endpoints Section 9.5.3.1 Adverse Events
Clarify the text for patients who are anti-drug antibody (ADA) positive at their last study visit (early termination or end of study) will be considered for follow-up based on the overall clinical presentation at that time. The sentence following this now reads: Patients who are "identified" instead of considered.	Synopsis: Study Design Section 3.1 Study Description and Duration Table 2: Schedule of Events –Follow-up Period footnote 6 Section 6.2.4 End-of-Study Visit/Visit 18/Day 197/Week 28 (± 3 Days) Section 6.3.4.2 Anti-drug Antibody Measurements and Samples

Amendment 3 (04 May 2016)

The purpose of this amendment is to:

- Modify inclusion criterion #2 and to clarify inclusion criteria #6 and #10 and exclusion criteria #9 and #16.
- Add "Diet History" to the Schedule of Events
- Update language for anti-drug antibody (ADA) measurements
- Make minor edits

Amendment 2 (08 MAY 2015)

The primary purpose of this amendment is to update the number of study sites and the enrollment criteria based on the principal investigators' feedback.

Amendment 1 (15 JAN 2015)

The purposes of amendment 1 are to:

- Make revision to indicate that the endolumenal functional lumen imaging probe (EndoFLIP) procedure to measure esophageal distensibility will be performed at all sites, instead of at selected site as previously stated.

- Revise inclusion criterion #2 to be clearer on the following points: (1) a patient must have a past diagnosis of eosinophilic esophagitis (EoE) by endoscopy prior to screening (not at screening), (2) the past diagnosis must be a documented one, and (3) the past diagnosis must have been made after at least 8 weeks of treatment with high dose (or twice-daily dosing) proton pump inhibitors (PPIs) and with a demonstration of intraepithelial eosinophilic infiltration (peak cell count ≥15 eosinophils/high power field [eos/hpf] [400X]) from esophageal biopsy specimens from endoscopy performed immediately after the PPI treatment.
- Move the following inclusion criterion to the end of the Inclusion Criteria section: "Index endoscopy performed at screening, with a demonstration of intraepithelial eosinophilic infiltration (peak cell count ≥15 eos/hpf) in at least 2 of the 3 biopsied esophageal regions (proximal, mid, or distal)", change "index" to "screening" for clarity, and add a note indicating that the screening endoscopy should be performed only if all other inclusion criteria are met and none of the exclusion criteria is met to avoid screen failed patients unnecessarily undergoing the screening endoscopy and biopsy procedure.
- Add Straumann Dysphagia Instrument (SDI) and Eosinophilic Esophagitis Activity Index (EEsAI) at telephone visits, and add a note to indicate that SDI and EEsAI should be performed by the patient electronically, weekly for SDI, and daily and weekly for EEsAI, and that site should confirm patient compliance for assessing SDI and EEsAI at each clinic visit
- Add serum total immunoglobulin E (IgE) test at the screening visit.
- Change the term "esophagogastroscopy" to "endoscopy" throughout the protocol for consistency and clarity
- Delete the exploratory endpoint "proportion of patients with change from baseline in EEsAI Histological Module Score", as the histological module score is not collected in this study
- Delete "storing study ISR photographs" from the electronic data capture (EDC) system functions as injection site reaction (ISR) photographs will not be collected in this study
- Add electronic patient diary in the list of electronic systems used in this study as it will be used for data capture and uploading for patient reported outcomes (PROs):

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Randomized, Double-Blind, Parallel, Placebo-Controlled Study of the Efficacy, Safety and Tolerability of Dupilumab in Adult Patients with Active Eosinophilic Esophagitis
Site Locations	United States (US)
Objectives	The primary objective of the study is to assess the clinical efficacy of repeat subcutaneous (SC) doses of dupilumab, compared with placebo, to relieve symptoms in adult patients with active, moderate to severe eosinophilic esophagitis (EoE). The secondary objectives of the study are: • To assess the safety, tolerability, and immunogenicity of SC doses of dupilumab in adult patients with active, moderate to severe EoE • To assess the effect of dupilumab on esophageal eosinophilic infiltration • To evaluate the pharmacokinetics (PK) of dupilumab in adult patients with EoE
Study Design.	This is a multicenter, double-blind, randomized, placebo-controlled study investigating the efficacy, safety, tolerability, PK, and immunogenicity of dupilumab in adult patients with EoE. Approximately 44 patients will be enrolled at up to 20 study sites in the US. After providing informed consent, patient eligibility will be assessed at the screening visit (to occur between day -35 and day -1). Patients who meet eligibility criteria will undergo day 1 baseline assessments. Patients will be randomized in a 1:1 ratio to receive dupilumab or placebo during the 12-week double-blind treatment phase. After the 12-week double-blind treatment phase, patients will be followed off-study drug for an additional 16 weeks. Patients may receive concomitant medications (except for prohibited medications specified in the protocol) as needed, at the discretion of the investigator, while continuing study treatment. Frequency of use and type of product will be documented. If medically necessary, rescue medications (eg, systemic and swallowed topical corticosteroids) or emergency esophageal dilation may be provided to study patients. Patients receiving rescue therapy will be discontinued from study treatment. These patients will remain blinded and will be asked to return to the clinic for all remaining study treatment visits and participate in all follow-up assessments according to the visit schedule. Efficacy, safety, and laboratory assessments, and samples for dupilumab concentration and potential anti-drug antibody (ADA) response to dupilumab, as well as research samples will be performed or collected at specified time points throughout the study. [redacted] Patients who are ADA positive at their last study visit (early termination or end of study) will be considered for follow-up based on the overall clinical presentation at that time. Patients who are identified for follow-up may be asked to return to the clinic to have additional ADA samples collected for analysis.

Study Duration	The duration of the study for each patient is approximately 28 weeks, excluding the screening period.
Population	
Sample Size	Approximately 44 patients are planned.
Target Population	The target population includes adult (18 to 65 years old) male or female patients with active EoE.
Treatments	
Investigational Drug Dose/Route/Schedule	Dupilumab SC, a loading dose of 600 mg on day 1 followed by weekly doses of 300 mg from week 1 to week 11.
Placebo Route/Schedule	Placebo (same formulation as dupilumab without the active substance, anti-IL-4R monoclonal antibody) SC, a volume matching the dupilumab loading dose on day 1 followed by weekly doses matching the volume of dupilumab weekly dose from week 1 to week 11.
Endpoints	
Primary:	The primary efficacy endpoint is: • Change in the Straumann Dysphagia Instrument (SDI) patient-reported outcome (PRO) score from baseline to week 10
Secondary:	The secondary endpoints: • Percent change in weekly Eosinophilic Esophagitis Activity Index (EEsAI) PRO score from baseline to week 10 • Change in weekly EEsAI PRO score from baseline to week 10 • Percent change in weekly EEsAI PRO score from baseline to week 12 • Change in weekly EEsAI PRO score from baseline to week 12 • Percent change in the SDI PRO score from baseline to week 10 • Percent change in the SDI PRO score from baseline to week 12 • Change in the SDI PRO score from baseline to week 12 • Change in Adult Eosinophilic Esophagitis Quality of Life (EoE-QOL-A) (questionnaire) PRO score from baseline to week 12 • Percentage of patients with SDI PRO response at week 10; where response is defined as a decrease of at least 3 points on the SDI compared to baseline • Percentage of patients who achieve ≥40% improvement in EEsAI score from baseline to week 10 • Percent change in overall peak esophageal intraepithelial eos/hpf (400X) from baseline to week 12 • Change in Eosinophilic Esophagitis-Endoscopic Reference Score

(EoE-EREFs) (endoscopy visual anatomical score) from baseline to week 12

- Percentage of patients with use of rescue medication or procedure (eg, esophageal dilation) through week 12
- Incidence of treatment-emergent adverse events (TEAEs)

Procedures and Assessments	Efficacy will be assessed during the study at specified clinic visits using PROs, including SDI, EEsAI, and the EoE-QOL-A questionnaire, as well as esophageal biopsies and photographs (endoscopy procedure). Measurement of inflammatory and remodeling esophageal features based on the EoE-EREFs will be included as part of the endoscopy procedure. The endolumenal functional lumen imaging probe (EndoFLIP) procedure to measure esophageal distensibility will be performed during the endoscopy procedures. Safety and tolerability will be assessed by physical examinations, vital signs, electrocardiograms (ECGs), clinical laboratory tests, and clinical evaluations. Patients will be asked to monitor all AEs experienced from the time of informed consent until their last study visit. Serum samples will be collected for assay of dupilumab level and PK parameters will be calculated using the dupilumab concentration data. Serum samples will be collected for assay of ADA, and exploratory analyses.
Statistical Plan	The sample size calculations are based on the change from baseline in SDI score to week 12. The study of Straumann 2010 has a 2-week treatment period and the 3-point improvement from baseline is observed at end of week 2. A 3-point improvement from baseline is assumed for the study at both week 10 and week 12, so the power calculation for change from baseline in SDI score to week 12 is the same as the one at week 10. A sample size of 18 patients per treatment arm will provide 94% power to detect a treatment effect, with an expected mean difference of 3 points in change from baseline to week 12 in SDI score between dupilumab and placebo at a 2-sided t-test with 5% significance level and an assumed standard deviation (SD) of 2.46. Taking into account the assumed 15% dropouts, 22 patients per treatment arm will be enrolled. The assumptions for SD and baseline values are based on Straumann 2010. Patients will be randomized at a 1:1 ratio into dupilumab and placebo group. The randomization will be stratified by baseline SDI PRO score ($\geq$5 and $\leq$7 versus >7; total score ranged from 0 to 9) that reflect EoE severity and frequency. For all efficacy variables, the analyses will be comparisons of the dupilumab and the placebo treatment groups. The following null and alternative hypotheses will be tested: H0: No treatment difference between dupilumab and placebo. H1: There is treatment difference between dupilumab and placebo. There will be no adjustment of multiplicity for the secondary efficacy endpoints. The efficacy endpoints will be analyzed using the full analysis set (FAS) that includes all randomized patients. Efficacy analyses will be based on the treatment allocated by the randomization. The primary efficacy endpoint, change in SDI score at week 10 from baseline, will be analyzed using multiple imputation with an analysis of covariance (ANCOVA) model with treatment group as fixed effect, and the baseline SDI value as a continuous covariate (primary approach). In addition, sensitivity analyses for the primary efficacy endpoint will be conducted. Continuous secondary efficacy endpoints will be analyzed using the same approach as that used for the analysis of the primary endpoint. For all continuous secondary efficacy endpoints except endpoints related to SDI, the ANCOVA model will include treatment group as fixed effect, the baseline SDI score and

relevant baseline value as continuous covariates.

Categorical secondary efficacy endpoints will be performed on responder data. Comparisons between dupilumab and placebo will be done using the Fisher exact test. Patients with early withdrawals or use of rescue medication or procedure will be counted as non-responders.

The efficacy data after week 12 will be summarized descriptively.

Safety, PK, and ADA data will be summarized descriptively.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CCL	Chemokine (C-C motif) ligand
CMH	Cochran-Mantel-Haenszel (test)
CPK	Creatine phosphokinase
CRF	Case report form
DP	Distensibility plateau
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EEsAI	Eosinophilic Esophagitis Activity Index
EndoFLIP	Endolumenal functional lumen imaging probe
EoE	Eosinophilic esophagitis
EoE-EREFS	Eosinophilic Esophagitis-Endoscopic Reference Score
EoE-QOL-A	Adult Eosinophilic Esophagitis Quality of Life (questionnaire)
EOS	End of study
eos/hpf	Eosinophils/high power field
EOT	End of treatment
ET	Early termination
FAS	Full analysis set
FLG	Filaggrin
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HDL	High-density lipoprotein

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent data monitoring committee
IFN-γ	Interferon-gamma
IgE	Immunoglobulin E
IL	Interleukin
IL-4Rα	Interleukin-4 receptor alpha
IRB	Institutional Review Board
ISR	Injection site reaction
IVRS/IWRS	Interactive voice and web response system
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model repeated measure
OIT	Oral immunotherapy
PCSV	Potentially clinically significant value
PK	Pharmacokinetic
PPI	Proton pump inhibitor
PRO	Patient-reported outcome
PT	Prothrombin time
PTT	Partial thromboplastin time
PVRM	Pharmacovigilance and Risk Management
QOL	Quality of life
qw	Once weekly
RBC	Red blood cell
qRT-PCR	Quantitative reverse transcriptase-polymerase chain reaction
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

SCIT	Subcutaneous immunotherapy
SD	Standard deviation
SDI	Straumann Dysphagia Instrument
SLIT	Sublingual immunotherapy
SOC	System organ class
SPRR3	Small proline-rich protein 3
TEAE	Treatment-emergent adverse event
Th2	Type 2 helper T cell
TSLP	Thymic stromal lymphopoietin
ULN	Upper limit of normal
WBC	White blood cell

1. INTRODUCTION AND RATIONALE

1.1. Introduction

Eosinophilic esophagitis (EoE) is an emerging, chronic, immune-/antigen-mediated disease characterized by esophageal dysfunction and eosinophil inflammation in the esophagus (Liacouras 2011, Weinbrand-Goichberg 2013, Zhang 2013). Adult patients with EoE have substantially impaired quality of life (QOL) due to dysphagia and the possible risk of food impaction (DeBrosse 2011, Falk 2014, Straumann 2008, Straumann 2003). Emergency endoscopy for prolonged food impactions is associated with a risk of severe esophageal injury.

The prevalence of EoE in the general population was reported to range from 0.5 to 1 case per 100,000 persons and estimates in the United States (US) ranged from 40 to 90 cases per 100,000 persons (Dellon 2014a). The largest study in the US reported an EoE prevalence of 57/100,000 or 152,000 cases in adults and pediatrics (Dellon 2014b). Eosinophilic esophagitis has been reported in all ages; however, most cases are in children and adults younger than 50 years (Dellon 2014a, Dellon 2014b, Dellon 2007, Kapel 2008, Liacouras 2011, Spergel 2009). Gender difference in EoE has been consistently reported, with males affected 3 to 4 times more often than females (Dellon 2014a). Racial difference has also been frequently reported, with EoE more frequently reported in whites compared with other races.

The pathogenesis of EoE is still unclear, however, growing evidence suggests that type 2 helper T cell (Th2)-mediated immune response plays an important role in the pathogenesis of EoE by provoking chronic eosinophil, mast cell, T cell, and lymphocyte induced inflammation via cytokines known to regulate eosinophilic accumulation in the esophagus, such as interleukin (IL)-4, IL-5, IL-13, and eotaxin-1, -2, and -3 (Abonia 2010, Abonia 2012, Blanchard 2006, Blanchard 2008, Blanchard 2010, Bullock 2007, Mishra 2003, Mishra 2009, Straumann 2001). Type 2 helper T cells are a subgroup of the T cells that help the activity of other immune cells by releasing Th2 cell cytokines. Interleukin-13 has been found to be upregulated in the esophageal epithelium of EoE patients (Blanchard 2007). The induction of eotaxin-3, an eosinophil chemoattractant, is thought to be an important factor in EoE pathogenesis (Blanchard 2006, Blanchard 2007). The two most up-regulated genes in esophageal biopsies from EoE patients (compared to normal controls) encode eotaxin-3 and periostin, another protein induced by Th2 cytokines and thought to promote inflammation and remodeling (Blanchard 2006, Blanchard 2008). Mutations in the eotaxin-3 (chemokine [C-C motif] ligand [*CCL26*]), thymic and stromal lymphopoeitin (*TSLP*), and filaggrin (*FLG*), whose functions are induced downstream of Th2 cytokines (such as IL-4 and IL-13), have been associated with EoE risk.

Impaired barrier function of the esophageal epithelium is thought to play a role in EoE pathogenesis. Several components of the epithelial differentiation complex, known to be down-regulated by Th2 cytokines with resultant barrier dysfunction of the skin, are also down-regulated in primary esophageal epithelial cells in vitro. Furthermore, decreased mRNA expression of epithelial differentiation complex components, *FLG*, and the esophagus-specific esophagin (small proline-rich protein 3 [*SPRR3*]), was observed in esophageal biopsies from EoE patients compared to normal controls (Blanchard 2010). The increased frequency at which *FLG* null alleles are found in EoE patients compared to controls provides further evidence of the

barrier hypothesis in EoE (Blanchard 2010). It is also known that *FLG* mRNA expression is directly suppressed by IL-4 and IL-13 (Howell 2007). The data suggest that Th2 cytokines may be driving not only an inflammatory response, but also epithelial barrier dysfunction in the esophagus.

Consistent with the Th2-mediated inflammation observed in esophageal tissue, patients with EoE have high rates of comorbid allergic diseases, especially food allergies, atopic dermatitis (AD), asthma, and allergic rhinitis (Arora 2012, Assa'ad 2008, Liacouras 2011, Moawad 2010, Roy-Ghanta 2008, Weinbrand-Goichberg 2013). The inflammatory damage to the esophageal epithelium results in symptoms of esophageal dysfunction, such as dysphagia. Chronic inflammation of the esophagus may also lead to remodeling, stricture formation, and fibrosis (Hirano 2014). The fibrotic aspect of progressed disease is not well understood, and whether or not this can be reversed with treatment is unknown.

Current therapeutic approaches include chronic dietary elimination, swallowed topical formulation corticosteroids (not approved for the treatment of EoE in the US), and esophageal dilation. Although swallowed topical corticosteroids have been reported in clinical trials to induce partial clinical responses and histologic remission, they are not uniformly effective and can be associated with fungal infections as well as disease recurrence after discontinuation. There are currently no approved drug therapies for EoE.

Dupilumab (also known as REGN668) is a human monoclonal antibody that targets the IL-4 receptor alpha subunit (IL-4Rα), a component of IL-4 receptors Type I and Type II, as well as the IL-13 receptor system. The binding of dupilumab to IL-4Rα results in blockade of the function of both IL-4 and IL-13 signal transduction. Dupilumab has demonstrated preliminary efficacy in 3 other Th2-mediated diseases: asthma, chronic sinusitis with nasal polyps, and moderate-to-severe AD. Because IL-4 and IL-13 are likely key pathomechanisms in EoE, dupilumab treatment may improve inflammation and clinical symptoms.

1.2. Rationale

1.2.1. Rationale for Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, 2-arm, parallel-group, proof-of-concept study. The primary purpose of this study is to evaluate the effect of dupilumab on relieving EoE clinical symptoms and reducing esophageal inflammation in adults. Currently there is no regulatory-approved endpoint for drug registration for this indication. Published clinical trials in EoE treatment with swallowed topical corticosteroids measured clinical responses and histological changes (Alexander 2012, Dellon 2012, Straumann 2010). However, emerging data show that there does not appear to be a correlation between histology changes, such as reduction in eosinophil counts, and clinical symptoms. Collaborative efforts by the international Eosinophilic Esophagitis Activity Index (EEsAI) study group with the Food and Drug Administration (FDA) are ongoing in developing and validating clinically meaningful endpoints, such as patient-reported outcome (PRO), for evaluating efficacy for approval of treatment for EoE (Fiorentino 2012). Therefore, efficacy in this study will be assessed based on clinical signs and symptoms using the EoE-specific PROs currently in development, as well as on anatomical and histological findings from endoscopy with esophageal biopsies. Esophageal biopsies will be used to assess histologic changes and to examine EoE gross esophageal mucosal

features based on a validated scoring system for inflammatory and remodeling aspects of the disease.

Study treatment assignment (dupilumab or placebo) will be allocated by randomization. The randomization will be stratified by baseline Straumann Dysphagia Instrument (SDI) PRO score (≥5 and ≤7 versus >7; total score ranged from 0 to 9) that reflect EoE severity and frequency (Section 6.3.2.1). The placebo control will provide a reliable reference for any apparent effects of the study treatment with active IL-4Rα inhibition.

Patients assigned to the dupilumab group will receive a subcutaneous (SC) dose of 300 mg once weekly (qw) after a loading dose of 600 mg on day 1. Study treatment will be administered for 12 weeks. The 12-week treatment period is considered appropriate for this proof-of-concept study with primary and secondary endpoints measuring changes in clinical symptoms and histological features, as (1) clinical trials with swallowed steroids treatment have used the same treatment period and reported histology change within 12 weeks and clinical improvement within 2 weeks after start of treatment, and (2) the onset of treatment effect of dupilumab was shown to be 2 to 4 weeks after the start of treatment in patients with AD. After the treatment period, patients will be followed for 16 weeks (ie, approximately 5 half-lives based on pharmacokinetic [PK] results from phase 2 studies), which will ensure that dupilumab clearance is virtually complete (plasma concentrations below the lower limit of quantification) before the end of study visit.

1.2.2. Rationale for Dose Selection

The SC 600 mg loading dose and 300 mg weekly dose of dupilumab regimen in this study was selected based on results from previous clinical studies in patients with AD. The loading dose will allow systemic concentrations of dupilumab to reach a potential effective level faster, therefore, potentially reduce the time to clinical effect. Repeat SC dose regimens as high as 300 mg qw (with or without a loading dose) for up to 16 weeks have previously been studied in phase 1 and phase 2 clinical trials in healthy subjects as well as in patients with AD or asthma and were well tolerated. Therefore, the repeat SC 300 mg qw dose, the highest SC repeat dose studied to date, was selected for this study.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to assess the clinical efficacy of repeat SC doses of dupilumab, compared with placebo, to relieve symptoms in adult patients with active, moderate to severe EoE.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To assess the safety, tolerability, and immunogenicity of SC doses of dupilumab in adult patients with active, moderate to severe EoE
- To assess the effect of dupilumab on esophageal eosinophilic infiltration
- To evaluate the PK of dupilumab in adult patients with EoE

2.3. Exploratory Objective

The exploratory objective of the study is to assess the effect of dupilumab on other esophageal biopsy pathologic features associated with EoE.

3. STUDY DESIGN

3.1. Study Description and Duration

This is a phase 2, multicenter, double-blind, randomized, placebo-controlled study investigating the efficacy, safety, tolerability, PK, and immunogenicity of dupilumab in adult patients with EoE.

After providing informed consent, patient eligibility will be assessed at the screening visit (to occur between day -35 and day -1). Patients who meet eligibility criteria will undergo day 1 baseline assessments. Patients will be randomized in a 1:1 ratio to receive dupilumab or placebo during the 12-week double-blind treatment phase. After the 12-week double-blind treatment phase, patients will be followed off-study drug for an additional 16 weeks.

Patients may receive concomitant medications (except for prohibited medications [see Section 5.5]) as needed, at the discretion of the investigator, while continuing study treatment. Frequency of use and type of product will be documented. If medically necessary, rescue medications (eg, systemic and swallowed topical corticosteroids) or emergency esophageal dilation may be provided to study patients. Patients receiving rescue therapy will be discontinued from study treatment. These patients will remain blinded and will be asked to return to the clinic for all remaining study treatment visits and participate in all follow-up assessments according to the visit schedule.

Efficacy, safety, and laboratory assessments, and samples for dupilumab concentration and potential anti-drug antibody (ADA) response to dupilumab, as well as research samples will be performed or collected at specified time points throughout the study.

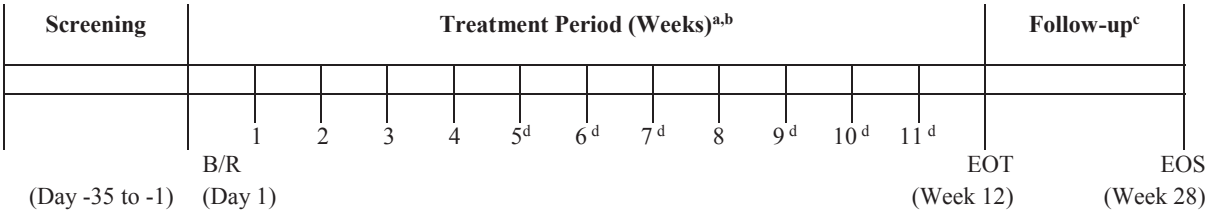
The end of treatment period visit occurs at week 12, 1 week after the last dose of study drug. The end of study visit occurs at week 28. The schedules of events for the 12-week treatment period and the follow-up period are provided in Table 1 and Table 2, respectively.

[redacted]

Patients who are ADA positive at their last study visit (early termination or end of study) will be considered for follow-up based on the overall clinical presentation at that time. Patients who are identified for follow-up may be asked to return to the clinic to have additional ADA samples collected for analysis (see Section 6.3.4.2 for details).

The study flow diagram is provided in Figure 1.

Figure 1: Study Flow Diagram



B/R = baseline/randomization; EOT = end of treatment; EOS = end of study.
Note: The scale is not linear.
[a] Patients will receive a weekly injection of study drug from day 1 through week 12 (with the last dose at week 11).
[b] Patients will be monitored at the study site for 30 minutes after each of the first 5 doses (visits 2 to 6) of study drug.
[c] Follow-up visits will occur every 4 weeks.
[d] Weeks 5, 6, 7, 9, 10, and 11 will be telephone visits.

3.2. Planned Interim Analysis

No interim analysis is planned. See Section 9 for description of database locks and analyses for week 12 outcome and final data.

3.3. Independent Data Monitoring Committee

An independent data monitoring committee (IDMC), composed of members who are independent from the sponsor and the study investigators, will monitor patient safety by conducting formal reviews of accumulated safety data that will be blinded by treatment group; if requested, the IDMC may have access to the treatment allocation code or any other requested data for the purposes of a risk-benefit assessment.

The IDMC will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in the study. The IDMC will also institute any measures that may be required for ensuring the integrity of the study results during the study execution.

All activities and responsibilities of the IDMC are described in the IDMC charter.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1. Number of Patients Planned

Approximately 44 patients will be enrolled at up to 20 study sites in the US.

4.2. Study Population

The target population includes adult patients with active EoE.

4.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Male or female, 18 to 65 years old
2. Documented diagnosis of EoE by endoscopy prior to or at screening

   Note: Must include a demonstration of intraepithelial eosinophilic infiltration (peak cell count ≥15 eosinophils/high power field [eos/hpf] [400X]) from esophageal biopsy specimens from endoscopy performed no more than 2 weeks after at least 8 weeks of treatment with high dose (or twice-daily dosing) proton pump inhibitors (PPIs)
3. History (by patient report) of on average at least 2 episodes of dysphagia (with intake of solids off anti-inflammatory therapy) per week in the 4 weeks prior to screening and on average at least 2 episodes of documented dysphagia per week in the weeks between screening and baseline; dysphagia is defined as trouble swallowing solid food, or having solid food stick, by patient report
4. Must remain on a stabilized diet for at least 6 weeks prior to screening and during the course of the study; stable diet is defined as no initiation of single or multiple elimination diets or reintroduction of previously eliminated food groups
5. SDI PRO score ≥5 at screening and baseline
6. Documented history of or presence of 1 or more of any of the following:
   - allergic disease (eg, allergic asthma, allergic rhinitis, AD, or food allergies),
   - peripheral eosinophil counts ≥0.25 GI/L,
   - serum total Immunoglobulin E (IgE) ≥100 kU/L
7. Willing and able to comply with all clinic visits and study-related procedures
8. Able to understand and complete study-related questionnaires
9. Provide signed informed consent
10. Endoscopy with photographs performed at screening, with a demonstration of intraepithelial eosinophilic infiltration (peak cell count ≥15 eos/hpf) in at least 2 of the 3 biopsied esophageal regions (proximal, mid, or distal)

4.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be ineligible to participate in this study:

1. Prior participation in a dupilumab (anti-IL-4R) clinical trial
2. Other causes of esophageal eosinophilia or the following diseases: hypereosinophilic syndromes, Churg-Strauss vasculitis, and eosinophilic gastroenteritis

3. History of achalasia, active *Helicobacter pylori* infection, Crohn's disease, ulcerative colitis, celiac disease, and prior esophageal surgery prior to screening
4. Any esophageal stricture unable to be passed with a standard, diagnostic, adult (9 to10 mm) upper endoscope or any critical esophageal stricture that requires dilation at screening
5. History of bleeding disorders or esophageal varices
6. Use of chronic aspirin, nonsteroidal agents, or anti-coagulants within 2 weeks prior to screening. Patients should not stop these agents solely to become eligible for entry into this study
7. Treatment with an investigational drug within 2 months or within 5 half-lives (if known), whichever is longer, prior to screening
8. Use of systemic corticosteroids within 3 months or swallowed topical corticosteroids within 6 weeks prior to screening
9. Use of inhaled or nasal corticosteroids within 3 months prior to screening and during the study, except stable dose for at least 3 months prior to screening biopsy, which cannot be changed during the study
10. Treatment with oral immunotherapy (OIT) within 6 months prior to screening
11. Allergen immunotherapy (sublingual immunotherapy [SLIT] and/or subcutaneous immunotherapy [SCIT], unless on stable dose for at least 1 year prior to screening
12. The following treatments within 3 months before the screening visit, or any condition that, in the opinion of the investigator, is likely to require such treatment(s) during the 3 months of study treatment:

    Systemic immunosuppressive/immunomodulating drugs (eg, omalizumab, cyclosporine, mycophenolate-mofetil, interferon-gamma [IFN-γ], Janus kinase inhibitors, azathioprine, methotrexate, leukotriene inhibitors [except stable dose for at least 3 months prior to screening], etc.)
13. Diagnosed with active parasitic infection; suspected parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization
14. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, or antifungals within 1 month prior to screening
15. Use of oral antibiotics/anti-infectives within 2 weeks prior to screening
16. Known or suspected immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis, 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
17. Known history of human immunodeficiency virus (HIV) infection

18. Positive or indeterminate hepatitis B surface antigen (HBsAg) or hepatitis C antibody at screening
19. Elevated transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) more than 3 times the upper limit of normal (>3 x upper limit of normal [ULN]) at screening
20. History of malignancy within 5 years prior to screening, except completely treated in situ carcinoma of the cervix and completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin
21. History of patient-reported alcohol or drug abuse within 6 months prior to screening
22. Any other medical or psychological condition including relevant laboratory abnormalities at screening that, in the opinion of the investigator, suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, case report form [CRF], etc.)
23. Severe concomitant illness(es) that, in the investigator's judgment, would adversely affect the patient's participation in the study.
24. Planned or anticipated use of any prohibited medications and procedures (as detailed in Section 5.5) during study treatment
25. Treatment with a live (attenuated) vaccine within 3 months prior to screening
26. Patient or his/her immediate family is a member of the investigational team.
27. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study
28. Women unwilling to use adequate birth control, if of reproductive potential* and sexually active. Adequate birth control is defined as agreement to consistently practice an effective and accepted method of contraception throughout the duration of the study and for 120 days after last dose of study drug. These include: hormonal contraceptives, intrauterine device, or double barrier contraception (ie, condom + diaphragm), or male partner with documented vasectomy.

    * For females, menopause is defined as at least 12 consecutive months without menses; if in question, a follicle stimulating hormone (FSH) of ≥25 U/mL must be documented. Hysterectomy, bilateral oophorectomy, or bilateral tubal ligation must be documented, as applicable; if documented, women with these conditions are not required to use additional contraception.

4.3. Premature Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and sponsor have the right to withdraw a patient from the study in the event of an intercurrent illness, adverse event (AE), treatment failure, protocol violation, cure, and for administrative or other reasons. An excessive rate of withdrawals would reduce the amount of data available for analysis and limit the ability to interpret the study results; therefore, unnecessary withdrawal of patients should be avoided.

Patients who withdraw prematurely from the study will be asked to complete study assessments per Section 6.2.5.

4.4. Replacement of Patients

Patients who are prematurely discontinued from the study will not be replaced.

5. STUDY TREATMENTS

5.1. Investigational and Reference Treatments

Dupilumab 150 mg/mL: Each 5 mL vial contains 2.5 mL (150 mg/mL) with a withdrawable volume of 2.0 mL or 300 mg of study drug.

Placebo matching dupilumab is prepared in the same formulation as dupilumab without the addition of protein (ie, active substance, anti-IL-4R monoclonal antibody).

Study drug (dupilumab or placebo) should be administered within 3 hours of preparation in the syringe. The procedure for preparing the study drug dose for SC injection will be provided in the pharmacy manual.

Patients will receive SC dupilumab 300 mg or matching placebo qw during the 12-week double-blind treatment phase. Patients will receive 2 injections (300-mg initial dose, followed by a 300-mg loading dose) on day 1, followed by weekly injections. Patients and/or caregivers will be trained on self-administration of study drug. Patients will be closely monitored at the study site at visits 2, 3, 4, 5, and 6 for a minimum of 30 minutes after the administration of study drug. In addition to the predose assessments, AEs will be assessed at 30 minutes (±10 minutes) postdose. On scheduled in-clinic study visit days, the study drug will be administered in the clinic (by site staff, the patient, or a caregiver). Study drug will be self-administered outside of the clinic in between in-clinic study visits. Patients may return to the clinic on a weekly basis if unable to self-administer study drug.

Subcutaneous injection sites should be alternated among the different quadrants of the abdomen (avoiding navel and waist areas) and upper thighs, so that the same site is not injected on 2 consecutive weeks. Instructions for recording and reporting injection site reactions (ISRs) will be provided in the study reference manual.

5.2. Dose Modification and Study Drug Discontinuation Rules

5.2.1. Dose Modification

Dose modification for an individual patient is not allowed.

5.2.2. Study Drug Discontinuation

Patients who permanently discontinue study drug treatment and who do not withdraw from the study will be asked to return to the clinic for all remaining study treatment visits and participate in all follow-up assessments according to the visit schedule.

Patients who opt to withdraw from the study will be asked to complete assessments per Section 6.2.5.

5.2.2.1. Reasons for Permanent Discontinuation of Study Drug

Patients will be permanently discontinued from study treatment in the event of:

- Anaphylactic reaction to study drug
- Treatment with any prohibited concomitant medication or procedure (Section 5.5.2)
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix or squamous or basal cell carcinoma of the skin
- Evidence of pregnancy
- Any infection that:
  - Requires parenteral treatment with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal 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 immunocompromised status
- Severe laboratory abnormalities, such as:
  - Neutrophil count $\leq 0.5 \times 10^3/\mu L$
  - Platelet count $\leq 50 \times 10^3/\mu L$
  - ALT and/or AST values >3 x ULN with total bilirubin >2 x ULN, excluding confirmed Gilbert's Syndrome
  - Confirmed AST and/or ALT >5 x ULN (for more than 2 weeks)
- Other reasons that may lead to the permanent discontinuation of study treatment include:
  - Certain AEs deemed related to the study drug (eg, severe and prolonged ISRs) or study procedures

5.2.2.2. Reasons for Temporary Discontinuation of Study Drug

Study drug dosing may be temporarily suspended in the event of:

- Clinically important laboratory abnormalities, such as:
  - Neutrophil count ≤1.0 x 103/µL but >0.5 x 103/µL

  - Platelet count ≤100 x 103/μL but >50 x 103/μL
  - Creatine phosphokinase (CPK) >10 ULN
- Short-term, self-limiting conditions (eg, infections resolving spontaneously or requiring ≤2 weeks of oral anti-infective treatment), with the exception of upper respiratory infections
- Other intercurrent illnesses

After the condition leading to suspension of dosing resolves, study treatment may resume.

A decision to temporarily discontinue study drug and/or to reinstitute study treatment should be discussed with the medical monitor. The investigator may suspend study treatment at any time, even without consultation with the medical monitor if the urgency of the situation requires immediate action and if this is determined to be in the patient's best interest. However, the medical monitor should be contacted as soon as possible in any case of study drug discontinuation. Resumption of study treatment after temporary discontinuation requires consultation and agreement between the investigator and the medical monitor.

5.3. Method of Treatment Assignment

Approximately 44 patients will be randomized on day 1 in a 1:1 ratio to receive dupilumab or placebo, according to a central randomization scheme provided by an interactive voice and web response system (IVRS/IWRS) to the designated study pharmacist (or qualified designee).

5.3.1. Blinding

Study patients, principal investigators, central pathology review pathologist, and study site personnel will remain blinded to all randomization assignments throughout the study. The Regeneron study director, medical monitor, study monitor, and any other Regeneron and contract research organization personnel who are in regular contact with the study site will remain blinded to all patient randomization assignments.

Selected individuals not involved in the conduct of the study, including members of the IDMC, may have access to unblinded data as needed for safety review or other data review.

Blinded study drug kits coded with a medication numbering system will be used. In order to maintain the blind, lists linking these codes with product lot numbers will not be accessible to individuals involved in study conduct.

Anti-drug antibody or drug concentration results, and post-treatment tissue eosinophil counts will not be communicated to the sites, and the sponsor operational team will not have access to results associated with patient identification until after the final database lock.

Information on emergency unblinding is provided in Section 5.3.2.

5.3.2. Emergency Unblinding

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency, or any other significant medical event (eg, pregnancy).

- If unblinding is required for a medical emergency:
  - Only the investigator will make the decision to unblind the treatment assignment.
  - Only the affected patient will be unblinded.
  - The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind the patient.
  - The investigator will notify Regeneron and/or designee immediately that the patient has been unblinded.

The treatment assignment is not to be provided to site personnel, including the investigator, at any time during the conduct of the study, except in the case of a true emergency. In the event that there is no study pharmacist, the principal investigator will remain as the only unblinded member of the site personnel.

5.4. Treatment Logistics and Accountability

5.4.1. Packaging, Labeling, and Storage

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

Study drug will be stored at the site [redacted] storage instructions will be provided in the pharmacy manual.

5.4.2. Supply and Disposition of Treatments

Study drug will be shipped [redacted] to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be returned to the sponsor or designee.

5.4.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

- dispensed to each patient,
- returned from each patient (if applicable), and

- disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

5.4.4. Treatment Compliance

All drug compliance records must be kept current and must be made available for inspection by the sponsor and regulatory agency inspectors.

5.5. Concomitant Medications and Procedures

Any treatment (including nutritional supplements) or procedure administered from the time of informed consent to the end of the final study visit is considered concomitant medication/procedures. This includes medications that were started before the study and are ongoing during the study. Concomitant medications and procedures are allowed with the exception of those listed in Section 5.5.2.

5.5.1. Permitted Medications and Procedures

Other than the prohibited medications listed in Section 5.5.2, treatment with concomitant medications are permitted during the study. This includes treatment with contraceptives, stable dose of PPIs (patients who are using PPIs at screening must not discontinue or change the dosing regimen prior to end of treatment [EOT] visit); stable dose (for at least 3 months prior to screening) of systemic leukotriene inhibitors, topical, nasal, and/or inhaled corticosteroids; oral antihistamines for any duration; and oral antibiotics for up to 2 weeks.

5.5.2. Prohibited Medications and Procedures

Treatment with the following concomitant medications is prohibited through week 12. Study drug will be permanently discontinued if any of the following are used through week 12:

- Medications used for the treatment of EoE (these are considered rescue medications):
  - Swallowed topical corticosteroids
  - Systemic corticosteroids
  - Start or dose change of systemic leukotriene inhibitors, topical, nasal, and/or inhaled corticosteroids
  - Systemic treatment for EoE with an immunosuppressive/immunomodulating substance (including, but not limited to, omalizumab, cyclosporine, mycophenolate-mofetil, azathioprine, methotrexate, IFN-γ, or other biologics)
- Allergen immunotherapy (SCIT and SLIT are allowed if dose is stable for 1 year or more; however, OIT is prohibited)
- Patients who are not using PPI in the 8 weeks prior to screening cannot start PPI therapy prior to EOT visit

- Treatment with a live (attenuated) vaccine

Chickenpox (varicella)	Oral typhoid
FluMist-Influenza	Rubella
Intranasal influenza	Smallpox (vaccinia)
Measles (rubeola)	Yellow fever
Measles-mumps-rubella combination	Bacille Calmette-Guerin
Measles-mumps-rubella-varicella combination	Rotavirus
Mumps	Varicella zoster (shingles)
Oral polio (Sabin)	

- Treatment with an investigational drug (other than dupilumab)

The following concomitant procedures are prohibited during study treatment (through week 12):

- Major elective surgical procedures
- Esophageal dilation (considered rescue procedure)
- Diet change (patients should remain on stable diet for at least 6 weeks prior to screening and during the course of the study; stable diet is defined as no initiation of single or multiple elimination diets or reintroduction of previously eliminated food groups)

5.5.3. Restricted Medications and Procedures after Week 12

Patients may receive the prohibited medications/procedures listed in Section 5.5.2 as needed after week 12, with the exception of live (attenuated) vaccine, which should not be used within 3 months after the last dose of study drug. Investigators are advised to prescribe prohibited medications/procedures judiciously, only when they are absolutely required for the appropriate management of study patients.

5.5.3.1. Prohibited Concomitant Medications or Procedures as Rescue

If medically necessary (eg, for treatment of intolerable EoE symptoms) patients may be rescued with a prohibited medication or procedure (as defined in Section 5.5.2) at the discretion of the investigator. Patients who receive rescue treatment with a prohibited medication or procedure through week 12 will be permanently discontinued from study drug. These patients will remain blinded and will be asked to return to the clinic for all remaining study treatment visits and participate in all follow-up assessments according to the visit schedule. Investigators should make every attempt to obtain efficacy measurements before initiation of rescue treatment.

6. STUDY SCHEDULE OF EVENTS AND VISIT DESCRIPTIONS

6.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 1 and Table 2.

Table 1: Schedule of Events – Screening and Treatment Period

Study Procedures	Screening	Treatment Period												
In-Clinic Visit (V) or Telephone Visit (TV)	Screening V1	Baseline V2	V3	V4	V5	V6	TV7[1]	TV8[1]	TV9[1]	V10	TV11[1]	TV12[1]	TV13[1]	EOT V14
Week (Wk)			Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk9	Wk10	Wk11	Wk12
Day (D)	D-35 to D-1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85
Visit Window in days (d)			±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d
Screening/Baseline:														
Informed consent[2]	X													
Inclusion/exclusion	X	X												
Medical history/demographics/height	X													
Randomization		X												
Treatment:														
Training for self-injection[3]		X	X	X	X	X								
Administer study drug		X[4]	X[4]	X[4]	X[4]	X[4]	X[1]	X[1]	X[1]	X[4]	X[1]	X[1]	X[1]	
Con meds/procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:[5]														
SDI/EEsAI (PRO)[6,7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EoE-QOL-A (PRO)[7,8]		X				X				X				X
EoE-EREFS[9]	X													X
Safety:[5]														
Weight	X	X	X	X	X	X				X				X
Vital signs	X	X[10]												X
Diet History	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination; ECG	X													X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedures	Screening	Treatment Period												
In-Clinic Visit (V) or Telephone Visit (TV)	Screening V1	Baseline V2	V3	V4	V5	V6	TV7[1]	TV8[1]	TV9[1]	V10	TV11[1]	TV12[1]	TV13[1]	EOT V14
Week (Wk)			Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk9	Wk10	Wk11	Wk12
Day (D)	D-35 to D-1	D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D78	D85
Visit Window in days (d)			±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d	±3 d
Laboratory Testing:[5]														
Hematology and serum chemistry	X	X		X		X				X				X
Coagulation[11]	X													X
Urinalysis	X	X				X				X				X
HBsAg and hepatitis C Ab	X													
Pregnancy testing	Serum	Urine				Urine				Urine				Urine
Serum FSH to confirm menopausal status	X													
Endoscopy with esophageal biopsies[12]	X[13]													X
Serum total IgE	X													
Research samples (serum/plasma)	X	X		X		X				X				X
[redacted]		X												
[redacted]	X	X												
PK and ADA Testing:[5]														
PK sample		X	X	X	X	X				X				X
ADA sample		X		X		X								X

ADA = anti-drug antibody; ECG = electrocardiogram; EEsAI = Eosinophilic Esophagitis Activity Index; EoE-EREFS = Eosinophilic Esophagitis-Endoscopic Reference Score; EoE-QOL-A = Adult Eosinophilic Esophagitis Quality of Life (questionnaire); EOT = end of treatment; PK = pharmacokinetic; PRO = patient-reported outcome; SDI = Straumann Dysphagia Instrument; TV = telephone visit; V = visit.

[1] The site will contact the patient by telephone to conduct these visits. The patient/caregiver will self-administer study drug outside clinic on these days. Patients will complete a dosing diary to document compliance with self-injection of study drug and to document any ISRs and concomitant medications. Patients may return to the clinic on a weekly basis if unable to self-administer study drug.

[redacted]

[3] Patients and/or caregivers will be trained on self-administration of study drug. Patients will be closely monitored at the study site at visits 2, 3, 4, 5, and 6 for a minimum of 30 minutes after the administration of study drug. In addition to the predose assessments, AEs will be assessed at 30 minutes (±10 minutes) postdose.

[4] On scheduled in-clinic study visit days, the study drug will be administered in the clinic (by site staff, the patient, or a caregiver).

[5] Assessments will be performed before the administration of study drug.

[6] Questionnaires will be completed before any other assessments or procedures.

[7] The SDI/EEsAI PROs should be done by the patient electronically, weekly for SDI, and daily and weekly for EEsAI from the beginning of screening through EOS or ET. Site should confirm patient compliance at each clinic visit.

[8] The EoE-QOL-A PRO should be recorded at baseline and then monthly through EOS or ET.

[9] EoE-EREFS should be completed when endoscopy with esophageal biopsies procedure is performed.

[10] Vital signs at predose and 30 (±10) minutes postdose.

[11] Coagulation tests should be performed before the procedure of endoscopy with esophageal biopsies on days the procedure is performed.

[12] The EndoFLIP procedure, with photographs, to measure esophageal distensibility will be performed during the endoscopy procedures.

[13] Screening endoscopy with esophageal biopsies, and photographs are to be performed during screening period to allow results to be available prior to day -1.

Table 2: Schedule of Events –Follow-up Period

Study Procedures	**Follow-Up Period**				**ET Visit** (if applicable)
In-Clinic Visit (V)	**V15**	**V16**	**V17**	**EOS Visit V18**	
Week (Wk)	**Wk16**	**Wk20**	**Wk24**	**Wk28**	
Day (D)	**D113**	**D141**	**D169**	**D197**	
Visit Window in days (d)	**±3 d**	**±3 d**	**±3 d**	**±3 d**	
Treatment:					
Concomitant medications/procedures	X	X	X	X	X
Efficacy:					
SDI/EEsAI (PRO)[1,2]	X	X	X	X	X
EoE-QOL-A (PRO)[1,3]	X	X	X	X	X
EoE-EREFS [4]					X
Safety:					
Weight	X	X	X	X	X
Diet History	X	X	X	X	X
Physical examination; ECG				X	X
Adverse events	X	X	X	X	X
Laboratory Testing:					
Hematology and serum chemistry	X	X	X	X	X
Coagulation					X
Urinalysis	X	X	X	X	X
Pregnancy testing		Urine		Serum	Serum
Endoscopy with esophageal biopsies [5]					X
Research samples (serum/plasma)		X		X	
PK and ADA Testing:					
PK sample	X	X	X	X	X

Study Procedures	**Follow-Up Period**				**ET Visit** (if applicable)
In-Clinic Visit (V)	**V15**	**V16**	**V17**	**EOS Visit V18**	
Week (Wk)	**Wk16**	**Wk20**	**Wk24**	**Wk28**	
Day (D)	**D113**	**D141**	**D169**	**D197**	
Visit Window in days (d)	**±3 d**	**±3 d**	**±3 d**	**±3 d**	
ADA sample [6]		X		X [6]	X [6]

ADA = anti-drug antibody; ECG = electrocardiogram; EEsAI = Eosinophilic Esophagitis Activity Index; EoE-EREFS = Eosinophilic Esophagitis-Endoscopic Reference Score; EoE-QOL-A = Adult Eosinophilic Esophagitis Quality of Life (questionnaire); EOS = end of study; ET = early termination; PK = pharmacokinetic; PRO = patient-reported outcome; SDI = Straumann Dysphagia Instrument.

[1] Questionnaires will be completed before any other assessments or procedures.

[2] The SDI/EEsAI PROs should be done by the patient electronically, weekly for SDI, and daily and weekly for EEsAI from the beginning of screening through EOS or ET. Site should confirm patient compliance at each clinic visit.

[3] The EoE-QOL-A PRO should be recorded at baseline and then monthly through EOS or ET.

[4] EoE-EREFS should be completed when endoscopy with esophageal biopsies procedure is performed.

[5] The EndoFLIP procedure, with photographs, to measure esophageal distensibility will be performed during the endoscopy procedures.

[6] Patients who are ADA positive at their last study visit (ET visit or EOS visit) will be considered for follow-up based on the overall clinical presentation at that time. Patients who are identified for follow-up may be asked to return to the clinic to have additional ADA samples collected for analysis (see Section 6.3.4.2 for details).

6.2. Study Visit Descriptions

6.2.1. Visit 1/Screening/Day –35 to Day -1

A screening assessment to determine study eligibility will be performed at this visit after the patient has provided signed informed consent. The patient will be assigned a unique patient number once the ICF has been signed.

Patients who fail screening for exclusion criteria, eg, concomitant medications, acute illness (upper respiratory tract infection), required drug-specific discontinuation periods, or laboratory tests, may be rescreened for study eligibility 1 additional time.

The following information will be collected:

- Inclusion/exclusion criteria
- Medical history, including diagnosis of chronic EoE
- Demographics (eg, date of birth, race, ethnicity)
- Concomitant medications/procedures
- AEs
- [redacted]

The following procedures will be conducted:

- SDI and EEsAI PROs (should be completed by the patient electronically before any other assessments or procedures; site should advise the patient to complete SDI weekly and EEsAI daily and weekly, and confirm patient compliance at each clinic visit)
- Weight
- Height
- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- Diet History
- Physical examination
- Electrocardiogram (ECG)
- Laboratory samples:
  - HBsAg
  - Hepatitis C antibody
  - Hematology w/differential
  - Serum chemistry
  - Coagulation (should be obtained before the procedure of endoscopy with biopsies)

  - Serum total IgE
  - Urinalysis
  - Serum human chorionic gonadotropin (hCG) – for women of childbearing potential
  - Serum FSH – for confirmation of menopausal status, if menopausal status is in question
  - Research samples (serum/plasma)
  - [redacted]

- Screening endoscopy with biopsies and photographs (to be performed during the screening period to allow results to be available prior to day -1 for assessment of eligibility).

  The Endolumenal Functional Lumen Imaging Probe (EndoFLIP) procedure with photographs to measure esophageal distensibility will be performed during the endoscopy procedure.

- Eosinophilic Esophagitis-Endoscopic Reference Score (EoE-EREFS)

6.2.2. Treatment Period

6.2.2.1. Visit 2/Baseline/Day 1

The following information will be collected:

- Confirm eligibility
- Concomitant medications/procedures
- AEs

The following procedures will be conducted by the investigator or designee:

- Questionnaires (should be completed by the patient in the following order before any other assessments or procedures)
  - SDI/EEsAI PROs (should be completed by the patient electronically; site should remind the patient to complete SDI weekly and EEsAI daily and weekly; confirm patient compliance)
  - Adult Eosinophilic Esophagitis Quality of Life (EoE-QOL-A) PRO
- Weight
- Vital signs (heart rate, blood pressure, body temperature, and respiration rate) at predose and 30 (±10) minutes postdose
- Diet History
- Laboratory samples:
  - Hematology w/differential

  - Serum chemistry
  - Urinalysis
  - Urine pregnancy test – for women of childbearing potential
  - Research samples (serum/plasma)
  - PK sample
  - ADA sample
  - [redacted]
  - [redacted]

- Randomization
- Administer study drug/train patient (or caregiver)/observe patient injection technique
  - Monitor the patient for a minimum of 30 minutes after the SC injection. In addition to the predose assessments, vital signs and AE assessments will be done at 30 minutes (±10 minutes) post injection.

6.2.2.2. Visit 3/Day 8/Week 1 (± 3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures will be conducted by the investigator or designee:

- SDI/EEsAI PROs (should be completed by the patient electronically before any other assessments or procedures; (should be completed by the patient electronically; site should remind the patient to complete SDI weekly and EEsAI daily and weekly; confirm patient compliance)
- Weight
- Diet History
- Laboratory samples:
  - PK sample
- Administer study drug/train patient (or caregiver)/observe patient injection technique
  - Monitor the patient for a minimum of 30 minutes after the SC injection. In addition to the predose assessments, AE assessments will be done at 30 minutes (±10 minutes) post-injection.

6.2.2.3. Visit 4/Day 15/Week 2 (± 3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures will be conducted by the investigator or designee:

- SDI/EEsAI PROs (should be completed by the patient electronically before any other assessments or procedures; (should be completed by the patient electronically; site should remind the patient to complete SDI weekly and EEsAI daily and weekly; confirm patient compliance)
- Weight
- Diet History
- Laboratory samples:
  - Hematology w/differential
  - Serum chemistry
  - Research samples (serum/plasma)
  - PK sample
  - ADA sample
- Administer study drug/train patient (or caregiver)/observe patient injection technique
  - Monitor the patient for a minimum of 30 minutes after the SC injection. In addition to the predose assessments, AE assessments will be done at 30 minutes (±10 minutes) post-injection.

6.2.2.4. Visit 5/Day 22/Week 3 (± 3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures will be conducted by the investigator or designee:

- SDI/EEsAI PROs (should be completed by the patient electronically before any other assessments or procedures; (should be completed by the patient electronically; site should remind the patient to complete SDI weekly and EEsAI daily and weekly; confirm patient compliance)
- Weight
- Diet History

- Laboratory samples:
  - PK sample
- Administer study drug/train patient (or caregiver)/observe patient injection technique
  - Monitor the patient for a minimum of 30 minutes after the SC injection. In addition to the predose assessments, AE assessments will be done at 30 minutes (±10 minutes) post-injection.

6.2.2.5. Visit 6/Day 29/Week 4 (± 3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures will be conducted by the investigator or designee:

- Questionnaires (should be completed by the patient in the following order before any other assessments or procedures)
  - SDI/EEsAI PROs (should be completed by the patient electronically; site should remind the patient to complete SDI weekly and EEsAI daily and weekly; confirm patient compliance)
  - EoE-QOL-A PRO
- Weight
- Diet History
- Laboratory samples:
  - Hematology w/differential
  - Serum chemistry
  - Urinalysis
  - Urine pregnancy test – for women of childbearing potential
  - Research samples (serum/plasma)
  - PK sample
  - ADA sample
- Administer study drug/train patient (or caregiver)/observe patient injection technique
  - Monitor the patient for a minimum of 30 minutes after the SC injection In addition to the predose assessments, AE assessments will be done at 30 minutes (±10 minutes) post injection.

6.2.2.6. Telephone Visit 7/Day 36/Week 5 (±3 Days)

The following information will be collected:

- SDI/EEsAI PROs (should be completed by the patient electronically; site should remind the patient to complete SDI weekly and EEsAI daily and weekly)
- Concomitant medications/procedures
- AEs
- Diet History

Study drug will be administered by the patient/caregiver off-site. Patients will complete a dosing diary to document compliance with self-injection of study drug and to document any ISRs and concomitant medications. Patients may return to the clinic on a weekly basis if unable to self-administer study drug.

6.2.2.7. Telephone Visit 8/Day 43/Week 6 (±3 Days)

The following information will be collected:

- SDI/EEsAI PROs (should be completed by the patient electronically; site should remind the patient to complete SDI weekly and EEsAI daily and weekly)
- Concomitant medications/procedures
- AEs
- Diet History

Study drug will be administered by the patient/caregiver off-site. Patients will complete a dosing diary to document compliance with self-injection of study drug and to document any ISRs and concomitant medications. Patients may return to the clinic on a weekly basis if unable to self-administer study drug.

6.2.2.8. Telephone Visit 9/Day 50/Week 7 (±3 Days)

The following information will be collected:

- SDI/EEsAI PROs (should be completed by the patient electronically; site should remind the patient to complete SDI weekly and EEsAI daily and weekly)
- Concomitant medications/procedures
- AEs
- Diet History

Study drug will be administered by the patient/caregiver off-site. Patients will complete a dosing diary to document compliance with self-injection of study drug and to document any ISRs and concomitant medications. Patients may return to the clinic on a weekly basis if unable to self-administer study drug.

6.2.2.9. Visit 10/Day 57/Week 8 (± 3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures will be conducted by the investigator or designee:

- Questionnaires (should be completed by the patient in the following order before any other assessments or procedures)
  - SDI/EEsAI PROs (should be completed by the patient electronically; site should remind the patient to complete SDI weekly and EEsAI daily and weekly; confirm patient compliance)
  - EoE-QOL-A PRO
- Weight
- Diet History
- Laboratory samples:
  - Hematology w/differential
  - Serum chemistry
  - Urinalysis
  - Urine pregnancy test – for women of childbearing potential
  - Research samples (serum/plasma)
  - PK sample
- Administer study drug

6.2.2.10. Telephone Visit 11/Day 64/Week 9 (±3 Days)

The following information will be collected:

- SDI/EEsAI PROs (should be completed by the patient electronically; site should remind the patient to complete SDI weekly and EEsAI daily and weekly)
- Concomitant medications/procedures
- AEs
- Diet History

Study drug will be administered by the patient/caregiver off-site. Patients will complete a dosing diary to document compliance with self-injection of study drug and to document any ISRs and concomitant medications. Patients may return to the clinic on a weekly basis if unable to self-administer study drug.

6.2.2.11. Telephone Visit 12/Day 71/Week 10 (±3 Days)

The following information will be collected:

- SDI/EEsAI PROs (should be completed by the patient electronically; site should remind the patient to complete SDI weekly and EEsAI daily and weekly)
- Concomitant medications/procedures
- AEs
- Diet History

Study drug will be administered by the patient/caregiver off-site. Patients will complete a dosing diary to document compliance with self-injection of study drug and to document any ISRs and concomitant medications. Patients may return to the clinic on a weekly basis if unable to self-administer study drug.

6.2.2.12. Telephone Visit 13/Day 78/Week 11 (±3 Days)

The following information will be collected:

- SDI/EEsAI PROs (should be completed by the patient electronically; site should remind the patient to complete SDI weekly and EEsAI daily and weekly)
- Concomitant medications/procedures
- AEs
- Diet History

Study drug will be administered by the patient/caregiver off-site. Patients will complete a dosing diary to document compliance with self-injection of study drug and to document any ISRs and concomitant medications. Patients may return to the clinic on a weekly basis if unable to self-administer study drug.

6.2.2.13. End-of-Treatment Visit/Visit 14/Day 85/Week 12 (± 3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures will be conducted by the investigator or designee:

- Questionnaires (should be completed by the patient in the following order before any other assessments or procedures)
  - SDI/EEsAI PROs (should be completed by the patient electronically; site should remind the patient to complete SDI weekly and EEsAI daily and weekly; confirm patient compliance)
  - EoE-QOL-A PRO
- Weight

- Vital signs (heart rate, blood pressure, body temperature, and respiration rate)
- Diet History
- Physical examination
- ECG
- Laboratory samples:
  - Hematology w/differential
  - Serum chemistry
  - Coagulation (should be obtained before the procedure of endoscopy with biopsies)
  - Urinalysis
  - Urine pregnancy test – for women of childbearing potential
  - Research samples (serum/plasma)
  - PK sample
  - ADA sample
- Endoscopy with biopsies and photographs (the EndoFLIP procedure to measure esophageal distensibility will be performed during the endoscopy procedure)
- EoE-EREFS

6.2.3. Follow-up Period

6.2.3.1. Visit 15/Day 113/Week 16 (± 3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures will be conducted by the investigator or designee:

- Questionnaires (should be completed by the patient in the following order before any other assessments or procedures)
  - SDI/EEsAI PROs (should be completed by the patient electronically; site should remind the patient to complete SDI weekly and EEsAI daily and weekly; confirm patient compliance)
  - EoE-QOL-A PRO
- Weight
- Diet History

- Laboratory samples:
  - Hematology w/differential
  - Serum chemistry
  - Urinalysis
  - PK sample

6.2.3.2. Visit 16/Day 141/Week 20 (± 3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures will be conducted by the investigator or designee:

- Questionnaires (should be completed by the patient in the following order before any other assessments or procedures)
  - SDI/EEsAI PROs (should be completed by the patient electronically; site should remind the patient to complete SDI weekly and EEsAI daily and weekly; confirm patient compliance)
  - EoE-QOL-A PRO
- Weight
- Diet History
- Laboratory samples:
  - Hematology w/differential
  - Serum chemistry
  - Urinalysis
  - Urine pregnancy test – for women of childbearing potential
  - Research samples (serum/plasma)
  - PK sample
  - ADA sample

6.2.3.3. Visit 17/Day 169/Week 24 (± 3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures will be conducted by the investigator or designee:

- Questionnaires (should be completed by the patient in the following order before any other assessments or procedures)
  - SDI/EEsAI PROs (should be completed by the patient electronically; site should remind the patient to complete SDI weekly and EEsAI daily and weekly; confirm patient compliance)
  - EoE-QOL-A PRO
- Weight
- Diet History
- Laboratory samples:
  - Hematology w/differential
  - Serum chemistry
  - Urinalysis
  - PK sample

6.2.4. End-of-Study Visit/Visit 18/Day 197/Week 28 (± 3 Days)

The following information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures will be conducted by the investigator or designee:

- Questionnaires (should be completed by the patient in the following order before any other assessments or procedures)
  - SDI/EEsAI PROs (should be completed by the patient electronically; site should remind the patient to complete SDI weekly and EEsAI daily and weekly; confirm patient compliance)
  - EoE-QOL-A PRO
- Weight
- Diet History
- Physical examination
- ECG
- Laboratory samples:
  - Hematology w/differential
  - Serum chemistry
  - Urinalysis

- Serum hCG – for women of childbearing potential
- Research samples (serum/plasma)
- PK sample
- ADA sample - Patients who are ADA positive at their last study visit will be considered for follow-up and may be asked to return to the clinic to have additional ADA samples collected for analysis (see Section 6.3.4.2 for details)

6.2.5. Early Termination Visit

Patients who withdraw from the study before the primary endpoint visit (week 12) will be asked to return to the clinic for 2 visits: once for early termination assessments, as listed below, and again at week 12 (primary endpoint visit), as described in Section 6.2.2.13. Patients who are withdrawn from the study after the primary endpoint visit will be asked to return to the clinic for early termination assessments only, as described below.

The following early termination information will be collected:

- Concomitant medications/procedures
- AEs

The following procedures will be conducted by the investigator or designee:

- Questionnaires (should be completed by the patient in the following order before any other assessments or procedures)
  - SDI/EEsAI PROs (should be completed by the patient electronically; confirm patient compliance)
  - EoE-QOL-A PRO
- Weight
- Diet History
- Physical examination
- ECG
- Laboratory samples:
  - Hematology w/differential
  - Serum chemistry
  - Coagulation (should be obtained before the procedure of endoscopy with biopsies; not needed the procedure is not performed)
  - Urinalysis
  - Serum hCG – for women of childbearing potential
  - PK sample

  - ADA sample - Patients who are ADA positive at their last study visit will be considered for follow-up and may be asked to return to the clinic to have additional ADA samples collected for analysis (see Section 6.3.4.2 for details)
- Endoscopy with biopsies and photographs procedure (not needed if already performed at week 12); the EndoFLIP procedure with photographs to measure esophageal distensibility will be performed during the endoscopy procedures.
- EoE-EREFS (not needed if the procedure of endoscopy with esophageal biopsies is not performed)

6.2.6. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted. Assessments should be performed as outlined in Table 2.

6.3. Study Procedures

6.3.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed only at the screening and/or baseline visit for the sole purpose of determining study eligibility or characterizing the baseline population: serum FSH (for confirmation of menopausal status), serum total IgE, HBsAg, and hepatitis C antibody.

6.3.2. Efficacy Procedures

6.3.2.1. Straumann Dysphagia Instrument - Patient-reported Outcome

The SDI is a non-validated PRO that has been used in clinical studies to determine the frequency and intensity of dysphagia (Straumann 2010). The SDI has a 1-week recall period. Frequency of dysphagia events is graded on a 5-point scale: 0 = none, 1 = once per week, 2 = several times per week, 3 = once per day, and 4 = several times per day, and intensity of dysphagia events is graded on a 6-point scale: 0 = swallowing unrestricted, 1 = slight sensation of resistance, 2 = slight retching with delayed passage, 3 = short period of obstruction necessitating intervention (eg, drinking, breathing), 4 = longer-lasting period obstruction only removable by vomiting, and 5 = long-lasting complete obstruction requiring endoscopic intervention. The total SDI score ranges from 0 to 9. In the Straumann study, a clinical response (improvement) was defined as a decrease in SDI score of at least 3 points from baseline.

This assessment will be completed by the patient electronically weekly in a questionnaire from the beginning of screening through end of study or early termination. Items utilized to quantitate the SDI are included in the EEsAI/SDI, which is provided in the study reference manual.

6.3.2.2. Eosinophilic Esophagitis Activity Index - Patient-reported Outcome

The EEsAI is a non-validated, multimodular index in development at University Hospital Inselspital (Berne, Switzerland) (Schoepfer 2013), a part of the international EEsAI study group. The EEsAI PRO module (questionnaire) used in this study includes items related to the intensity and frequency of dysphagia, the influence of specific food groups on dysphagia symptoms, and

other symptoms independent of eating or drinking (ie, heartburn, acid regurgitation, and chest pain). The total EEsAI PRO score ranges from 0 to 100. The EEsAI PRO utilizes 24-hour and 1-week recall periods.

This assessment will be completed by the patient electronically daily and weekly in a questionnaire from the beginning of screening through end of study or early termination. A copy of the SDI/EEsAI is provided in the study reference manual.

6.3.2.3. Adult Eosinophilic Esophagitis Quality of Life Questionnaire - Patient-reported Outcome

The EoE-QOL-A questionnaire is a validated disease-specific measure of health-related quality of life in EoE patients (Taft 2011). The instrument used in this study, the EoE-QOL-A v.3.0, includes 30 items related to established domains such as social functioning, emotional functioning, and disease impact of daily life experiences. The EoE-QOL-A has a 1-week recall period. The items are graded on a 5-point scale: 'Not at All,' 'Slightly,' 'Moderately,' 'Quite a bit,' and 'Extremely'.

This assessment will be recorded by the patient in a questionnaire at baseline and then monthly through end of study or early termination. A copy of the EoE-QOL-A is provided in the study reference manual.

6.3.2.4. Endoscopy with Esophageal Biopsies and Photographs

Esophageal biopsies will be obtained by endoscopy at the screening and week 12 visits. The screening endoscopy should be performed during the screening period to allow results to be available prior to day -1 for assessment of eligibility. A total of 9 mucosal pinch biopsies will be collected at each time point from 3 esophageal regions: 3 proximal, 3 mid, and 3 distal. Two samples from each region will be used for the histology (needed for study inclusion criteria, as well as secondary endpoint). To participate in the study, patients must have a peak intraepithelial eosinophil count ≥15 eos/hpf (400X) in at least 2 of the 3 esophageal regions sampled. Change in peak esophageal eos/hpf (400X) from baseline to week 12 is a secondary endpoint; this will be determined by counting eosinophils in the most inflamed areas of each esophageal region sampled at each time point and calculating the change in the peak count at each site obtained at baseline compared to the count obtained at week 12. As an exploratory objective, the change in the mean of all 3 peak counts, ie, the peak count at each of the 3 esophageal regions for each patient at each time point (screening and week 12) will be calculated. Tissue blocks remaining after the histological assessment will be banked for exploratory research. The third sample from each region will be processed to bank tissue RNA for exploratory research (Section 6.3.5). Biopsy samples will be sent to a central pathology laboratory for processing and analysis. If required by the investigator institution, biopsy samples will be processed and analyzed by the local laboratory, and the processed specimen will be sent to the central pathology laboratory for central reading.

The EoE-EREFS will be used to measure the endoscopically identified EoE esophageal mucosal inflammatory and remodeling features. This instrument includes a total of 17 items related to the presence and severity of esophageal features. The specific esophageal features include: rings (absent, mild, moderate, severe, not applicable); stricture (yes, no, not applicable); diameter of

the stricture (if applicable); exudates (absent, mild, severe), furrows (absent, present); edema (absent, present); crêpe paper esophagus (absent, present); overall general appearance incorporating all endoscopically identified EoE findings (ie, fixed rings, strictures, whitish exudates, furrowing, edema, and crêpe paper mucosa). In addition, 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 EoE esophageal characteristics will be analyzed based on the EoE-EREFS, a validated scoring system for inflammatory and remodeling features of disease using both overall scores and scores for each individual characteristic (Hirano 2013). The EoE-EREFS should be performed by the physician who performs the endoscopy procedure.

The assessment of esophageal distensibility utilizing the endolumenal functional lumen imaging probe (EndoFLIP, Crospon, Ireland) will also be performed, with measurements taken as part of the endoscopy procedure performed at screening and week 12. The EndoFLIP device is a catheter based procedure that measures the cross sectional area at multiple sites along the esophagus with simultaneous intraluminal pressure recordings during volumetric distension of the esophagus. The analyses of cross sectional area versus pressure relationships of the esophagus allow for determination of esophageal compliance as well as the distensibility plateau (DP). The DP has been shown to be significantly reduced in patients with EoE compared to healthy controls (Kwiatek 2011). Moreover, the esophageal distensibility has been associated with outcomes of both food impaction and need for esophageal dilation (Nicodème 2013). Details of the EndoFLIP procedure will be provided in the study manual.

Histology results will be interpreted by a pathologist at a central pathology reading center who will be blinded to the treatment assignment. Detailed instructions for biopsy sample collection and handling will be provided in the site manual. A copy of the EoE-EREFS is provided in the study reference manual.

Photographs may be taken by the site as part of the endoscopic procedure and biopsy collection. A copy of these photos will be requested for this study. Details for collecting and sending these photographs will be provided in the study reference manual.

6.3.3. Safety Procedures

6.3.3.1. Physical Examination

A thorough and complete physical examination will be performed at time points according to Section 6.2 and Table 1 and Table 2. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

6.3.3.2. Vital Signs

Vital signs, including heart rate, blood pressure, body temperature, and respiration rate, will be collected at time points listed in Section 6.2 and Table 1 and Table 2. Heart rate and blood pressure will be measured with the patient in sitting position, after the patient has rested comfortably for at least 5 minutes.

6.3.3.3. Electrocardiogram

Electrocardiograms will be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at time points listed in Section 6.2 and Table 1 and Table 2. The ECG strips or reports will be retained with the source documentation, and the results will be documented in the electronic case report form (eCRF).

Electrocardiogram results will be interpreted by a central reading center. Instructions for performing the assessment and transmitting ECG data are provided in the study reference manual.

6.3.3.4. Laboratory Testing

Hematology, chemistry, urinalysis, and serum pregnancy samples will be analyzed by a central laboratory.

Blood samples for chemistry and hematology testing (safety labs) will be collected at screening, baseline, and subsequent study visits listed in Section 6.2 and Table 1 and Table 2. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites. Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total and indirect bilirubin
Potassium	Creatinine	Total cholesterol
Chloride	Blood urea nitrogen (BUN)	Low-density lipoprotein (LDL)
Carbon dioxide	AST	High-density lipoprotein (HDL)
Calcium	ALT	Triglycerides
Glucose	Alkaline phosphatase	Uric acid
Albumin	Lactate dehydrogenase (LDH)	CPK

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils

Urinalysis

Microscopic analysis will only be done in the event of abnormal dipstick results.

Color	Glucose	RBC
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBC	Yeast

Other Laboratory Tests

- Pregnancy testing will be performed for all women of childbearing potential. Serum or urine pregnancy testing will be performed at time points listed in Section 6.2 and Table 1 and Table 2. A serum FSH test will be performed if menopausal status is in question.
- Coagulation testing (prothrombin time [PT] and partial thromboplastin time [PTT]) will be performed at the screening, end of study treatment, and early termination (if applicable) visits. Samples for coagulation tests should be obtained before the procedures of endoscopy with esophageal biopsies are performed.
- Serum total IgE will be performed at screening.

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the investigator or authorized designee.
- Significantly abnormal tests must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the medical monitor must be consulted.
- The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 7.2.5.

6.3.4. Pharmacokinetic and Antibody Procedures

6.3.4.1. Drug Concentration Measurements and Samples

Samples for drug concentrations will be collected predose at time points listed in Section 6.2 and Table 1 and Table 2.

6.3.4.2. Anti-drug Antibody Measurements and Samples

Serum samples for ADA assessments will be collected at time points as shown in Table 1 and Table 2 and Section 6.2.

Patients who are ADA positive at their last study visit (early termination or end of study) will be considered for follow-up based on the overall clinical presentation at that time. Patients who are identified for follow-up may be asked to return to the clinic to have additional ADA samples collected for analysis.

6.3.5. Research Assessments

Results for the assessments described in the subsections below will not be reported in the clinical study report but will be available in separate reports.

Any unused samples collected for drug concentration and ADA measurements may be used for exploratory research, described in Section 6.3.5.1.

6.3.5.1. Research Samples

Research samples (serum/plasma/esophageal biopsies) will be collected at time points listed in Section 6.2 and Table 1 and Table 2.

Use and Storage of Research Samples (Serum/Plasma/Esophageal Biopsies)

Research serum, plasma, and esophageal biopsy samples will be banked and may be used to study the effects of the study drug on target pathway modulation and EoE pathophysiology. Stored samples may also be used to discover markers predictive of dupilumab response as well as identify markers associated with toxicity. Details for banking samples will be provided in the study manual.

Technologies that may be employed include circulating protein marker analyses (eg, ELISA, electrochemiluminescence, etc.), immunohistochemistry and/or histology of biopsies, and/or transcriptome analyses of blood and/or biopsy samples (eg, microarray, transcriptome sequencing, and/or quantitative reverse transcriptase-polymerase chain reaction [qRT-PCR]).

Detailed instructions for sample collection and handling will be provided in the laboratory manual.

7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1. Definitions

7.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug, which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

7.1.2. Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or prolongation of existing hospitalization. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 1 of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

7.2. Recording and Reporting Adverse Events

7.2.1. Adverse Events

The investigator (or designee) will record all AEs that occur from the time the informed consent is signed until the end of study. Refer to the study reference manual for the procedures to be followed.

Detailed information about ISRs will be recorded by the site (or patient if the ISR occurs outside the clinic) using a worksheet provided in the study reference manual.

Information on follow-up for AEs is provided in Section 7.2.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 7.2.5.

7.2.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study drug, must be reported to the sponsor (or designee) within 24 hours. Refer to the study reference manual for the procedure to be followed.

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.

The investigator must promptly report to the Institutional Review Board (IRB)/Ethics Committee (EC) all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs related to the use of the study drug. It is recommended that all SAEs be reported to the IRB/EC, regardless of assessed causality.

In the event the investigator is informed of an SAE after the patient completes the study, the following will apply:

- SAE with an onset within 30 days of the end of study/early termination visit - the SAE will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered chronic and/or stable.
- SAE with an onset day greater than 30 days from the end of study/early termination visit - only fatal SAEs and those deemed by the investigator to be drug-related SAEs will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.

7.2.3. Other Events that Require Accelerated Reporting

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

Symptomatic Overdose of Study Drug: Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE

Pregnancy: Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee) by telephone within 24 hours of identification, any pregnancy occurring in a female patient or female partner of a male patient, during the study or within 120 days of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus, and/or newborn must be reported as an SAE.

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

- Anaphylactic reactions or acute allergic reactions that require immediate treatment
- Severe ISRs that last longer than 24 hours
- Any severe infection, any bacterial infection requiring treatment with parenteral antibiotics or treatment with oral antibiotics for longer than 2 weeks, any clinical endoparasitosis, any opportunistic infection, any viral infection requiring antiviral treatment
- Note: Generally, all uncommon, atypical, peculiar, or unusually persistent infections, especially viral infections, should be reported as AESI.

Refer to the study reference manual for the procedures to be followed.

7.2.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from the study must be reported to the sponsor's medical monitor within 30 days.

Refer to the study reference manual for procedures to be followed.

7.2.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

The criteria for determining whether an abnormal objective test finding should be reported as an AE include:

- the test result is associated with accompanying symptoms, and/or
- the test result requires additional diagnostic testing or medical/surgical intervention, and/or
- the test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), discontinuation from the study, significant additional concomitant drug treatment, or other therapy

Contact the medical monitor in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale presented in Section 7.3.1.

7.2.6. Follow-up

Adverse event information will be collected until the patient's last study visit.

Serious adverse event information will be collected until the event is considered chronic and/or stable.

7.3. Evaluation of Severity and Causality

7.3.1. Evaluation of Severity

The severity of AEs will be graded according to the following scale:

- **Mild:** Does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.
- **Moderate:** Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.
- **Severe:** Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

7.3.2. Evaluation of Causality

The relationship of AEs to study drug is a clinical decision that will be made, based on all available information, by the investigator who will answer the following question:

Is there a reasonable possibility that the AE was caused by the study drug?

The possible answers are:

Not related: There is no reasonable possibility that the event may have been caused by the study drug

Related: There is a reasonable possibility that the event may have been caused by the study drug (ie, a causal relationship cannot reasonably be ruled out)

The investigator will provide a comment on the SAE reporting form to explain the basis of the causality assessment for SAEs.

7.3.2.1. Causality Evaluation Factors

Factors to consider when determining the relationship of an AE to study drug are included below.

Not Related:

- Existence of a clear alternative explanation or non-plausibility (eg, the patient is struck by an automobile when there is no indication that the drug caused disorientation, or cancer diagnosed a few days after the first drug administration)
- Due to external causes such as other treatment(s) being administered
- Due to patient's disease state or clinical condition
- Does not follow a reasonable temporal sequence following the time of administration of the dose of study drug
- Does not appear to worsen when dosing with study drug is resumed (ie, negative re-challenge)
- Is not a known response to the study drug based upon pre-clinical data or prior clinical data

Related:

- Could not be explained by other treatment(s) being administered
- Could not be explained by the patient's disease state or clinical condition
- Follows a reasonable temporal sequence following the time of administration of the dose of study drug
- Resolves or improves after discontinuation of study drug
- Reappears or worsens when dosing with study drug resumes (ie, positive re-challenge)
- Known to be a response to the study drug based upon pre-clinical data or prior clinical data
- Known to be strongly associated with drug exposure (eg, angioedema, Stevens-Johnson Syndrome)

7.4. Safety Monitoring

The investigator will monitor the safety of study patients at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The medical monitor will have primary responsibility for the emerging safety profile of the compound. The study monitor will be supported by other departments (eg, Pharmacovigilance and Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an on-going basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

In addition, the IDMC will conduct safety review for all dupilumab studies (see details in Section 3.3)

7.5. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the Investigator's Brochure, and has a reasonable suspected causal relationship to the medicinal/investigational product).

8. STUDY VARIABLES

8.1. Demographic and Baseline Characteristics

Demographic characteristics will include standard demography (eg, age, race, and weight), medical history, and medication history for each patient. Characteristics of disease, including duration, and disease symptoms, will be collected.

8.2. Primary and Secondary Endpoints

8.2.1. Primary Endpoint

The primary endpoint in the study is change in the Straumann Dysphagia Instrument (SDI) patient-reported outcome (PRO) score from baseline to week 10

8.2.2. Secondary Endpoints

The secondary endpoints are:

- Percent change in weekly Eosinophilic Esophagitis Activity Index (EEsAI) PRO score from baseline to week 10
- Change in weekly EEsAI PRO score from baseline to week 10
- Percent change in weekly EEsAI PRO score from baseline to week 12
- Change in weekly EEsAI PRO score from baseline to week 12
- Percent change in the SDI PRO score from baseline to week 10
- Percent change in the SDI PRO score from baseline to week 12
- Change in the SDI PRO score from baseline to week 12
- Change in EoE-QOL-A PRO score from baseline to week 12
- Percentage of patients with SDI PRO response at week 10; where response is defined as a decrease of at least 3 points on the SDI compared to baseline
- Percentage of patients who achieve ≥40% improvement in EEsAI score from baseline to week 10
- Percent change in overall peak esophageal intraepithelial eos/hpf (400X) from baseline to week 12

- Change in EoE-EREFs (endoscopy visual anatomical score) from baseline to week 12
- Percentage of patients with use of rescue medication or procedure (eg, esophageal dilation) through week 12
- Incidence of treatment-emergent AEs

8.2.3. Exploratory Endpoints

The exploratory efficacy endpoints are:

- Change in mean esophageal intraepithelial eosinophil counts (eos/hpf) [calculated using peak count from each esophageal site] from baseline to week 12
- Proportion of patients who achieve esophageal intraepithelial eosinophil count <1 eos/hpf at week 12
- Change in Collins Histology Score from baseline to week 12
- Change in esophageal distensibility plateau as measured by functional lumen imaging from baseline to week 12

8.3. Pharmacokinetic Variables

The PK variables may include, but are not limited to, the following:

- C_{trough}
- C_{last}
- t_{last}

8.4. Anti-Drug Antibody Variables

Anti-drug antibody variables include status (positive or negative) and titer as follows:

- Total positive at any time
- Preexisting immunoreactivity - a positive ADA response at baseline
- Treatment-emergent - defined as either any positive response when baseline results are negative, or if any post treatment ADA response is greater-than or equal to 4-fold over baseline titer levels
- Persistently positive
- Transiently positive
- Titer value category
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)

9. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The final SAP will be issued before the database is locked.

There will be 2 database locks for this study. The first database lock will occur when the last patient completes the week 12 visit. The purpose of this database lock is to inform the sponsor with regard to a possible phase 3 program. The analysis of primary and secondary efficacy endpoints at the first database lock is considered to be the final analysis of the primary and secondary endpoints. The second database lock will occur when the last patient completes the last visit of the study. For the first database lock, a designated unblinding team (eg, statisticians, SAS programmers, etc.) that is not involved in the conduct of the study will perform the analysis of week 12 outcomes. The study conduct will not be affected by the unblinded week-12 results. The analysis results will be made available only to a limited group of people who are not involved in the daily conduct of the study. Individuals involved in the continuing conduct of the study will remain blinded until after the final database lock. Following the second database lock, efficacy and safety results during the follow-up period will be summarized.

Analysis variables are listed in Section 8.

9.1. Statistical Hypothesis

For all efficacy variables, the analyses will be comparisons of the dupilumab and the placebo treatment groups. The following null and alternative hypotheses will be tested:

H_0: No treatment difference between dupilumab and placebo.

H_1: There is treatment difference between dupilumab and placebo.

Statistical significance will be at a 2-sided 5% level. There will be no adjustment of multiplicity for the secondary efficacy endpoints.

9.2. Justification of Sample Size

The sample size calculations are based on the change from baseline in SDI score to week 12. SDI PRO score ranges from 0 to 9. A 3-point improvement from baseline in the SDI PRO score was defined as a clinical response (Straumann 2010), and is used in this study as well. The study of Straumann 2010 has a 2-week treatment period and the 3-point improvement from baseline is observed at end of week 2. A 3-point improvement from baseline is assumed for the study at both week 10 and week 12, so the power calculation for change from baseline in SDI score to week 12 is the same as the one at week 10.

A sample size of 18 patients per treatment arm will provide 94% power to detect a treatment effect, with an expected mean difference of 3 points in change from baseline to week 12 in SDI score between dupilumab and placebo at a 2-sided t-test with 5% significance level and an assumed SD of 2.46. Taking into account the assumed 15% dropouts, 22 patients per treatment arm will be enrolled.

9.3. Analysis Sets

9.3.1. Efficacy Analysis Set

The full analysis set (FAS) includes all randomized patients. Efficacy analyses will be based on the treatment allocated by the IVRS/IWRS at randomization (as randomized). This is the primary analysis population for efficacy analyses.

9.3.2. Safety Analysis Set

The safety analysis set (SAF) includes all randomized patients who received any study medication and will be analyzed as treated. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

9.3.3. Pharmacokinetic Analysis Set

The PK analysis set includes all randomized patients who received any study medication and who had at least 1 non-missing concentration of functional dupilumab in serum following the first dose of the study medication.

9.3.4. Anti-Drug Antibody Analysis Set

The ADA analysis set includes all treated patients who received any study medication and had at least 1 non-missing post-baseline ADA assay result.

9.4. Patient Disposition

The following will be provided:

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the informed consent form (ICF)
- The total number of randomized patients: received a randomization number
- The total number of patients in each analysis set
- The total number of patients who discontinued the study treatment and the reasons for discontinuation
- The total number of patients who discontinued the study, and the reasons for discontinuation
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation
- A listing of patients prematurely withdraw from study, along with reasons for withdrawal

9.5. Statistical Methods

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, median, standard deviation (SD), minimum, and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category.

9.5.1. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group.

9.5.2. Efficacy Analyses

After rescue medication, the efficacy data (SDI, EEsAI, peak esophageal intraperitoneal eosinophils/high power field (eos/hpf) (400X), EoE-QOL-A scores) will be treated as missing. All collected data can be used in the exploratory analysis. Efficacy data after week 12 will be summarized.

9.5.2.1. Analysis of the Primary Efficacy Endpoints

The change in the SDI score at week 10 from baseline will be analyzed in the FAS using multiple imputation, followed by an analysis of covariance (ANCOVA). Missing data from the FAS will be imputed multiple times (ie, 50 times) to generate a complete dataset at each imputation by using SAS procedure MI. These complete datasets will be analyzed using an ANCOVA model with treatment group as fixed effect and baseline SDI score as a continuous covariate. The SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from these multiple analyses using Rubin's formula. To account for the impact of rescue medication on the efficacy effect: if a patient receives rescue medication, the efficacy data collected after rescue medication is initiated will be treated as missing.

In addition, sensitivity analyses of the primary endpoint will be performed using an analysis of covariance (ANCOVA) model with treatment as the fixed effect, and the baseline SDI values as covariate. The last observation carried forward (LOCF) method will be used to impute missing values for ANCOVA model.

9.5.2.2. Analyses of Secondary Efficacy Endpoints

The continuous secondary efficacy endpoints will be analyzed using the same approach as that used for the analysis of the primary endpoint. For all continuous secondary efficacy endpoints except endpoints related to SDI, the ANCOVA model will include treatment group as fixed effect, the baseline SDI score and relevant baseline value as continuous covariates.

In addition, sensitivity analyses of the secondary continuous variables will be performed using an ANCOVA model with treatment as the fixed effect, baseline SDI score, and relevant baseline values as covariates. The LOCF method will be used to impute missing values for ANCOVA model.

Categorical analyses will be performed on responder data. Comparisons between dupilumab and placebo will be done using the Fisher exact test.-Patients with early withdrawals or use of rescue medication or procedure will be counted as non-responders.

The efficacy data after week 12 will be summarized descriptively.

9.5.3. Safety Analysis

The safety analysis will be based on the SAF. This includes TEAEs and other safety information (ie, clinical laboratory evaluations, vital signs, and 12-lead ECG results). A summary of safety results will be presented for each treatment group.

9.5.3.1. Adverse Events

Definitions

For safety variables, 2 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment-emergent period is defined as day 1 (from start of administration of the first dose of study drug) through the end of the study.
- The treatment-emergent period includes the 12-week treatment period and follow-up period
  - The 12-week treatment period is defined as day 1 from start of administration of the first dose of study drug through week 12 (85 days starting from the first dose of study drug if the date of week 12 treatment visit is unavailable).
  - Follow-up period is defined as from week 12 to end of study.

Treatment-emergent adverse events are defined as those that are not present at baseline or those that represent an exacerbation of a preexisting condition during the treatment-emergent period.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to the lowest level terms. The verbatim text, the preferred term, and the primary system organ class (SOC) will be listed.

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and preferred term
- TEAEs by severity (according to the grading scale outlined in Section 7.3.1), presented by SOC and preferred term
- TEAEs by relationship to treatment (related, not related), presented by SOC and preferred term

Deaths and other SAEs will be listed and summarized by treatment group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized by treatment group.

9.5.3.2. Other Safety

Vital Signs

Vital signs (heart rate, blood pressure, body temperature, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Number and percentage of patients with a treatment-emergent potentially clinically significant value (PCSV) will be summarized for each clinical laboratory test.

Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out of laboratory range values.

9.5.3.3. Treatment Exposure

The duration of exposure during the study will be presented by treatment and calculated as:

(Date of last study drug injection – date of first study drug injection) + 7

The number (%) of patients randomized and exposed to double-blind study drug will be presented by specific time periods for each treatment group. The time periods of interest will be specified in the SAP.

In addition, duration of exposure during the study will be summarized for each treatment group using number of patients, means, standard deviation, minimums, medians, and maximums.

A summary of the number of doses by treatment group will be provided. A summary of the impact of body weight on dupilumab exposure and clinical response will be provided.

9.5.3.4. Treatment Compliance

The compliance with protocol-defined study drug will be calculated as follows:

Treatment Compliance =

(Number of investigational product injections during exposure period)/(Number of planned investigational product injections during exposure period) x 100%

The treatment compliance will be presented by specific ranges for each treatment group. The ranges of interest will be specified in the SAP.

9.5.4. Analysis of Drug Concentration Data

For this study, sampling will be sparse and the types of analyses will be descriptive statistics at each sampling time. No formal statistical analysis will be performed.

9.5.5. Analysis of Anti-Drug Antibody Data

The ADA variables described in Section 8.4 will be analyzed using descriptive statistics. Drug concentration data will be examined and the influence of ADAs on individual concentration-time profiles will be evaluated. Assessment of the impact of ADA on safety and efficacy may be provided.

9.6. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

- The baseline assessment will be the latest, valid predose assessment available.

General rules for handling missing data:

- If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication, except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study medication date, then the start date by the study medication intake date will be imputed, otherwise, the missing day or month by the first day or the first month will be imputed.
- No imputations for missing laboratory data, ECG data, vital sign data, or physical examination data will be made.

Visit windows:

- Assessments taken outside of protocol allowable windows will be displayed according to the CRF assessment recorded by the investigator. Details will be specified in the SAP.

9.7. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

10.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, releasing) will be maintained and stored at Regeneron.

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, medication, medical history/surgical history, etc.) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an EDC tool.

10.2. Electronic Systems

Electronic systems used to process and/or collect data in this study will include the following:

- IVRS/IWRS system – randomization and study drug supply
- EDC system – data capture/uploading
- Electronic patient diary – data capture/uploading
- Central ECG reading center-digital images
- nQuery Advisor – sample size calculations
- Statistical Analysis Software (SAS) – statistical review and analysis
- Pharmacovigilance and Risk Management (PVRM) safety system

11. STUDY MONITORING

11.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. In accordance with ICH guidelines, the monitor will compare the CRF entries with the appropriate source documents. Additional review may include, but is not limited to, patient ICFs, documentation of patient recruitment and follow-up, AEs, SAEs, and concomitant therapy; as well as records of study drug dispensing, compliance, and accountability. A copy of the drug dispensing log must be provided to the sponsor upon request.

11.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents).

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an eCRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

11.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on eCRFs by trained site personnel. A CRF must be completed for each and every patient enrolled in the study. After review of the clinical data for each patient, the investigator must provide an electronic signature.

A copy of each CRF page is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the system. For corrections made via data queries, a reason for any alteration must be provided.

12. AUDITS AND INSPECTIONS

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

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

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH Guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF and documentation of approval must be provided to the sponsor before study medication will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

13.3. Patient Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by their initials and a patient identification number, only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH Guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/EC should be informed as soon as possible

- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design or operation of the protocol or ICF without an IRB/EC-approved amendment.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

16. STUDY DOCUMENTATION

16.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRFs must be signed by the investigator. This certification form accompanies each set of CRFs. The signed form will be provided to the sponsor with the final set of CRFs for each patient.

16.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer if a longer period is required by relevant regulatory authorities. The investigator must consult with the sponsor before discarding or destroying any essential study documents following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor and the relevant records will be transferred to a mutually agreed-upon destination.

17. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

18. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

19. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

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21. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Randomized, Double-Blind, Parallel, Placebo-Controlled Study of the Efficacy, Safety, and Tolerability of Dupilumab in Adult Patients with Active Eosinophilic Esophagitis, amendment 4, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonization Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

Signature of Sponsor's Responsible Officers

(Scientific/Medical Monitor, Regulatory Representative, Clinical Study Team Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the conduct of the study.

Study Title: A Randomized, Double-Blind, Parallel, Placebo-Controlled Study of the Efficacy, Safety, and Tolerability of Dupilumab in Adult Patients with Active Eosinophilic Esophagitis.

Protocol Number: R669-EE-1324.04

See appended electronic signature page

Sponsor's Responsible Scientific/Medical Monitor
[redacted]

See appended electronic signature page

Sponsor's Responsible Regulatory Representative
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Sponsor's Responsible Clinical Study Team Lead
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