NCT Number: NCT03633617

STATISTICAL ANALYSIS PLAN
VERSION: AMENDMENT 1

Clinical Study Protocol Title:

A Phase 3, Randomized, 3-Part Study To Investigate The Efficacy And Safety Of Dupilumab In Adult And Adolescent Patients With Eosinophilic Esophagitis

Part A/Part C

Compound: Dupilumab (REGN668)

Protocol Number: R668-EE-1774.04

Clinical Phase: Phase 3

Sponsor: Regeneron Pharmaceuticals, Inc.

Study Biostatistician: [redacted]

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The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Ab	Antibody
ACQ-5	Asthma Control Questionnaire-5
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
BID	Twice (two times) a day
BUN	Blood urea nitrogen
CMH	Cochran-Mantel-Haenszel (test)
CPK	Creatine phosphokinase
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
C_{trough}	Trough concentration
DMC	Data monitoring committee
DSQ	Dysphagia Symptom Questionnaire
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eCOA	Electronic clinical outcome assessment
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EoE	Eosinophilic esophagitis
EoE-EREFS	Eosinophilic Esophagitis-Endoscopic Reference Score
EoEHSS	EoE Histology Scoring System
EoE-IQ	EoE Impact Questionnaire
EoE-SQ	EoE Symtom Questionnaire
EOS	End of study (visit)
eos/hpf	Eosinophils/high power field
EOT	End of treatment
ET	Early termination
FAS	Full analysis set

FSH	Follicle stimulating hormone
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
IA	Interim analysis
IAF	Informed assent form
ICF	Informed consent form
ICH	International Council for Harmonisation
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
IL	Interleukin
IL-4Rα	Interleukin-4 receptor alpha
ISR	Injection site reaction
IVRS/IWRS	Interactive voice/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
NAb	Neutralizing antibody
OIT	Oral immunotherapy
PCSV	Potentially clinically significant value
PGIC	Patient Global Impression of Change of Dysphagia
PGIS	Patient Global Impression of Severity of Dysphagia
PK	Pharmacokinetic
POEM	Patient-Oriented Eczema Measure
PPI	Proton pump inhibitor
PRO	Patient-reported outcome
PT	Preferred term (MedDRA)
QOL	Quality of life
Q2W	Once every two weeks
QW	Once weekly

RBC	Red blood cell
RQLQ(s)+12	Rhinoconjunctivitis Quality of Life Questionnaires for 12 years and older
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SD	Standard deviation
SLIT	Sublingual immunotherapy
SOC	System organ class
TARC	Thymus and activation-regulated chemokine
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
Th2	Type 2 helper T cell
TNSS	Total Nasal Symptom Score
ULN	Upper limit of normal
WBC	White blood cell
WOCF	Worst observation carried forward

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for R668-EE-1774 study Part A. This SAP will also describe the descriptive summary of Part A patients' data in Part C as extended active treatment and in the 12-week follow-up period. A separate Part B SAP will be prepared for the analysis of data from Part B, and Part B patients' data in Part C and 12-week follow-up period (no separate SAP for Part C).

This plan may be revised during the conduct of study Part A to accommodate protocol amendments and/or to make changes to adapt to unexpected issues in study execution and/or data that affect planned analyses. These revisions will be based on blinded review of the study and data. This plan will be finalized prior to the data lock for end of Part A, i.e., the last Part A patient reaching week 24 visit.

1.1. Background/Rationale

Eosinophilic esophagitis (EoE) is a chronic, inflammatory, allergic/immune-mediated disease of the esophagus. The disease is characterized by local eosinophilic inflammation leading to symptoms of esophageal dysfunction. The primary clinical manifestations of EoE in both adults and adolescents are dysphagia and food impaction (Hudgens, 2017). Growing evidence suggests that a Type 2 cytokine-mediated immune response plays an important role in the development of EoE. 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.

Current therapeutic approaches include high dose proton pump inhibitors, chronic dietary modification with specific food elimination, swallowed topical formulation corticosteroids (not approved for the treatment of EoE in adolescents or in adults outside the European Union [EU]), and esophageal dilation when esophageal narrowing occurs or strictures develop. The therapies for eosinophilic esophagitis are limited by variable response rates, relapse after therapy cessation, and adverse effects on quality of life. High dose proton pump inhibitors lead to histologic remission in approximately half of the patients (Lucendo, 2016). Swallowed topical corticosteroids have been reported in clinical trials to induce partial clinical responses and histologic remission; however, they are not uniformly effective and have been associated with local fungal infections. Endoscopy for prolonged and/or painful food impaction is an emergent procedure utilized for symptomatic relief if the patient cannot pass the food or induce vomiting. It is associated with a risk of severe esophageal injury and does not alter the underlying pathogenesis or progression of the disease. As such, there is a significant unmet need for new treatments across the age spectrum targeting key pathways driving the inflammation in EoE (Rothenberg, 2015, Spergel, 2012, Greuter, 2017).

Dupilumab is a human monoclonal immunoglobulin G4 (IgG4) antibody (Ab) that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4 receptor alpha (IL-4Rα) subunit shared by the IL-4 and IL-13 receptor complexes. Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 Type 2 cytokine-induced responses, including the release of pro-inflammatory cytokines,

chemokines, and IgE. Additionally, preclinical data demonstrate that treatment with dupilumab prevents infiltration of eosinophils into tissues. For these reasons, dupilumab was evaluated in adult patients with EoE in a phase 2, multicenter, double-blind, randomized, placebo-controlled study (R668-EE-1324), where it demonstrated substantial improvements in clinical (based on the Straumann Dysphagia Instrument), histologic, and endoscopic aspects of the disease. Dupilumab was well tolerated in the study, with safety data generally consistent with other dupilumab studies in AD patients, asthma patients, and patients with chronic rhinosinusitis with nasal polyps. No safety signal associated with dupilumab use was identified in the EoE patient population have been identified. The results from phase 2 support the phase 3 evaluation of dupilumab in EoE.

Additional background information on the study drug and development program can be found in the Investigator's Brochure.

This phase 3 study will investigate the efficacy and safety of dupilumab in adult and adolescent patients with EoE in 3 study parts. Part A and Part B are 24-week treatment, randomized, double-blind, placebo-controlled study phases. Patients are randomized in Part A to receive dupilumab 300 mg QW or placebo; patients are randomized in Part B to receive dupilumab 300 mg Q2W, dupilumab 300 mg QW, or placebo. Patients who participate in Part A are not eligible to participate in Part B. At the end of Part A, eligible patients will enter Part C as an extended treatment period to receive dupilumab 300 mg QW. At the end of Part B, eligible patients will enter Part C to receive dupilumab 300 mg Q2W or dupilumab 300 mg QW in a blinded fashion. Patients in Parts A/B who do not enter Part C will enter a 12-week follow-up period immediately after Part A/B.

Two SAPs will be prepared to describe the strategy and statistical methods to be used in the analysis of data for this study:

- This SAP will cover Part A patients' data in Part A, Part C, and the 12-week follow-up period.
- A separate SAP will cover Part B patients' data in Part B, Part C and the 12-week follow-up period.

1.2. Study Objectives

1.2.1. Primary Objectives

Part A

To determine the treatment effect of dupilumab compared with placebo in adult and adolescent patients with EoE after 24 weeks of treatment as assessed by histological and clinical measures, and to inform/confirm the final sample size determination for Part B.

Part C

To assess the safety and efficacy of dupilumab treatment in adult and adolescent patients with EoE after up to 52 weeks of treatment as assessed by histological and clinical measures.

1.2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety, tolerability, and immunogenicity of dupilumab treatment for up to 52 weeks in adult and adolescent patients with EoE
- To explore the relationship between dupilumab concentration and responses in adult and adolescent patients with EoE, using descriptive analyses
- To evaluate the molecular effects of dupilumab on transcriptomic signatures associated with EoE and type 2 inflammation

1.2.3. Modifications from the Statistical Section in the Final Protocol

Modifications from protocol amendment 4:

- Removed the sensitivity analysis using the Mixed Effect Model for Repeated Measure (MMRM) as it's based on the same assumption for missing data (missing at random) as the primary analysis using multiple imputations (MI).

1.2.4. Revision History for SAP Amendments

The purpose of this amendment is to: (1) specify the methods for handling missing data due to the COVID-19 pandemic and additional analyses for potentially affected endpoints; and (2) describe the handling of DSQ data collected during the time when DSQ device navigation malfunctions occurred.

Section	Description of Additions/Updates
1.2.3 Modifications from the Statistical Section in the Final Protocol	Updated per protocol amendment 4. Removed items that are no longer modifications from the latest protocol amendment.
2.4 Study plan	Added provisions introduced in protocol amendment 4 allowing for certain study procedures to occur outside the protocol specified time points and/or outside of the clinic environment.
5.4 Subject Disposition	Added summaries of patient disposition due to the COVID-19 pandemic
5.6.1 Analysis of Co-Primary Efficacy Variable(s)	Specified that in the primary analysis of the co-primary endpoint of histologic response, patients with missing week 24 data due to the COVID-19 pandemic will be imputed by multiple imputation (MI). Sensitivity analysis considering patients with missing week 24 data due to the COVID-19 pandemic as non-responders is added. Clarified that DSQ data collection and analyses are not expected to be affected by the COVID-19 pandemic.

Section	Description of Additions/Updates
	Specified DSQ data collected during the time when some devices were impacted by navigation malfunction will not be used in the analyses. Specified that in the primary analyses of the secondary histological and endoscopic efficacy endpoints at week 24, missing data due to the COVID-19 pandemic will be imputed by MI. Sensitivity analysis where missing data due to the COVID-19 pandemic will be imputed by WOCF is added. Specified that for PRO endpoints intended to be collected at clinic visits, data collected via phone interview will be included in the primary summary. Additional summaries will be provided with exclusion of data collected through phone interviews.

2. INVESTIGATION PLAN

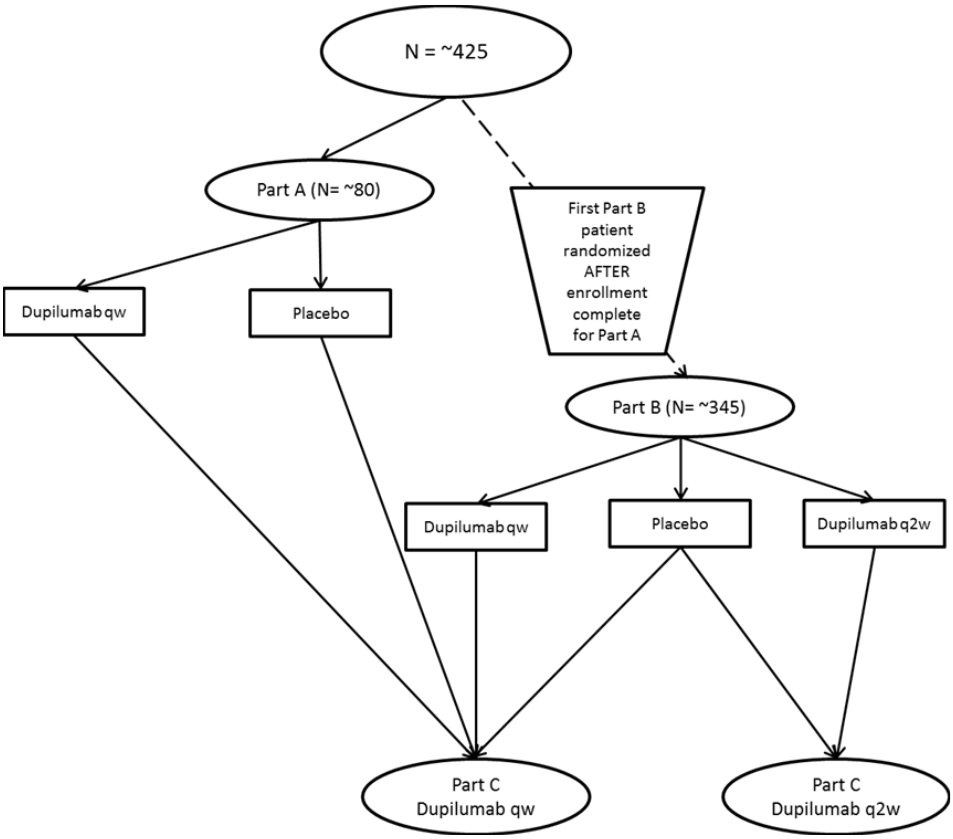
2.1. Study Design and Randomization

Part A is a 24-week treatment, randomized, double-blind, placebo-controlled study phase to determine the treatment effect of dupilumab compared with placebo in adult and adolescent patients with EoE as assessed by histological and clinical measures, and to inform/confirm the final sample size determination for Part B. After a screening period up to 12 weeks, patients will be centrally randomized via interactive web response system (IWRS) in a 1:1 ratio to dupilumab 300 mg SC QW or placebo SC and treated double-blind for 24 weeks in Part A. At the end of Part A, eligible patients will enter Part C, which consists of a 28-week period of dupilumab 300 mg SC QW treatment. Patients in Parts A who do not enter Part C will enter a 12-week follow-up period immediately after Part A. Patients who participate in Part A are not eligible to participate in Part B.

Approximately 80 patients (40 per treatment group) are planned to be randomized in Part A from multiple global sites. Approximately 345 patients (115 per treatment group) are planned to be randomized in Part B from multiple global sites. Any re-estimation of sample size for Part B will be documented in the Part B statistical analysis plane (SAP) before its database lock.

The design of the overall study is depicted below in Figure 1. Detailed description of the design and analysis for Part B will be provide in a separate SAP. As Part A and Part B are carried out as 2 separate sub-studies with no overlap in patients, Part A and Part B will each have a separate 2-sided alpha level of 0.05.

Figure 1: Overall Study Design



2.2. Statistical Hypothesis

For the comparison of dupilumab 300 mg QW to placebo, the following hypotheses of the co-primary endpoints will be tested, where p_d is the true proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24 and μ_d is the true mean change from baseline in the DSQ total score at week 24 in the dupilumab group; and p_p and μ_p are the corresponding true values in the placebo group.

- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24
  - Null hypothesis (H_0): $p_p = p_d$, ie, the proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24 is the same between the dupilumab group and the placebo group.
  - Alternative hypothesis (H_1): $p_p \neq p_d$, ie, the proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24 is different between the dupilumab group and the placebo group.
- Change from baseline in the DSQ total score at week 24
  - Null hypothesis (H_0): $\mu_p = \mu_d$, ie, the mean change from baseline in the DSQ total score at week 24 is the same between the dupilumab group and the placebo group.

– Alternative hypothesis (H_1): $\mu_p \neq \mu_d$, ie, the mean change from baseline in the DSQ total score at week 24 is different between the dupilumab group and the placebo group.

Part A is considered positive when the co-primary endpoints both achieve statistical significance with two-sided significance level 0.05.

2.3. Sample Size and Power Considerations

Efficacy assessment employs the following co-primary endpoints measuring histologic and clinical symptoms of disease, respectively:

- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24
- Absolute change in Dysphagia Symptom Questionnaire (DSQ) score from baseline to week 24

The assumptions used in sample size calculations are based on results from a phase 2 study of dupilumab (R668-EE-1324) and reported data of a phase 2 study of budesonide in patients with EoE as follows:

(1) In the study of dupilumab, a treatment difference of 65.2% was observed in the proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf after 12 weeks of treatment (placebo 0% vs. dupilumab 65.2%). DSQ was not assessed in this study. The overall dropout rate was 8.5% during the 12-week treatment period.

(2) In the study of budesonide oral suspension (Dellon, 2017b), a treatment difference of 36% was observed in the proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf after 12 weeks of treatment (placebo 3% vs. budesonide 39%). The mean (standard deviation [SD]) of change from baseline in DSQ total score at week 12 was -7.5 (10.7) in placebo and -14.3 (13.0) in the budesonide group, corresponding to a treatment group difference of -6.8. The overall dropout rate was 6.5% during the 12 week treatment period.

With the data of two phase 2 studies from Dupilumab and budersonide, the planned sample size for Part A is approximately 40 patients in each treatment group such that for the comparison of dupilumab 300 mg QW to placebo:

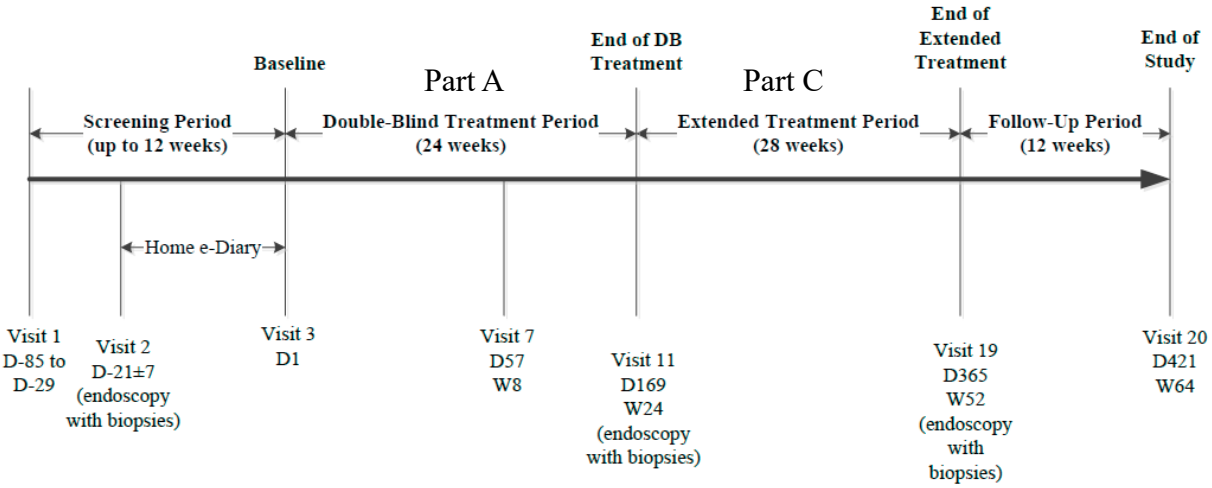
- This sample size will yield >99% power to detect a treatment difference of 62% in the proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24 (placebo 3% vs. dupilumab 65%) at a 2-sided significance level of 5% using Fisher's exact test.
- With respect to the treatment group difference in the mean change from baseline in DSQ total score, assuming a common SD of 13.0, this sample size is expected to generate a 95% confidence interval whose half-width is 5.7. If the true treatment difference is -9.0 points, the statistical power for the co-primary endpoint of DSQ will be 80% using a two-sample t-test.

A dropout rate of 15% is assumed for the calculations above considering that a higher dropout rate may be observed in Part A (24 weeks treatment period) than in the previous phase 2 dupilumab study (dropout rate of 8.5% in the 12-week treatment period) or budesonide study (dropout rate of 5.4% in the 12-week treatment period).

2.4. Study Plan

Patients will undergo a screening period (up to 12 weeks), a double-blind treatment period of 24 weeks (Part A), a 28-week extended active treatment period (Part C), and a 12-week follow-up period as depicted in Figure 2. All patients will be followed up for an additional 12 weeks after completing Part C. Patients in Parts A who choose not to participate in or are ineligible for Part C will be followed for an additional 12 weeks immediately after Part A.

Figure 2: Study Flow Diagram for Part A and Part C



DB = double-blind.

Note: For patients who do not have at least 11 daily entries during the 14 days immediately preceding the planned randomization date (baseline), randomization should be postponed until this requirement is met, but without exceeding the 85-day maximum duration for screening.

After adult patients provide informed consent and adolescent patients and/or their legal parents/legal guardians provide informed consent and informed assent (as appropriate), patients will be assessed for study eligibility at visit 1.

Study participants are required to have a confirmed diagnosis of EoE which may be established *either* by a prior historical biopsy showing ≥15 intraepithelial eosinophils per high-power field (eos/hpf) from at least one esophageal region after at least 8 weeks of treatment with a high-dose proton pump inhibitor (PPI) using any approved PPI *or* by biopsies performed after approximately 8 weeks of high-dose PPI treatment initiated prior to screening or during the screening period, which demonstrate ≥15 intraepithelial eos/hpf in at least 2 out of 3 esophageal regions (proximal, mid, and distal); see Protocol Figure 3 for endoscopy/biopsy procedure flow chart. Patients who are on PPIs during the screening period and are eligible to enroll in the study must continue a high-dose PPI regimen during the study (see details in Protocol Section 7.2). Patients are allowed to switch among the approved background therapy options for high-dose PPI use during the study.

All patients who meet the other clinical and laboratory eligibility criteria will undergo endoscopy with biopsies at visit 2 (day -21±7) both to establish a baseline reference measure and to ensure eligibility. For patients without a historical biopsy, the visit 2 biopsy will serve as both confirmation of EoE diagnosis and the baseline reference measure.

All biopsies performed during this study will be evaluated by pathologists at a central pathology laboratory who will be blinded to treatment assignment.

Note: Biopsy specimens from the stomach and/or duodenum will be obtained in all patients <18 years of age to rule out alternate etiologies of esophageal eosinophilia. Targeted, stomach and/or duodenal biopsies will be obtained in adults only in the event of abnormal endoscopic findings (other than typical EoE findings) or clinical suspicion of alternate etiologies. All randomized patients found to have stomach and/or duodenal abnormalities at baseline will have follow-up stomach and/or duodenal biopsies at week 24 and week 52.

After confirmation of EoE diagnosis, patients will be given an electronic diary (eDiary) to record dysphagia symptoms on a daily basis during the 2 weeks prior to the baseline visit (visit 3).

Patients may be re-screened once if they fail the screening evaluation, unless the reason for screen failure is related to histologic or clinical disease severity inclusion criteria. The baseline endoscopy with biopsy and EoE-EREFS scoring will not be repeated for re-screened patients. These results will continue to be valid baseline data. Re-screening must occur within 6 months of the screen failure.

For patients whose DSQ diary compliance does not meet eligibility requirements within the 21-day interval between Visit 2 and Visit 3 (at least 11 daily entries during the 14 days immediately preceding the planned randomization date), randomization may be postponed as long as the total duration of the screening period does not exceed the 85-day maximum.

At the baseline visit (visit 3), patients who continue to meet eligibility criteria will enter the 24-week, placebo-controlled, double-blind treatment period and be randomized in a 1:1 ratio to dupilumab 300 mg SC QW or placebo SC. Randomization will be stratified by age (≥18 vs. ≥12 to <18 years of age) and use of PPI at randomization (yes vs. no).

During the 24-week, placebo controlled, double-blind treatment period, clinic visits are scheduled per the schedule of events (Section 10.2). Patients and parents/caregivers will be trained on injecting study drug at the first 3 visits during the double-blind treatment period. Patients will be closely monitored at the study site at visits 3 to 6 (baseline visit, study weeks 1, 2, and 4) for a minimum of 30 minutes after the administration of study drug. During weeks when no clinic visit is scheduled, the patient or parent/caregiver will administer study drug. Doses of study drug administered at home should be administered one week after the prior dose of study drug. Study drug administration that occurs in clinic should occur per the Schedule of Events in Section 10.2. Patients and parents/caregivers who prefer to have clinic staff administer study drug may choose to have injections administered in the clinic.

The end of treatment visit for the double-blind treatment period is at week 24. The co-primary endpoints will be assessed at week 24, one week after the last dose of study drug during the double-blind treatment period.

Patients who prematurely discontinue study treatment will be encouraged to remain in the study and attend all subsequent scheduled visits.

At the end of double-blind treatment visit (week 24), eligible patients in Part A may enter Part C, which consists of a 28-week extended active treatment period. Patients who do not enter Part C may enter a 12-week follow-up period.

In protocol amendment 4, provisions were added to allow study procedures to occur at outside the protocol specified timepoint and/or outside of the clinic environment and will remain in effect only for the duration of the public health emergency due to the COVID-19 pandemic.

- Endoscopy with biopsies may be delayed for visit 11/week 24, visit 19/week 52, early termination, and before initiating rescue treatment
- At-home study drug dosing is permitted for all visits except for visit 3/day 1 and visit 11/week 24
- If the for-cause endoscopy with biopsies cannot occur due to COVID-19 restrictions, rescue treatment should be initiated without delay and these patients will be eligible to participate in Part C
- Safety and laboratory procedures (vital signs, weight, PK/ADA sample collection, hematology and chemistry urine sample collection) may be delayed or occur at-home when possible
- The patient reported outcome questionnaires that are intended to be completed during clinic visits may be conducted via phone interviews after visit 3/day 1

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH, 1998), the following population of analysis will be used for all statistical analysis.

The full analysis set (FAS) is the primary analysis population for Part A efficacy analyses. The per protocol set (PPS) is the supportive analysis population for Part A efficacy analyses. The Part A safety analysis set (SAF) is the basis for Part A safety analyses.

The Part C SAF is the basis for both efficacy and safety analyses of Part C.

3.1. The Full Analysis Set (FAS)

The Part A full analysis set (FAS) includes all randomized patients in Part A. Efficacy analyses will be based on the treatment allocated by the IWRS at randomization (as randomized).

Note: Two randomization transactions were made for Part A patient 840118002 at Visit 3 due to internet connection issues. Each transaction allocated a randomization number and a study drug kit to this patient. The patient was administered study drug from both kits at Visit 3. The patient continued participation in the study as randomized per the first randomization transaction and subsequent kits were dispensed based on that transaction. Details about this randomization irregularity is documented in a note-to-file. In efficacy analyses, this patient will be analyzed based on the treatment allocated by the first IWRS randomization transaction.

3.2. The Per Protocol Set (PPS)

The Part A per protocol analysis set (PPS) includes all patients in the Part A FAS except for those who are excluded because of specified important protocol violations in Part A. A preliminary list of such important protocol violations is provided in Section 10.5 and a final list of patients excluded from FAS will be generated prior to Part A database lock.

Final determinations of the PPS will be made in the blinded manner prior to Part A database lock. There is no PPS for Part C.

3.3. The Safety Analysis Set (SAF)

Part A:

The Part A safety analysis set (SAF) includes all randomized patients who received any study drug in Part A; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables in Part A will be analyzed using the Part A SAF.

Part C:
The Part C SAF includes all patients who were randomized in Part A/B, entered Part C, and received any study drug in Part C. Efficacy, treatment compliance/administration, and all clinical safety data from Part C through a pre-specified cut-off date (approximately March 15th, 2020) around the time of Part A completion will be analyzed for Part C SAF patients who entered Part C from Part A.

The actual treatment group as treated for Part A is defined by the following rules:

- For a patient randomized to dupilumab 300 mg QW, if the patient received all placebo injections in Part A, the actual treatment will be assigned as placebo.
- Regardless of the treatment group a patient is randomized to, if the patient received at least 1 dupilumab injection in Part A, the actual treatment will be assigned as dupilumab 300 mg QW.

The Part A treatment group assignment for analysis of Part C data will be the same as the SAF for Part A.

For safety summaries, the following analysis periods are defined:

- Part A week 24 treatment period is defined as
  - For patients who entered Part C: Day 1 to the date of first dose of Part C study drug (or week 24 visit if patient entered Part C but never received any Part C study drug).
  - For patients who did not enter Part C:
    - Day 1 to the week 24 visit if patients completed week 24 visit with known visit date.
    - Day 1 to study day 169 (24 weeks times 7 days/week), or to patient's last study participation date, whichever comes earlier, if patients did not complete week 24 visit or had missing week 24 visit date.
- Part C extended treatment period for patients who entered Part C is defined as
    - Time after the first dose of study drug in Part C to the date of week 52 visit if patients completed week 52 with known visit date.
    - Time after the first dose of study drug in Part C to study day 365 (52 weeks times 7 days/week), or to patient's last study participation date, whichever comes earlier, if patients did not complete week 52 visit or had missing week 52 visit date.
- Follow-up period is defined as
  - For patients who entered Part C: the day after the end of Part C extended treatment period to the patient last study participation date.
  - For patients who did not enter Part C: the day after the end of Part A week 24 treatment period to the patient last study participation date.

The Part A and Part C SAFs will be the basis for the analyses for the Part A treatment period and Part C treatment period, respectively; however, for the analyses for the follow-up period, only a subset of the corresponding SAFs will be included, which is defined as the patients who entered the follow-up period and had at least one visit after week 24 visit (for Part A SAF) and week 52 visit (for Part C SAF).

3.4. The Pharmacokinetic Analysis Set (PKAS)

The PK analysis set for Part A and Part C includes all randomized patients who received any study drug and who had at least one non-missing drug concentration result following the first dose of study drug in the corresponding study part.

3.5. The Immunogenicity Analysis Set

The ADA analysis set (AAS) for Part A and Part C includes all patients who received any study drug and had at least one non-missing ADA result from the dupilumab ADA assay after first dose of the study drug in the corresponding study part. Patients will be analyzed according to the treatment actually received.

The neutralizing antibody (NAb) analysis set (NAS) for Part A and Part C includes all patients who received any study drug and who are negative in the dupilumab ADA assay or with at least one non-missing result in the dupilumab NAb assay after first dose of the study drug in the corresponding study part. Patients who are ADA negative are set to negative in the NAb analysis set. Patients will be analyzed according to the treatment actually received.

3.6. Subgroups

Subgroups are defined by key baseline factors recorded on the eCRF (unless otherwise specified) and listed as follows.

Subgroups to be considered for both efficacy and safety analyses:

- Age group (years; 12 to <18, ≥18)
- Sex (Male, Female)
- Duration of EoE (years from start date of EoE to randomization date; <5, ≥5)
- Baseline weight group (<60 kg, ≥60 kg)
- Prior use of swallowed topical steroids for the treatment of EoE (Yes, No)
- History of atopic dermatitis (Yes, No)
- History of asthma (Yes, No)
- History of allergic rhinitis (Yes, No)
- History of food allergy (Yes, No)

Note: subgroups defined by race, ethnicity, and region are not included as majority of patients in Part A are anticipated to be in one major category of these demographic factors.

Subgroups to be considered for efficacy analyses only:

- Baseline BMI group (<25, ≥25-<30, ≥30)
- Use of PPI at randomization (Yes, No)
- Prior esophageal dilations (Yes, No)

- Subject on a food elimination diet at the time of screening (Yes, No)
- Subject on a food elimination diet in the past (Yes, No)

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and Baseline characteristics variables will be summarized:

- Demographic variables: Age at screening as a continuous variable and with grouping (years;12 to <18, ≥18 to <40, ≥40 to <65, ≥65), Sex (Male, Female), Ethnicity with grouping (Hispanic or Latino, Not-Hispanic or Latino), Race with grouping (White, Black or African American, Asian, Other), Region (North America, or Rest of World), Country, Baseline weight as a continuous variable and with grouping (kg; <60, ≥60), Height (m), and calculated BMI (kg/m^2; <15, ≥15-<25, ≥25-<30, ≥30), randomization stratification factors (age [years; 12 to <18, ≥18] and use of PPI at randomization [Yes, No]).
- Baseline characteristics:
  - DSQ total score
  - Number of days with dysphagia in the 2 weeks prior to baseline as a continuous variable and with group (4, 5, 6, 7, 8, etc.)
  - Amount of pain patient had experienced when swallowing food
  - Peak esophageal intraepithelial eosinophil count (eos/hpf) of three regions (proximal, mid, and distal)
  - Eosinophilic Esophagitis-Endoscopic Reference Score (EREFS) total score
  - Mean stage score from the EoE Histology Scoring System (EoEHSS) summed over 3 regions
  - Mean grade score from the EoEHSS summered over 3 regions
  - Total EoEHSS histology stage score (excluding lamina propria fibrosis) summed over 3 regions
  - Total EoEHSS histology grade score (excluding lamina propria fibrosis) summed over 3 regions
  - Patient global impression of severity (PGIS) level (none, mild, moderate, or severe)
  - EoE Impact Questionnaire (EoE-IQ) score
  - EoE Symptom Questionnaire (EoE-SQ) frequency score and severity score
  - Total Nasal Symptom Score (TNSS) for patients with history of allergic rhinitis
  - Rhinoconjunctivitis Quality of Life Questionnaire score for patients aged 12+ years [RQLQ(S)+12] for patients with history of allergic rhinitis

- Asthma Control Questionnaire-5 (ACQ-5) score for patients with history of asthma
- Patient-Oriented Eczema Measure (POEM) score for patients with history of atopic dermatitis
- Baseline blood eosinophil count as a continuous variable and with grouping (Giga/L; <0.15, ≥0.15; <0.30, ≥0.30; <0.50, ≥0.50)
- Baseline serum total immunoglobulin E (IgE) as a continuous variable and with grouping (IU/mL; <100, ≥100)
- Patients treated with PPI at randomization (Yes, No)
- Prior use of swallowed topical corticosteroids for EoE (Yes, No)
- Prior esophageal dilations (Yes, No)
- Prior use of swallowed topical corticosteroids for EoE and prior esophageal dilation (Yes, No)
- Number of prior esophageal dilations
- Age at the first esophageal dilation with grouping (years; 0 to 11, 12 to 18, 19 to 24, 25 to 50, >50), calculated as the number of years between patient birth year and the year of the first esophageal dilation (prior to screening)
- Duration of EoE as a continuous variable and with grouping (years; <5, ≥5)
- Age at EoE onset with grouping (years; 0 to 18, 19 to 24, 25 to 50, >50), calculated as the number of years between patient birth year and the start year of EoE
- Historical esophageal biopsy showing ≥ 15 (eso/hpf [400 X]) after 8 weeks of high-dose PPI (Yes, No)
- Patient on food elimination diet in past (Yes, No)
- Patient on food elimination diet at screening (Yes, No)

4.2. Medical History

Medical history will be coded to a Preferred Term (PT) and associated Primary System Organ Class (SOC) according to the latest available version of MedDRA at the coding CRO. Information related to EoE and other atopic medical conditions includes diagnosis of EoE, atopic dermatitis, asthma, allergic rhinitis, allergic conjunctivitis, chronic rhinosinusitis, nasal polyps, food allergy, hives, contact dermatitis, and other allergies [medications, animals, plants, mold, dust, mites, etc.]). Patient dietary status at the time of screening is also collected with information on whether patient is on food elimination diet, food type eliminated, and reason for elimination of specific food.

4.3. Pre-treatment / Concomitant Medications and Procedures

Medications/Procedures will be recorded from the day of informed consent until the EOS visit.

Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug Dictionary (WHODD) at the coding CRO. Patients will be counted once in all ATC categories linked to the medication. Medications of interest include PPIs and swallowed topical/systemic corticosteroids for the treatment of EoE.

Procedures will be coded to a Preferred Term (PT), High Level Term (HLT) and associated primary System Organ Class (SOC) according to the latest available version of MedDRA in effect.

Pre-treatment medications/procedures: medications taken or procedures performed prior to administration of the first dose of study drug.

Concomitant medications/procedures (CMs/CPs): medications taken or procedures performed following the first dose of study drug through the EOS visit. This includes medications that were started before the study and are ongoing during the study. Furthermore, CM/CP will be categorized according to analysis periods (as defined in Section 3.3):

- CMs/CPs taken during the Part A week 24 treatment period
- CMs/CPs taken during the Part C extended active treatment period
- CMs/CPs taken during the follow-up period

Prohibited concomitant medications/procedures during the study:

Treatment with the following concomitant medications is prohibited through week 52:

- Swallowed topical corticosteroids (may be used as rescue treatment for EoE)
- Systemic corticosteroids (may be used as rescue treatment for EoE)
- Systemic immunosuppressive/immunomodulating drugs (including, but not limited to, omalizumab, cyclosporine, mycophenolate-mofetil, azathioprine, methotrexate, IFN-γ, or other biologics)
- Treatment with an investigational drug (other than dupilumab)
- Initiation, discontinuation, or change in dosage regimen of the following medications within 8 weeks prior to the baseline endoscopy (stable doses of these medications are allowed)
  - Proton pump inhibitors, unless used for a required PPI trial during the screening period or in patients who present at the initial screening visit with current use of PPIs
  - Systemic leukotriene inhibitors
  - Nasal and/or inhaled corticosteroids
- Initiation of SCIT, or change in dose for those patients on a stable dose of SCIT within 1 year prior to screening

- SLIT
- OIT
- Treatment with an investigational drug (other than dupilumab)
- Treatment with a live (attenuated) vaccine (see protocol Section 7.1.1 for the list of vaccine).

The following concomitant procedures are prohibited during study treatment (through week 52):

- Major elective surgical procedures
- Esophageal dilation (may be used as rescue procedure)
- Initiation or change of food-elimination diet regimen

Patients may receive the prohibited medications/procedures listed above as needed during the follow-up period, 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.

Blinded adjudication of prohibited medications and procedures will be performed by the medical monitor before database locks with documented procedures.

Rescue treatments (including both medications and procedures): If medically necessary (eg, for treatment of intolerable EoE symptoms), rescue medications (systemic and/or swallowed topical corticosteroids) or emergency esophageal dilation are allowed for study patients in Parts A and C. An endoscopy with biopsy will be performed prior to the initiation of rescue therapy. Patients who undergo an endoscopy with biopsy due to the initiation of rescue therapy will not undergo the scheduled end of treatment visit endoscopy/biopsy at weeks 24 and 52. Patients who receive rescue treatment in Part A will not be eligible for the Part C extended active treatment period unless an endoscopy with biopsy is performed prior to the initiation of rescue treatment. Patients receiving rescue therapy may continue to receive study drug. They will remain blinded and will be asked to return to the clinic for all remaining study visits and participate in all assessments for these visits except for endoscopy/biopsy, as noted above.

Blinded adjudication of rescue treatments will be implemented before database locks by considering the type of medication or procedure, indication, timing, frequency and the potential impact of the use of the medication or procedure. The rescue treatments will be adjudicated by the medical director (or medical monitor) with documented procedures.

Gastric/Duodenum and Targeted Biopsy

Biopsy specimens from the stomach and/or duodenum will be obtained at visit 2 in all patients <18 years of age to rule out alternate etiologies of esophageal eosinophilia. Stomach and/or duodenal biopsies will be obtained in adults only in the event of abnormal endoscopic findings (other than typical EoE findings) or clinical suspicion of alternate etiologies. All randomized patients found to have stomach and/or duodenal abnormalities at baseline will have follow-up stomach and/or duodenal biopsies at week 24 and week 52.

4.4. Efficacy Variable

4.4.1. Primary Efficacy Variable (s)

The co-primary endpoints for Part A are:

- Proportion of patients achieving peak esophageal intraepithelial eosinophil count (from all 3 regions) of ≤6 eos/hpf at week 24
- Absolute change in DSQ score from baseline to week 24

Peak esophageal intraepithelial eosinophil count

Peak esophageal intraepithelial eosinophil count will be measured from esophageal biopsies. 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 and other tissue analyses. The third sample from each region will be processed for RNA analyses. The quantity of eosinophils in the most inflamed high power field (HPF) for each of the 3 esophageal regions (proximal, mid and distal) will be determined by a pathologist at a central pathology reading center who will be blinded to the treatment assignment. The peak esophageal intraepithelial eosinophil count at each visit is the maximum of the quantities of eosinophils in the most inflamed HPFs across the 3 regions. For example, if for a particular patient, at week 24, the quantity of eosinophils in the most inflamed HPF is 2/hpf, 3/hpf, and 4 /hpf from the proximal, mid, and distal regions, respectively, the peak eosinophil count is 4/hpf for week 24. If the quantity of eosinophils is missing for 1 or 2 esophageal regions, the peak eosinophil count will be the maximum of the quantities of eosinophils from the region(s) where eosinophil quantities are available. To participate in the study, patients must have a peak intraepithelial eosinophil count ≥15 eos/hpf (400×) in at least 2 of the 3 esophageal regions sampled.

Esophageal biopsies will be obtained by endoscopy at the second screening visit (visit 2, day -21 ± 7), week 24 and week 52 (EOS) or ET visits. For patients who receive rescue treatment during Part A, the endoscopy/biopsy procedures will be performed prior to the initiation of rescue treatment. Patients undergoing endoscopy/biopsy prior to rescue will not undergo the scheduled endoscopy/biopsy at weeks 24 and 52.

Dysphagia Symptom Questionnaire (DSQ) Score

The DSQ is a validated PRO that has been used in clinical studies to measure the frequency and intensity of dysphagia (Hudgens, 2017). For patients who respond "No" to question 1 ("Since you woke up this morning, did you eat solid food?"), a modification was made to the DSQ by asking a follow-up question to probe if patients avoided solid food due to their problems with swallowing solid food. The DSQ uses a daily recall period and will be completed by the patient daily using an eDiary from screening through end of study or ET visit.

The questions and scoring of DSQ are presented in the table below. Question 1 is a screening question; patients will proceed with the questionnaire depending on their response to question 1:

- If the response to question 1 is 'No', question 1a will be asked to collect reason for not eating solid food and the remaining items on the DSQ are not scored. Data for that day is considered to be missing for analysis but diary completion is considered compliant for that day.

- If the response to question 1 is 'Yes', patient will skip question 1a and move on to questions 2, 3 and 4. Only questions on the frequency (question 2) and severity (question 3) of dysphagia contribute to the total DSQ score. Although question 4 related to pain was included in the DSQ, pain was not highlighted as an important symptomatic factor based on interviews of adolescent and adult patients with EoE. Thus, question 4 was considered as a standalone item for exploratory analysis.

Dysphagia Symptom Questionnaire (DSQ) (Adapted from Hudgens, 2017)

Question Number	Response Option	Score
1. *Since you woke up this morning, did you eat solid food?*	No	No score assigned
	Yes	No score assigned
[redacted]	[redacted]	[redacted]
2. *Since you woke up this morning, has food gone down slowly or been stuck in your throat?*	No	0
	Yes	2
3. *For the most difficult time you had swallowing food today (during the past 24 hours), did you have to do anything to make the food go down or to get relief?*	No, it got better or cleared up on its own	0
	Yes, I had to drink liquid to get relief	1
	Yes, I had to cough and/or gag to get relief	2
	Yes, I had to vomit to get relief	3
	Yes, I had to seek medical attention to get relief	4
4. *The following question concerns the amount of pain you have experienced when swallowing food. What was the worse pain you had while swallowing food over the past 24 hours?*[b]	None, I had no pain	0
	Mild	1
	Moderate	2
	Severe	3
	Very Severe	4

[a] DSQ is modified with the addition of Question 1a when response to Question 1 is 'No'.

[b] Question 4 does not assess dysphagia and is considered a standalone item to be evaluated as an exploratory outcome.

The DSQ score is calculated based on the daily responses to question 2 (frequency) and question 3 (severity) over a 14-day period using the formula from (Hudgens, 2017):

$$DSQ\ Score = \frac{(sum\ of\ points\ from\ questions\ 2\ and\ 3\ from\ daily\ DSQ\ diary) \times 14\ days}{number\ of\ diary\ days\ reported\ with\ non\text{-}missing\ data}$$

To calculate the DSQ score, a minimum of 8 diary entries (including days when patient responded 'No' to question 1) is required for each 14-day period to derive a standardized total score based on the cumulative scores through 14 days. If there are less than 8 diary entries for a 14-day period, the DSQ score is considered to be missing for that period. The primary analysis will be based on DSQ score calculated using this algorithm. If there are multiple diary entries on the same day, the first entry on that day will be used in calculating DSQ score for analysis. DSQ scores can theoretically range from 0 to 84, with a lower score indicating less-frequent or less-severe dysphagia.

As a sensitivity analysis, DSQ will be scored using an alternative algorithm that takes into account patient's response to question 1a about reason for not eating solid food:

- If not eating solid food because of patient problems with swallowing solid food, a daily score of 6 will be assigned for that day for analysis but not for consideration of eligibility and used in the formula given above to calculate DSQ score over a 14-day period after randomization.
- If the patient responds to question 1a by indicating that he/she did not eat solid food since waking up in the morning because of something NOT related to their problems with swallowing solid food, no score will be assigned. Data for that day is considered to be missing for analysis but diary completion is considered compliant for that day.

Baseline DSQ scores will be calculated from daily responses recorded during the 14 days just prior to the first dose date. For example, if a patient is randomized and takes the first dose of study drug on Jan 15th, DSQ score will be calculated from daily responses recorded during Jan 1st through Jan 14th as baseline. DSQ scores at time points after baseline will be calculated for each 14-day period starting from the day of patient receiving their first dose of study drug (see detailed analysis time point window in Section 6.4).

4.4.2. Secondary Efficacy Variable(s)

The **key secondary** endpoints for Part A are:

- Absolute change in EoE EREFS total score from baseline to week 24
- Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 24
- Absolute change in EoEHSS mean grade score from baseline to week 24
- Absolute change in EoEHSS mean stage score from baseline to week 24

Eosinophilic Esophagitis-**E**ndoscopic **Ref**erence **S**core (EoE EREFS)

EoE-EREFS is a validated scoring system for inflammatory and remodeling features of disease that are visible through endoscopy (Hirano, 2013). The proximal and distal esophageal regions will be scored separately. The score for each region is the sum of assigned scores for each of the 5 major features and ranges from 0 to 9. The total score (summing scores for the proximal and distal regions) ranges from 0 to 18 and is the final score used for the analysis. If score is available only from 1 of the 2 regions, that available score will be used as total score. For example, if score is 8 from the proximal region and missing from the distal region, the total score will be 8.

The major esophageal features include:

- Edema (absent [0], present [1])
- Rings (absent [0], mild [1], moderate [2], severe [3])
- Exudates (absent [0], mild [1], severe [2])
- Furrows (absent [0], mild [1], severe [2])
- Stricture (absent [0], present [1])

The EoE-EREFS should be performed and scored by the physician conducting the endoscopy procedure before biopsies. In addition to the major features above, data for the following minor features will also be captured but not included in the EoE-EREFS scoring:

- Crepe paper esophagus (mucosal fragility or laceration upon passage of diagnostic endoscope): absent, present
- Narrow caliber esophagus (reduced luminal diameter of the majority of the tubular esophagus): absent, present
- Stricture diameter

Mucosal changes associated with gastroesophageal reflux disease will also be recorded (but not included in the EoE-EREFS scoring) using the Los Angeles classification system for erosions (No Erosions or Grade A, B, C, or D).

EoE-EREFS will be assessed by endoscopy at the second screening visit, week 24 and week 52 (EOS) or ET visits, and immediately prior to start of rescue medication or procedures. Patients undergoing endoscopy/biopsy prior to rescue will not undergo the scheduled endoscopy/biopsy at weeks 24 and 52.

Eosinophilic Esophagitis **H**istology **S**coring **S**ystem (EoEHSS)

The EoEHSS is a method for evaluating the grade and stage of multiple pathologic features in esophageal biopsies from EoE patients that extend observations beyond the presence of tissue eosinophils (Collins, 2017). EoEHSS evaluates eight features: eosinophil inflammation (EI), basal zone hyperplasia (BZH), eosinophil abscess (EA), eosinophil surface layering (SL), dilated intercellular spaces (DIS), surface epithelial alteration (SEA), dyskeratotic epithelial cells (DEC), and lamina propria fibrosis (LPF). Severity (grade) and extent (stage) of abnormalities will be scored by a central, blinded pathologist for each feature using a 4-point scale (0 normal; 3 maximum change). The detailed scoring scheme for each feature is provided in Section 10.6.

The mean grade or mean stage score from EoEHSS for each biopsy is the ratio of the sum of the assigned scores for each feature evaluated divided by the maximum possible score for that biopsy (the maximum possible score for each biopsy is 24). For example, if all 8 features have maximum grade of 3 for a biopsy, the mean grade score will be 24/24 = 1. If a feature is not evaluated, the maximum possible score is reduced by 3. Most maximum possible score reductions may occur because lamina propria is not present; if all other features are evaluable, the maximum possible score for a biopsy lacking lamina propria is reduced from 24 to 21 because 7 instead of 8 features were evaluated. Both mean grade and mean stage scores will be determined for biopsies from 3 esophageal regions (proximal, mid and distal). The mean grade and mean stage scores summed across the 3 regions is the final score used in the primary analysis of these endpoints. In the example given in the table below, the mean grade score is 0.33, 0.33, and 0.42 from the proximal, mid, and distal regions, respectively, and the final mean grade score is 1.08 (0.33 + 0.33 + 0.42).

Feature	Esophageal region		
	Proximal	Mid	Distal
Eosinophilic inflammation (EI)	3	3	3
Basal zone hyperplasia (BZH)	2	3	3
Eosinophil abscess (EA)	2	2	3
Surface layering (SL)	0	0	0
Dilated intercellular spaces (DIS)	0	0	0
Surface epithelial alteration (SEA)	0	0	0
Dyskeratotic epithelial cells (DEC)	0	0	0
Lamina propria fibrosis (LPF)	missing	0	1
8-feature Mean Grade Score	(3+2+2)/21=0.33	(3+3+2)/24=0.33	(3+3+3+1)/24=0.42

Due to the anticipation that lamina propria may not be present in many biopsies, a total grade or total stage score by summing scores from the other 7 individual features will be calculated for an exploratory analysis. In the example given above, the total grade score excluding lamina propia is (3 + 2 +2) + (3 + 3 + 2) + (3 + 3 + 3) = 24.

Esophageal biopsies will be obtained by endoscopy at the second screening visit (visit 2, day 21 ± 7), week 24 and week 52 (EOS) or ET visits, and immediately prior to the start of rescue medication or procedures. Patients undergoing endoscopy/biopsy prior to rescue will not undergo the scheduled endoscopy/biopsy at weeks 24 and 52.

The **other secondary** endpoints are:

- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf at week 24
- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤1 eos/hpf at week 24
- Percent change in DSQ from baseline to week 24
- Normalized Enrichment Scores (NES) for the relative change from baseline to week 24 in the EoE diagnostic panel (EDP)
- NES of the relative change from baseline to week 24 in the type 2 inflammation signature
- Absolute change from baseline to week 24 in health-related QOL average score as measured by EoE Impact Questionnaire (EoE-IQ)
- Absolute change from baseline to week 24 in severity of EoE symptoms other than dysphagia and pain with swallowing as measured by EoE Symptom Questionnaire (EoE-SQ)
- Absolute change from baseline to week 24 in frequency of EoE symptoms other than dysphagia and pain with swallowing as measured by EoE Symptom Questionnaire (EoE-SQ)

- Proportion of patients who receive rescue medications or procedures during the 24-week placebo-controlled treatment period
- All the above co-primary and secondary endpoints assessed at week 24 will be assessed at week 52 as additional secondary endpoints.

Transcriptome Endpoints

The differential gene expression profiles of esophageal biopsies of EoE patients compared to healthy controls is the EoE disease transcriptome (Sherrill, 2014). This disease gene expression signature was further refined to a smaller gene set to be used as an EoE diagnostic panel (EDP) (Dellon, 2017a). A gene signature representing type 2 inflammation has been curated from the literature, pre-clinical experiments performed at Regeneron, and dupilumab response signatures from atopic dermatitis and a phase 2 study of EoE (unpublished). The gene lists comprising each one of these transcriptomes can be found in Section 10.7.

Normalized Enrichment Score (NES) reflects the degree to which the activity level of a set of transcripts is overrepresented at the extremes (top or bottom) of the entire ranked list of transcripts within a sample and is normalized by accounting for the number of transcripts in the set (Subramanian, 2005, Barbie, 2009). NES of the relative change from baseline to week 24 will be calculated for the respective gene sets based on expression levels of each individual gene averaged over 3 esophageal regions (proximal, mid, and distal). If data are missing from region(s), the average will be taken from the available regions for each individual gene.

EoE **I**mpact **Q**uestionnaire (EoE-IQ)

The EoE-IQ is a disease-specific measure of health-related QoL in EoE patients developed by the sponsor. The EoE-IQ measures EoE impact on emotional, social, work and school, and sleep aspect of a patient. Patient is asked to respond to 11 questions based on experience living with EoE during the past 7 days.

Item No.	Question
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Response to each item is on a 5-point scale (1 = 'Not at all', 2 = 'A little', 3 = 'Somewhat', 4 = 'Quite a bit', 5 = 'Extremely'). The EoE-IQ average score is the sum of the non-missing responses divided by the number of items with non-missing response (note: response of "I do not go to school or work at a paying job" to item 9 or 10 is considered as missing response). The average score could range from 1 to 5; a higher score is indicative of a more negative impact of EoE on patient QoL.

The EoE Impact Questionnaire will be recorded by the patient using electronic questionnaire at baseline visit (visit 3), week 12, week 24, week 36, week 52 (EOS) or ET visits, and immediately prior to start of rescue medication or procedures.

EoE **S**ymptom **Q**uestionnaire (EoE-SQ)

The EoE-SQ is a questionnaire measuring the frequency and severity of symptoms other than dysphagia and pain with swallowing. It is developed by the sponsor. The EoE-SQ asks about symptoms that patients with EoE may have (chest pain, stomach pain, burning feeling in your chest, food or liquid coming back up into your throat, throwing up) during the past 7 days. Response to the frequency of each symptom is on a 5-point scale (1 = 'Never', 2 = 'One day', 3 = ' 2-6 days', 4 = 'Once a day', 5 = 'More than once a day'). The EoE-SQ frequency score is calculated as the sum of the frequency scores from the 5 items which could range from 5 to 25; a higher score is indicative of higher frequency of symptoms.

Response to the severity of each symptom based on the worst experience in the past 7 days is on a scale of 0 to 10 (higher is worse), with 0 and 10 indicating severity levels for the respective symptoms as follows:

Questions	Severity Scale	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[a] Questions 4 and 5 are not included in EoE severity scoring.

The EoE-SQ severity score is calculated as the sum of the severity scores from questions 1 to 3, which could range from 0 to 30; a higher score is indicative of more severe symptoms. If patient answers 'Not at all' to an item question about frequency, they will not be asked to answer the corresponding severity question and in that case a severity score of 0 will be assigned for that item.

The EoE Symptom Questionnaire will be recorded by the patient using electronic questionnaire at baseline visit (visit 3), week 12, week 24, week 36, week 52 (EOS) or ET visits, and immediately prior to start of rescue medication or procedures.

Proportion of patients who receive rescue medications or procedures

Rescue medications or procedures are described in Section 4.3.

4.4.3. Exploratory Efficacy Variable(s)

Exploratory efficacy endpoints include:

- Percent change from baseline to week 24 in *average* esophageal intraepithelial eosinophil count (eos/hpf) of 3 esophageal regions
- Absolute change from baseline to week 24 in EREFS (excluding stricture)
- Absolute change from baseline to week 24 in EREFS inflammation subscore
- Absolute change from baseline to week 24 in EREFS remodeling subscore
- Absolute change in EoEHSS total grade score (excluding lamina propria) from baseline to week 24
- Absolute change in EoEHSS total stage score (excluding lamina propria) from baseline to week 24
- Patient global impression of change (PGIC) of dysphagia: proportion of patients who rate their dysphagia symptoms as “a little better”, “moderately better”, or “very much better” at week 24
- Patient global impression of severity (PGIS) of dysphagia: proportion of patients with no symptom and proportion of patients with no symptom or mild symptoms at week 24
- Absolute change in TNSS from baseline to week 24
- Absolute change in POEM from baseline to week 24
- Absolute change in ACQ-5 from baseline to week 24
- Absolute change in RQLQ 12+ from baseline to week 24
- Absolute change in pain related to dysphagia (based on question 4 of the DSQ) from baseline to week 24
- All the above exploratory endpoints assessed at week 24 will be assessed at week 52 as additional exploratory endpoints.

Average esophageal intraepithelial eosinophil count (eos/hpf) of 3 esophageal regions

The average esophageal intraepithelial eosinophil count at each visit is the average of the quantities of eosinophils in the most inflamed HPFs across the 3 esophageal regions. For example, if for a partifular patient, at week 24, the quantity of eosinophils in the most inflamed HPF is 2/hpf, 3/hpf, and 4 /hpf from the proximal, mid, and distal regions, respectively, the average eosinophil count is 3/hpf (mean of 2, 3, 4/hpf) for week 24.

EREFS (excluding stricture), Inflammation, and Remodeling Sub-scores

The EREFS (excluding stricture), inflammation, and remodeling sub-scores for each region is the sum of assigned scores for each of the included major features as listed below. The sub-scores summed for the proximal and distal regions will be used for analysis.

Sub-score	**Major features included**	**Range (per region)**	**Range (proximal+distal)**
EREFS (excluding stricture) total score	Edema + Rings + Exudates + Furrows	0-8	0-16
Inflammation subscore	Edema + Exudates + Furrows	0-5	0-10
Remodeling subscore	Rings + Stricture	0-4	0-8

Patient Global Impression of Severity (PGIS) of Dysphagia

The PGIS is a one-item questionnaire that asks patients to provide the overall self-assessment of difficulty of swallowing food on a 4-point scale for the past week. Response choices are: 1 = 'none', 2 = 'Mild', 3 = 'Moderate', 4 = 'Severe'. The PGIS will be completed by patients using electronic questionnaire at baseline visit (visit 3), week 12, week 20, week 24, week 36, week 52 (EOS) or ET visits, and immediately prior to start of rescue medication or procedures.

Patient Global Impression of Change (PGIC) of Dysphagia

The PGIC is a one-item questionnaire that asks patients to provide the overall self-assessment of change in difficulty of swallowing food on a 7-point scale, compared to just before patient started taking the study injection. Response choices are: 0 = 'Very much better', 1 = 'Moderately better', 2 = 'A little better', 3 = 'No change', 4 = 'A little worse', 5 = 'Moderately worse', 6 = 'Very much worse'.

The PGIC will be completed by patients using electronic questionnaire at week 12, week 20, week 24, week 36, week 52 (EOS) or ET visits, and immediately prior to start of rescue medication or procedures.

Total Nasal Symptom Score (TNSS)

The Total Nasal Symptom Score (TNSS) is a 3-item composite symptom assessment of congestion, itching/sneezing, and rhinorrhea for the last week. Each symptom is graded on a 0-3 scale as below:

Score	**Symptoms**
0	No symptoms
1 = mild	Awareness but not troubled
2 = moderate	Troublesome but not interfering with normal daily activities or sleep
3 = severe	Interfering with normal daily activities or sleep

The TNSS total score is the sum of scores for each of the symptoms (congestion, itching/sneezing, rhinorrhea) and could range from 0 to 9 (a higher score suggests worse nasal symptoms).

The TNSS will be administered only to patients with a documented history of allergic rhinitis and who fluently speak a language in which the questionnaire is presented (based on availability of translations in participating countries). It will be completed by patients at the baseline visit (visit 3), week 12, week 24, week 36, and week 52 (EOS) or ET visits, and immediately prior to start of rescue medication or procedures.

Patient-Oriented Eczema Measure (POEM)

The POEM is a 7-item, validated questionnaire used in clinical practice and clinical trials to assess disease symptoms in children and adults with AD (Charman, 2004). The format is a response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) using a 5-point scale, based on frequency of occurrence during the past week. The possible scores for each question were: 0 (no days), 1 (1 to 2 days), 2 (3 to 4 days), 3 (5 to 6 days), and 4 (every day). The total score is the sum of scores for each of the 7 items; a higher score is indicative of more severe AD.

The following POEM banding scores have been established (Charman, 2004): 0 to 2=clear or almost clear; 3 to 7=mild eczema; 8 to 16=moderate eczema; 17 to 24=severe eczema; and 25 to 28=very severe eczema.

If one question of the seven is left unanswered, then that question is scored as 0 and the scores are summed and expressed as usual out of a maximum of 28. If two or more questions are left unanswered, then the questionnaire is not scored and is set to missing.

The POEM will be administered only to patients with a documented history of AD and who fluently speak a language in which the questionnaire is presented (based on availability of validated translations in participating countries). It will be completed by patients at the baseline visit (visit 3), week 12, week 24, week 36, and week 52 (EOS) or ET visits, and immediately prior to start of rescue medication or procedures.

Juniper Asthma Control Questionnaire (ACQ)

The 5-question version of the Juniper ACQ (ACQ-5) is a validated questionnaire to evaluate asthma control. The ACQ-5 has 5 questions which assess the top-scoring five asthma symptoms:

- Frequency in past week awoken by asthma during the night
- Severity of asthma symptoms in the morning
- Limitation of daily activities due to asthma
- Shortness of breath due to asthma
- Frequency of wheezing

Patients are asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0=no impairment, 6= maximum impairment).

A global score is calculated: the questions are equally weighted and the ACQ-5 score is the mean of the 5 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). A higher score indicates lower asthma control. Scores less than 1.0 reflect adequately controlled asthma, and scores 1.0 or greater reflect inadequately controlled asthma. On the 7-point scale of the ACQ-5, a change or difference in a score of 0.5 is the smallest change that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID)

defined by the developer. The recommended change of 0.50 is a reasonable threshold to define a meaningful individual-level change.

Based on the manual of ACQ, any more than one missing value is not acceptable. If more than one of the questions has a missing value, the global score is invalid and will be considered as missing. If only one question has a missing value, it will be interpolated (pro-rated) using the completed questionnaires from the previous visit. For example, if answer to question 5 is missing at week 24 visit and all questions are completed at week 12 visit, the score for question 5 at week 24 visit will be imputed as: (sum of score at week 24 visit/sum of scores excluding question 5 at week 12 visit) × score of question 5 at week 12 visit. If the questionnaire from the previous visit is not complete, the missing value will be imputed as the average of the completed questions within the current visit.

The ACQ-5 will be administered only to patients with a documented history of asthma. It will be completed by patients using electronic questionnaires at the baseline visit (visit 3), week 12, week 24, week 36, and week 52 (EOS) or ET visits, and immediately prior to start of rescue medication or procedures.

Standardized Rhinoconjunctivitis Quality of Life Questionnaire for ages 12+ [RQLQ(S)+12]

RQLQ(S)+12 is a self-administered questionnaire to measure health-related QOL in those 12 years of age and above, as a result of perennial or seasonal allergic rhinitis. There are 28 items on the RQLQ(S) in 7 domains: activity limitation, sleep problems, nasal symptoms, eye symptoms, non-nasal/eye symptoms, practical problems, and emotional function. The RQLQ(S)+12 responses are based on a 7-point Likert scale with responses ranging from 0 (not troubled) to 6 (extremely troubled). The overall RQLQ(S)+12 score is the mean of all 28 responses and the individual domain scores are the means of the items in those domains. No interpolation will be performed for missing scores. Higher scores indicated more health-related QOL impairment (lower scores were better). A change of 0.5 point or more in total score is considered to be clinically meaningful.

The RQLQ(S)+12 will be administered only to patients with a documented history of allergic rhinitis. It will be completed by patients using electronic questionnaires at the baseline visit (visit 3), week 12, week 24, week 36, and week 52 (EOS) or ET visits, and immediately prior to start of rescue medication or procedures.

Pain related to dysphagia

Pain related to dysphagia is assessed daily by question 4 in the DSQ questionnaire. Patient will respond to this question only when they answer Yes to question 2 “Since you woke up this morning, has food gone down slowly or been stuck in your throat?”. If the answer is No to question 2, a score of 0 will be assigned to pain related to dysphagia. The pain score over a 14-day period is calculated using the formula:

$$\textit{Dysphagia Related Pain Score} = \frac{(\textit{sum of points from question 4 from daily DSQ diary}) \times 14\ \textit{days}}{\textit{number of diary days reported with non-missing data}}$$

The rules for a minimum of 8 diary entries and non-missing data are the same as used for DSQ score calculation as described in Section 4.4.1.

4.5. Safety Variables

4.5.1. Adverse Events and Serious Adverse Events

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the study. All adverse events are to be coded to a "Preferred Term (PT)," "High Level Term," and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA, the latest available version in effect).

An **Adverse Event** 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.

A **Serious Adverse Event** is any untoward medical occurrence that at any dose, results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, 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. More information on criteria for SAE is specified in the protocol. SAE is based on investigator report in the CRF.

The pre-treatment AE and treatment-emergent AE (TEAE) is defined as following:

- Pre-treatment signs and symptoms (Pre-treatment AEs) are AEs that developed or worsened in severity during the pre-treatment period.
- Treatment-emergent AEs (TEAEs) are AEs that developed or worsened in severity compared to the baseline during the treatment-emergent period. As the worsening pre-existing AEs and new AEs that occur during the treatment and follow-up period will be collected on the AE case report form, all AEs with an onset date during the treatment and follow-up periods are considered as TEAEs.

The following AESIs (as revised in protocol amendment 3) will be analyzed:

- Anaphylactic reactions
- Systemic hypersensitivity reactions
- Helminthic infections

For detailed definition of these AESIs, please see Section 10.4.

4.5.2. Laboratory Safety Variables

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory. Samples will be collected predose at the initial screening visit (visit 1), baseline visit (visit 3), week 12, week 24, week 36, week 52 (EOS) or ET visits. 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)	Creatine phosphokinase (CPK)[1]

[1] CPK isoenzymes will be measured when CPK >5 × ULN

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

4.5.3. Vital Signs

Vital signs, including heart rate, blood pressure, respiration rate, and body temperature will be collected predose and 30 minutes post-dose at the initial screening visit (visit 1), every scheduled visit and the unscheduled visit before rescue treatment. Heart rate and blood pressure will be measured with the patient in a sitting position, after the patient has rested comfortably for at least 5 minutes. Weight is measured at the initial screening visit (visit 1), every scheduled visit (except week 1, week 40, week 44, and week 48 visits). Height is measured at the initial screening visit (visit 1), week 24, and week 52 (EOS) or ET visits.

4.5.4. 12-Lead Electrocardiography (ECG)

Standard 12-Lead ECG parameters include: Ventricular HR, PR interval, QRS interval, corrected QT interval (QTc Fridericia [QTcF] =QT/[RR0.33] and QTc Bazett [QTcB]=QT/[RR0.5]). Electrocardiogram results will be interpreted by a central reading center and categorized to: normal, abnormal not clinical significant or abnormal clinical significant

ECG will be performed predose at the initial screening visit (visit 1), week 24, and week 52 (EOS) or ET visits. ECG will be performed before blood is drawn during visits requiring blood draws.

4.5.5. Physical Examination Variables

The physical examination variable values are dichotomized to normal and abnormal.

A thorough and complete physical examination will be performed at the initial screening visit (visit 1), week 24, and week 52 (EOS) or ET visits.

4.6. Pharmacokinetic Variables

Serum samples for measuring functional dupilumab concentrations will be collected at time points according to Section 10.2. PK variables consist of functional dupilumab concentration and time (both actual and nominal).

4.7. Immunogenicity Variables

The immunogenicity variables are ADA response status, titer, NAb response status, and time-point/visit.

ADA response are specifically defined as follows:

- ADA Negative, defined as an ADA negative response in the ADA assay at all time points collected, regardless of any missing samples.
- Pre-existing immunoreactivity, defined as either an ADA positive response in the dupilumab ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than 4-fold over baseline titer levels.
- Treatment-emergent response, defined as a positive response in the dupilumab ADA assay post first dose when baseline results are negative or missing. The treatment-emergent responses will be further characterized as Persistent, Indeterminate or Transient.
  - Persistent Response: Treatment-emergent ADA positive response with two or more consecutive ADA positive sampling time points, separated by greater than 12-week period (based on nominal sampling time), with no ADA negative samples in between, regardless of any missing samples.
  - Indeterminate Response: Treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay.
  - Transient Response: Treatment-emergent ADA positive response that is not considered persistent or indeterminate, regardless of any missing samples.
- Treatment-boosted response, defined as a positive response in the dupilumab ADA assay post first dose that is greater than or equal to 4-fold over baseline titer levels, when baseline results are positive

Serum samples for ADA will be collected at the clinic visits specified in Section 10.2.

4.8. Biomarker Variables

Biomarkers to be analyzed in this study are:

- TARC
- Total serum IgE
- Allergen specific IgEs
- Allergen specific IgG4s
- Lactate dehydrogenase (LDH) [which will be measured as part of the blood chemistry]
- Eotaxin-3

Serum samples for measurements of biomarkers to study the pharmacodynamic activity of dupilumab in EoE patients will be collected at time points according to Section 10.2.

4.9. Patient Reported Outcomes for Psychometric Validity Assessment

The psychometric validity of 3 patient-reported outcome measures (DSQ, EoE-SQ, and EoE-IQ as described in Section 4.4.1 and Section 4.4.2) will be assessed.

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, median, Q1, Q3, standard deviation, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category. Missing values at baseline will not be imputed unless otherwise specified.

5.1. Demographics and Baseline Characteristics

Demographics and Baseline Characteristics will be summarized by treatment groups and for study total based on the FAS. A separate summary may be provided for Part C SAF patients who entered Part C from Part A. Listing of demographics and baseline characteristics will be presented.

5.2. Medical History

Medical history will be summarized by primary SOC and PT for each treatment group and for study total based on the SAF. The table will be sorted by decreasing frequency of SOC followed by PT based on the overall incidence across treatment groups.

Medical history will be listed, sorted by treatment groups based on the SAFs.

5.3. Prior/Concomitant Medications/Procedures

Number and proportion of subjects taking prior/concomitant medications, prohibited medications/procedures and rescue medications/procedures will be summarized for each treatment group and study total, based on the study part specific SAFs, by ATC Level 2 and ATC Level 4, sorted by decreasing frequency of ATC Level 2 and ATC level 4 in the dupilumab treatment group.

Number and proportion of subjects taking PPIs for the treatment of EoE will be summarized by PPI therapy name.

Number and proportion of subjects undergoing prior/concomitant procedures will be summarized for each treatment group and study total, based on the study part specific SAFs, by system organ class (SOC) and preferred term (PT), and sorted by decreasing frequency of SOC and PT in the dupilumab treatment group.

The detailed information of rescue medications/procedures including duration of use and incidence of use will be summarized, particularly for swallowed topical/systemic corticosteroids used to treat EoE. Kaplan Meier curves for time to first rescue use will be generated.

Separate summaries will be provided for Part A and Part C concomitant medications/procedures. For CMs/CPs taken during the follow-up period, separate summaries will be provided for patients who entered follow-up after Part C vs. patients who entered follow-up immediately after Part A. If there is a limited number of patients entering follow-up immediately after Part A, only listing will be provided.

Listing of pre-treatment medication and concomitant medications will include generic name and ATC levels 2 and 4, indication, study day of onset (for medications started before treatment, the study day of onset = date of medication start - date of the first dose; for medications started on or after treatment, the study day of onset = date of medication start - date of the first dose+1), the study day of medication end date (defined similarly as for study day of onset), ongoing status, dose, frequency, route.

A listing of protocol deviations with respect to prohibited medication use and prohibited procedures will be provided.

5.4. Subject Disposition

The following summaries will be provided for each treatment group and study total (unless otherwise specified):

- The total number of screened patients (for study total only)
- The total number of randomized patients: received a randomization number from IWRS
- The total number of patients in each analysis set
- The total number of patients who discontinued the study treatment in Part A and the reasons for discontinuation
- The total number of patients who discontinued the study during Part A, and the reasons for discontinuation
- Number of patients who entered into Part C
- The total number of patients who discontinued the study treatment in Part C and the reasons for discontinuation
- The total number of patients who discontinued the study during Part C, and the reasons for discontinuation

- Number of patients who entered the 12-week follow-up period from Part A and Part C, respectively

The following listings will be provided for Part A and Part C separately:

- Listing of subject disposition including: date of randomization, date of the last visit, received dose, completed Part A study drug dosing or discontinued by reason, completed Part C study drug dosing or discontinued by reason, completed study or discontinued by reason
- A listing of patients treated but not randomized, patients randomized but not treated, and patients randomized but not treated as randomized, if applicable
- A listing of patients prematurely discontinued from the study or treatment, along with reasons for discontinuation
- Summary table and listing of protocol deviations will be provided

The following summaries will be provided for each treatment group and study total:

- Number of patients who discontinued the treatment due to the COVID-19 pandemic and the reasons for discontinuation
- Number of patients who discontinued the study due to the COVID-19 pandemic and reasons for discontinuation
- Number of patients who had occurrence(s) of visits impacted by the COVID-19 pandemic and reasons

5.5. Extent of Study Treatment Exposure and Compliance

5.5.1. Measurement of Compliance

Compliance with protocol-defined study drug administration will be calculated separately for Part A and Part C as follows:

Treatment Compliance = (Number of study drug injections during the respective study part)/(Number of planned study drug injections during the respective study part) x 100%

Treatment compliance will be summarized separately for Part A and Part C as a continuous variable with descriptive statistics for each treatment group. Treatment compliance will also be presented by the following specific ranges for each treatment group: <80% and ≥80%.

Listing of treatment compliance will be presented with information on first dose date/time, last dose date/time, treatment completed or discontinued, number of planned doses, number of doses taken, compliance rate.

If subjects received Part A treatment different from their randomized treatment, listings will be provided.

5.5.2. Exposure to Study Drug and Observation Period

The duration of exposure to study drug is calculated separately for Part A, Part C, and the overall study as follows:

(Date of last study drug injection in the respective study part – date of first study drug injection in the respective study part) + 7

Note: exposure will be calculated based on the last study drug injection date and first study drug injection date regardless of temporary dosing interruption.

Summary of exposure to study drug will include the number of study drug doses administered and the duration of exposure. Duration of exposure will be summarized for each treatment group using number of patients, mean, SD, minimum, median, Q1, Q3, and maximum. These summaries will be provided for Part A and Part C separately.

In addition, the duration of exposure will be summarized categorically by counts and percentages for each of the following categories and cumulatively by these categories as well:

≥ 7 days, ≥ 14 days, ≥ 21 days , ≥ 28 days, ≥ 35 days, ≥ 42 days, ≥ 49 days, ≥ 56 days, ≥ 63 days, ≥ 70 days, ≥ 77 days, ≥ 84 days, ≥ 91 days, ≥ 98 days, ≥ 105 days, ≥112 days, ≥ 119 days, ≥ 126 days, ≥ 133 days, ≥140 days, ≥ 147 days, ≥ 154 days, ≥ 161 days, ≥168 days, with an increment of 2 weeks for each subsequent category.

In addition, for patients who received at least 1 dose of dupilumab, the total duration of exposure to dupilumab during the study (throughout Part A and Part C) is calculated as:

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

The duration of observation period during the study is calculated as:

[Date of the last study visit – date of the first study injection] +1.

The duration of observation period will be summarized descriptively using number of patients, mean, SD, median, Q1, Q3, minimum and maximum. In addition, the number (%) of subjects with observation periods will be presented by specific time periods. The time periods of interest is specified as: ≥ 8 days, ≥ 15 days, ≥ 22 days, ≥ 29 days, ≥ 36 days, ≥ 43 days, ≥ 50 days, ≥ 57 days, ≥ 64 days, ≥ 71 days, ≥ 78 days, ≥ 85 days, ≥ 92 days, ≥ 99 days, ≥ 106 days, ≥113 days, ≥ 120 days, ≥ 127 days, ≥ 134 days, ≥141 days, ≥ 148 days, ≥ 155 days, ≥ 162 days, ≥169 days, ≥ 183 days, with an increment of 2 weeks for each subsequent category.

Listing of dose administration will be presented with information on administration date/time, study day, locations of injections, kit numbers, and whether or not the total dose is administered for each dose will be presented.

5.6. Analyses of Efficacy Variables

The analyses of efficacy variables are described in the subsections below and summarized in Section 10.1.

5.6.1. Analysis of Co-Primary Efficacy Variable(s)

Histologic response (binary endpoint)

The proportion of patients achieving a histologic response of peak esophageal intraepithelial eosinophil (eos) count (from all 3 regions) of ≤6 eos/hpf at week 24 will be analyzed using the Cochran-Mantel-Haenszel (CMH) test to assess the difference in the proportion of responders in the FAS adjusting for the randomization stratification factors (age group [≥18 vs. ≥12 to <18 years

of age] and use of PPI at randomization [yes vs. no]). Estimates of treatment difference and its 95% confidence interval will be presented.

Data may be collected after the patient discontinued treatment and will be included in the analyses.

To account for use of rescue treatment (see Section 4.3), data will be set to missing for all time points subsequent to the use of rescue treatment in the primary analysis.

If week 24 biopsy is performed after the date when the first dose of Part C study drug is administered, data from that biopsy will be set to missing in the analysis.

Missing data at week 24 will be handled according to the reason for missingness as follows:

- Due to the COVID-19 pandemic, the last few Part A patients may not be able to return to site on schedule for their week 24 endoscopy with biopsies. In the primary analysis, the peak esophageal intraepithelial eosinophil count at week 24 will be missing for these patients and will be imputed by multiple imputation (MI) for 10 times based on patients who have non-missing eos counts at week 24. The MI will utilize the regression method with treatment group, randomization stratification, baseline eos count, and week 24 eos count included in the regression model. For each patient, the average value of the imputed week 24 eos counts across the 10 imputation sets will determine whether that patient will be classified as a responder or non-responder.
- If a patient has missing value for the histological response (peak esophageal intraepithelial eosinophil count) at week 24 due to reasons not related to the COVID-19 pandemic, the patient will be classified as a non-responder at week 24.

The complete dataset after the above steps will be analyzed by the CMH test.

In anticipation of sparse responders in the placebo group, the Fisher's exact test will be performed.

DSQ total score (continuous endpoint)

The absolute change from baseline in the DSQ total score at week 24 will be analyzed using an analysis of covariance (ANCOVA) model for the FAS with treatment group, randomization stratification factor, and relevant baseline measurement as covariates included in the model. The cumulative distribution function (CDF) of the absolute change from baseline in the DSQ total score at week 24 will be graphed to present the between-treatment-group differences at each level of the change.

Data may be collected after the patient discontinued treatment and will be included in the analyses.

To account for use of rescue treatment (see Section 4.3), data will be set to missing for all time points subsequent to the use of rescue treatment in the primary analysis.

If a patient has missing value for the DSQ total score at week 24, their data for Week 24 will be imputed by multiple imputation (MI) based on patients who remained in the trial with observed values relevant to analysis. To account for the uncertainty in the imputation, missing data at week 24 will be imputed 50 times to generate 50 complete datasets by using the MI procedure in Statistical Analysis Software (SAS).

MI will follow the 2 steps below using a random seed number of 6681774 in both steps:

1. Step 1: Use the Markov Chain Monte Carlo (MCMC) method to fill in intermittent missing values (ie, those missing values followed by observed values at subsequent visits) so that a monotone missing pattern will be formed.
2. Step 2: Using the datasets from step 1, missing data through week 24 will be imputed using the regression method with treatment group, randomization stratification, relevant baseline measurement, and post-baseline measurement up to week 24 included in the regression model.

Once imputations are made, the week 24 data of each of the complete datasets will be analyzed using ANCOVA. The results from the 50 analyses on the complete datasets will be combined to generate a valid overall statistical inference according to Rubin's formula (Rubin, 1987) using the SAS MIANALYZE procedure.

During the COVID-19 pandemic, DSQ data continued to be collected by the electronic handheld devices that were with the patients at home. This is consistent with how the DSQ data was collected for the entirety of the study and does not require consideration for COVID-19 impact in the analysis.

Handling of DSQ Data Collected During the Electronic Handheld Device Malfunction Period

In the normal flow of DSQ diary question on the electronic handheld device, patients are directed to question 2 if they answer Yes to question 1 and will be directed to question 1a only if they answer No to question 1 (**Figure 3**).

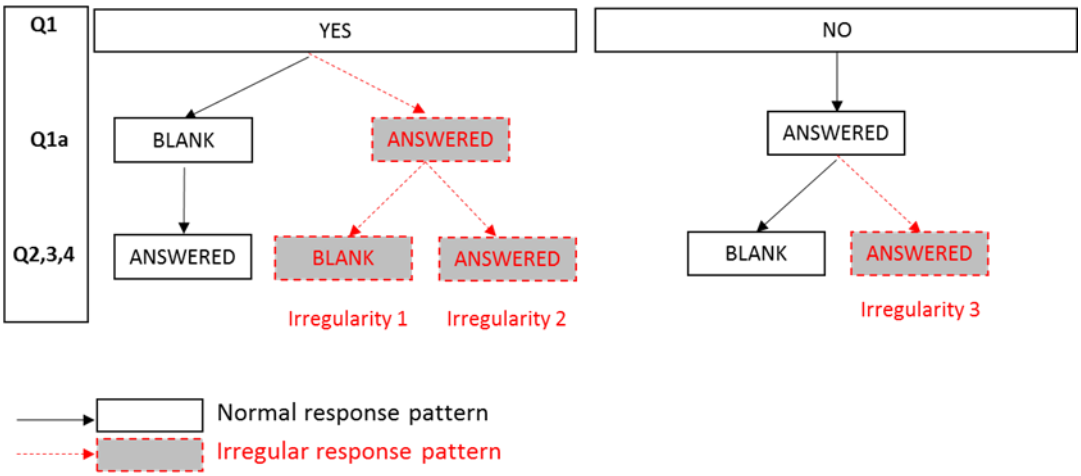
Figure 3: Flow Diagram of DSQ eDiary

When the YPrime Change Control Form (CCF) 023 update was released on 13Mar2020, it caused a DSQ navigation error issue to some devices (listed in Section Section 10.8) **after patients synchronized their devices** with the YPrime eCOA system (this marks the start of the period when patient's device did not direct DSQ questions properly). Details are reported in a note to file for this issue.

As a result, the devices of 16 patients randomized in Part A were affected by this navigation malfunction and irregular response patterns (as shown in Figure 4) were observed from patients using the affected devices.

A software update to resolve this malfunction was sent to devices on 27Mar2020 and impacted patients were instructed to upgrade the device software to fix the issue. The date when each affected patient upgraded the software on their device is provided in Section 10.8.

Figure 4: Response Patterns of DSQ eDiary



In the primary analysis, for patients using the affected devices, the daily DSQ scores will be set to missing for all days during the time when patient's device did not direct DSQ questions properly. Diary entries are considered as "not completed" on the affected days and thus will not contribute to the requirement of a minimum of 8 diary entries during a 14-day period to calculate the DSQ total score for that period.

Sensitivity analyses

Sensitivity analyses will assess alternative methods to impute missing data and include the following for the co-primary endpoints.

Histologic responder:

1. Last observation carried forward-multiple imputation (LOCF-MI): data will be set to missing for all time points subsequent to the use of rescue treatment. Missing values of peak eos count at week 24 due to the COVID-19 pandemic will be imputed using MI as in the primary analysis. Missing values of peak eos count at week 24 due to reasons not related to the COVID-19 pandemic will be imputed with patient's last available post-baseline value prior to week 24 (including eos counts taken just prior to initiation of rescue treatment). The baseline value will be carried forward if no post-baseline data. The imputed peak eos count at week 24 will determine patient's responder status.

2. All observed data, regardless of whether rescue treatment is used, will be included in the analysis. Patients with missing data will be counted as non-responders.
3. Data will be set to missing for all time points subsequent to the use of rescue treatment. Patients with missing week 24 data due to any reasons (regardless of whether related to the COVID-19 pandemic or not) will be considered as non-responders in the analysis.

DSQ total score:

1. MI regardless rescue treatment: All observed data, regardless of whether rescue treatment is used, will be included in the analysis. Missing data will be imputed using MI. Data after imputation will be analyzed by ANCOVA with treatment group, randomization stratification factor, and baseline DSQ in the model.
2. Last observation carried forward (LOCF): data will be set to missing for all time points subsequent to the use of rescue treatment. Missing values will be imputed with patient's last available post-baseline value. Baseline value will be carried forward if no post-baseline data. Data after imputation will be analyzed by ANCOVA with treatment group, randomization stratification factor, and baseline DSQ in the model.
3. Worst observation carried forward (WOCF): data will be set to missing for all time points subsequent to the use of rescue treatment. Missing values will be imputed with patient's worst available post-baseline value; baseline value will be used if no post-baseline value. Data after imputation will be analyzed by ANCOVA with treatment group, randomization stratification factor, and baseline DSQ in the model.
4. Tipping point analysis: after Step 1 and Step 2 in the aforementioned MI procedure, for each imputed dataset, a positive amount *d* will be added to the imputed week 24 values in the dupilumab group and a negative amount *p* will be added to the imputed week 24 values in the placebo group. Change from baseline to week 24 will then be calculated and analyzed using the same ANCOVA model followed by the SAS MIANALYZE procedure as in the primary analysis. The steps of adding the positive and negative amounts to the dupilumab and placebo group will be repeated iteratively until the p-value for estimated treatment effect from the ANCOVA analysis is greater than 0.05. Note: the tipping point analysis may not be conducted if the rate of missing data is very low.

Two DSQ data collection issues were noted and two sensitivity analyses are planned accordingly:

- This study does not allow collection of DSQ responses from paper screen reports and entering such paper sourced data in the eDiary database. However, before this decision was taken, patient [redacted] had DSQ diary collected through the paper source for one day during the baseline period. A sensitivity analysis will be conducted by excluding this paper sourced DSQ data point when calculating DSQ score.
- Two subjects at a site in Spain, [redacted] and [redacted], completed DSQ on handheld eDiary device with pre-linguistic validation screens (i.e., using certified translation screens which were not linguistically validated via patient interviews) during both the baseline period and part of the post-baseline periods. A sensitivity analysis will be conducted by excluding these two subjects from the analysis.

As in the primary analysis, DSQ data collected during the time when patient's device did not direct DSQ questions properly will not be used in the above sensitivity analyses.

5.6.2. Analysis of Secondary Efficacy Variables

Binary endpoints at week 24:

Secondary efficacy endpoints that measure binary responses at week 24 will be analyzed in the same fashion as the co-primary endpoint of histologic response of peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf, including the method to handle missing data and planned sensitivity analyses.

Continuous endpoints at week 24:

Continuous secondary efficacy endpoints at week 24 will be analyzed using ANCOVA in a similar fashion to the co-primary endpoint of change from baseline in the DSQ total score. In the main analyses of these endpoint, data will be set to missing for all time points subsequent to the use of rescue treatment. For endoscopy/biopsy-based endpoints (i.e., esophageal intraepithelial eos count, EREFS, EoE-HSS), if week 24 endoscopy/biopsy is performed after the date when the first dose of Part C study drug is administered, data from that endoscopy/biopsy will be set to missing in the analysis.

For continuous efficacy data that are scheduled to be measured repeatedly post-baseline up to week 24 (eg, percent change in DSQ score from baseline to week 24), as a primary analysis, missing data will be imputed by MI as described in the primary efficacy analysis of the DSQ co-primary endpoint. Sensitivity analyses similar to those specified for the DSQ co-primary endpoint may be conducted.

For continuous efficacy data that are to be measured only once post-baseline up to week 24 (eg, percent change in peak eos/hpf from baseline to week 24), as a primary analysis, a hybrid approach WOCF-MI will be used to handle missing data. That is, missing values at week 24 due to the COVID-19 pandemic will be imputed using MI as described in the primary analysis of the co-primary endpoint of histologic response in Section 5.6.1, and missing values at week 24 due to reasons not related to the COVID-19 pandemic will be imputed with patient's baseline value or the available post-baseline value up to week 24, whichever is worse, ie, a worst observation carried forward (WOCF) approach. The 10 complete datasets after the imputations will be analyzed using ANCOVA. The results from the 10 analyses will be combined using the SAS MIANALYZE procedure. A sensitivity analysis, using the LOCF-MI approach to impute missing values at week 24, will be performed (i.e., MI for missing data due to the COVID-19 pandemic and LOCF otherwise). Another senstitivity analysis will use WOCF to impute all missing data at week 24 regardless of whether the missingness is related to the COVID-19 pandemic or not. ANCOVA with treatment group, randomization stratification factor, and relevant baseline value (e.g., for the analysis of absolute change in EREFS, baseline EREFS value will be used) in the model will be used for these sensitivity analyses.

For transcriptome endpoints, the Wilcoxon rank-sum test will be used to test if the difference in median NES of the relative change from baseline to week 24 between the dupilumab and placebo groups is statistically significant. P-values will be reported.

Secondary endpoints in Part C

Secondary endpoints assessed in Part C (through week 52) will be summarized with descriptive statistics for Part C SAF patients who entered Part C from Part A as a single group, as well as based on the treatment assignment in Part A (as randomized). Descriptive statistics will include number of patients, mean, median, Q1, Q3, standard deviation, minimum, and maximum for continuous efficacy variables; and patient counts and proportions for categorical efficacy variables. No formal statistical hypothesis testing will be performed. Inferential statistics will only be provided as needed.

All observed values, regardless of whether rescue treatment is used or data are collected after withdrawal from study treatment, will be used for analysis. No missing values will be imputed.

For categorical efficacy variables, the proportion of patient meeting response criteria at each visit will be calculated using the number of patients with non-missing value at the visit as the denominator.

For efficacy variables whose calculations involve baseline values, e.g., absolute (or percent) change from baseline, separate summaries will be provided for analyses using the study baseline and Part C baseline values. The study baseline is the latest available valid measurement taken prior to or on the date of the first dose of study drug administration (scheduled to be administered at the baseline visit [visit 3]). Part C baseline is the last available valid measurement taken prior to or on the date of the first dose of extended active treatment (scheduled to be administered at week 24 visit [visit 11]). For DSQ, week 24 score will be used as Part C baseline; if week 24 score is missing, the latest available DSQ score prior to week 24 will be Part C baseline.

Provision was introduced in protocol amendment 4, after the Part C cut-off date of March 15, 2020, to permit PROs, intended to be completed during clinic visits, to be conducted via phone interviews during the COVID-19 pandemic. This provision is implemented for Part A subjects who are ongoing in Part C during the COVID-19 pandemic. Data collected via phone interview will be included from the primary summary of these PRO endpoints. Additional summaries may be provided by excluding data collected via phone interview. A listing of PRO assessments conducted via phone interviews will be provided.

5.6.3. Adjustment for Multiple Comparison

Part A and Part B will be carried out as 2 separate sub-studies with no overlap in patients. Therefore, each of Part A and Part B will have their own 2-sided significance level of 0.05.

Part A is considered positive when the co-primary endpoints both achieve statistical significance with two-sided significance level 0.05.

Statistical significance of both co-primary efficacy endpoints will be required before drawing inferential conclusions about any secondary efficacy endpoints. If both co-primary endpoints are statistically significant, the testing will proceed to the key and other secondary efficacy endpoints following a hierarchical procedure. The hierarchical order is as follows at the 2-sided significance level of 0.05 for the comparison of dupilumab 300 mg qw to placebo:

1. Co-primary endpoints:
   - Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24
   - Absolute change in DSQ score from baseline to week 24
2. Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 24
3. Absolute change in EoEHSS mean grade score from baseline to week 24
4. Absolute change in EoEHSS mean stage score from baseline to week 24
5. Absolute change in EoE EREFS total score from baseline to week 24
6. Proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf at week 24
7. Percent change in DSQ from baseline to week 24
8. Normalized Enrichment Scores (NES) for the relative change from baseline to week 24 in the EoE diagnostic panel (EDP) transcriptome signature
9. NES of the relative change from baseline to week 24 in the type 2 inflammation transcriptome signature

Subgroups described in Section 3.6 for the primary and key secondary efficacy endpoints (as listed in Section 4.4.1 and Section 4.4.2) will be summarized. Treatment difference and its 95% confidence interval in subgroups of patients will be presented in forest plots. Interactions between the subgroups and treatment groups will be tested.

5.6.4. Analysis of Exploratory Efficacy Variables

The analysis of other efficacy variables will be the same as the primary analysis described in Section 5.6.1 Section 5.6.2.

5.7. Analysis of Safety Data

The analysis of safety and tolerability will be performed on the SAF, as defined in Section 3.3.

The safety analysis will be based on the reported AEs, clinical laboratory evaluations, vital signs and 12-lead ECG.

Thresholds for treatment-emergent Potential Clinically Significant Values (PCSVs) in laboratory variables, vital signs and ECG are defined in Section 10.3. Treatment-emergent PCSV is any PCSV developed or worsened in severity compared to the baseline during the treatment and follow-up period. When identifying treatment-emergent PCSVs in Part C, baseline is the last available valid measurement taken prior to the first dose of extended active treatment in Part C (scheduled to be administered at week 24 visit [visit 11]).

The time interval to detect any event or abnormality is between the first injection of study medication and EOS.

The summary of safety results will be presented for each study part by treatment received in the corresponding part. For safety variables/summaries involving baseline values, e.g., absolute change from baseline or shift table, study part specific baselines will be used. Summaries for Part A will use the study baseline (i.e., the latest available valid measurement prior to the first dose of study drug in the study). Summaries for Part C and follow-up period will use Part C baseline (i.e., the last available valid measurement prior to the first dose of extended active treatment in Part C).

5.7.1. Adverse Events

The number and proportion of patients reporting TEAEs will be summarized for Part A week 24 treatment period, Part C extended active treatment period, and follow-up period, as described in Section 3.3.

- For the summary of Part A treatment period, TEAEs with onset date during the Part A treatment period will be included. TEAEs that had an onset during the Part A treatment period and continued afterwards into Part C treatment period or the follow-up period will be counted only once as TEAEs during the Part A treatment period.
- For the summary of Part C extended treatment period, TEAEs with onset during the Part C extended treatment period will be included. TEAEs that had an onset during the Part C treatment period and continued afterwards into the follow-up period will be counted only once as TEAEs during the Part C extended treatment period.
- For the follow-up period, TEAEs with onset during the follow-up period will be included.

AE incidence tables will be presented by treatment group for the SAF as well as for selected subgroups. TEAE summaries will present the number (n) and percentage (%) of subjects experiencing an TEAE by SOC and PT, sorted by decreasing frequency of SOC and PT for the dupilumab treatment group. Multiple occurrences of AEs of the same PT (or SOC) in the same subject will be counted only once for that PT (or SOC). For tables presenting severity of events, the worst severity will be chosen for subjects with multiple instances of the same event. The denominator for computation of percentage is the number of patients in each treatment group for the corresponding analysis period as specified in Section 3.3.

An overall summary of TEAEs will be provided with number and proportions of patients with any:

- TEAE
- Serious TEAE
- TEAE of special interest (AESI)
- TEAE leading to death
- TEAE leading to permanent treatment discontinuation

Detailed summaries of TEAEs will include:

- TEAEs
  - TEAEs by SOC/PT
  - TEAEs by SOC/HLT/PT

  - TEAEs by PT
  - TEAEs by SOC/HLT/PT with incidence of PT ≥5% in any treatment group
  - TEAEs by SOC/PT with incidence of PT ≥5% in any treatment group
  - TEAEs by severity by SOC/PT
  - Severe TEAEs by SOC/PT
  - TEAEs related to study medication as assessed by the investigator by SOC/PT
  - Severe TEAEs related to study medication as assessed by the investigator by SOC/PT
  - TEAE of special interest/TEAE by category (see Section 10.4)
- Serious TEAEs:
  - Serious TEAEs by SOC/PT
  - Serious TEAEs by SOC/HLT/PT
  - Serious TEAEs related to study medication as assessed by the investigator by SOC/PT
- TEAEs leading to permanent discontinuation of study treatment by SOC/PT
- Death by SOC/PT

The time to first AESIs (TEAE by category) or TEAE leading to permanent treatment discontinuation will be assessed by Kaplan-Meier estimates (K-M plot). In order to detect any safety signals, the hazard ratio (HR) will be provided together with the corresponding 95% confidence interval (CI) for the selected adverse events during the Part A treatment period. Hazard ratios will be calculated using a Cox model including factors of treatment group, and randomization strata. The time is defined as the date of first event – the date of first dose + 1. Patients without an event will be censored at the end of Part A treatment period. Graphs of cumulative incidence rate over time will be presented by treatment group.

Patient data listings will be provided for all SAEs, death, and TEAEs leading to permanent treatment discontinuation. The following variables will be included in the listing:

- Patient ID
- Treatment group
- Study part
- Age/sex/race
- System Organ Class (SOC)
- High Level Term (HLT)
- Preferred Term (PT)
- Verbatim Term
- AE start date and end date/ongoing (including both calendar days and study days)

- AE Duration
- Relationship of AE to study drug: unrelated or related
- Action taken: Dose withdrawn, Dose interrupted, Dose not changed, Dose increased, Dose reduced, Unknown, or Not applicable
- Severity: using a 3–point scale (mild, moderate, or severe)
- Treatment: none, medication, surgery, or others
- Outcome: recovered/resolved, recovered/resolved with sequelae, recovering/ resolving, not recovered/not resolved, fatal, or unknown

5.7.2. Clinical Laboratory Measurements

Laboratory measurements include clinical chemistry, hematology and urinalysis results, and will be converted to values in standard international units. Summaries of laboratory variables will include:

- Descriptive statistics of laboratory result and change from baseline by visit.
- The number (n) and percentage (%) of subjects with treatment-emergent PCSVs. This summary will be provided based on all patients in the SAF as well as in the subgroup of SAF patients who did not meet the PCSV criterion at baseline.
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

Listing of all laboratory parameters normal range, abnormal flag and treatment-emergent PCSV by subject and visit will be provided.

5.7.3. Analysis of Vital Signs

Summaries of vital sign variables will include:

- Descriptive statistics of vital sign variable and change from baseline by visit
- The number (n) and percentage (%) of subjects with treatment-emergent PCSV
- Shift tables based on baseline normal/abnormal and other tabular and graphical methods may be used to present the results for parameters of interest

Listings will be provided with flags indicating the treatment-emergent PCSVs.

5.7.4. Analysis of 12-Lead ECG

Summaries of 12-lead ECG parameters will include:

- Descriptive statistics for each ECG parameter and change from baseline
- The number (n) and percentage (%) of subjects with PCSV
- ECG status (i.e. normal, abnormal) summarized by a shift table

Listings will be provided with flags indicating PCSVs.

5.7.5. Physical Exams

Shift tables based on baseline normal/abnormal status will be provided for assessments of each physical exam category and presented by visit.

5.8. Analysis of Pharmacokinetic Data

The following analyses will be conducted:

- Descriptive statistics of functional dupilumab concentrations in serum at each sampling time by dose
- Graphical presentations of median and mean (+/- SD) functional dupilumab concentration in serum vs nominal time
- Graphical presentations of individual functional dupilumab concentration in serum vs actual sampling time
- Assessment of the impact of anti-drug antibodies on functional dupilumab concentrations in serum.

No formal statistical analysis will be performed.

5.9. Analysis of Immunogenicity Data

5.9.1. Analysis of ADA

The immunogenicity variables mentioned in Section 4.7 will be summarized using descriptive statistics. Immunogenicity will be characterized by ADA responses as defined in Section 4.7 and titers observed in patients in the ADA analysis set.

The following listings will be provided:

- Number (n) and percent (%) of ADA-negative patients (i.e., pre-existing immunoreactivity or negative in the ADA assay at all time points) by treatment groups
- Number (n) and percent (%) of treatment-emergent ADA positive patients by treatment groups and ADA titer categories
  - Number (n) and percent (%) of persistent treatment-emergent ADA positive patients
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive patients
  - Number (n) and percent (%) of transient treatment-emergent ADA positive patients
- Number (n) and percent (%) of treatment-boosted ADA positive patients by treatment groups and ADA titer categories

Listing of all ADA titer levels will be provided for pre-existing, treatment-emergent and treatment-boosted ADA response patients.

Titer categories (Maximum titer values)

- Low (titer <1,000)
- Moderate (1,000 ≤ titer ≤ 10,000)
- High (titer >10,000)

5.9.2. Analysis of Neutralizing Antibody (NAb) Data

Samples positive in the dupilumab ADA assay will be further characterized for the presence of NAb to dupilumab. The absolute occurrence (n) and percent of patients (%) with NAb status will be provided for patients in the NAb analysis set by treatment groups.

5.10. Association of Immunogenicity with Exposure, Safety and Efficacy

5.10.1. Association of immunogenicity with exposure

Potential association between ADA responses and systemic exposure to dupilumab will be explored by treatment groups. Plots of dupilumab concentration may be provided for analyzing the potential impact of ADA response status, titer and NAb on individual patient drug concentration profile.

5.10.2. Immunogenicity and Safety/Efficacy

Potential association between ADA responses and safety may be explored with a primary focus on the following safety events during the TEAE period:

- Injection site reaction (serious or severe and lasting 24 hours or longer)
- Hypersensitivity (SMQ: Hypersensitivity [Narrow])
- Anaphylaxis (SMQ: Anaphylaxis [Narrow])

Potential association between ADA responses and impact on individual patient efficacy endpoint profiles may be explored (e.g. scatter plot or spaghetti plot).

The safety and efficacy analyses mentioned above will be conducted using the following ADA response categories:

- ADA negative patients, that is patients with pre-existing immunoreactivity or negative in the ADA assay at all time points.
- ADA positive patients, that is patients with treatment-emergent or treatment-boosted response.
- Patients with persistent treatment-emergent ADA response
- NAb positive patients, that is ADA positive patients who were positive in the NAb assay at any time point analyzed.
- Maximum post-first dose titer in treatment-emergent or treatment-boosted ADA positive patients:
  - Low (titer <1,000)

- Moderate (1,000 ≤ titer ≤ 10,000)
- High (titer >10,000)

5.11. Analysis of Biomarker Data

Descriptive statistics for the observed values, change from baseline and percent change from baseline values by treatment and visit will be provided for the biomarker variables as described in Section 4.8.

The Wilcoxon signed-rank test will be used to test if the change or percentage change from baseline value is significantly different from zero. Nominal p-value will be reported.

For Part A, exploratory analyses for the difference between the dupilumab group and the placebo group in the change and percent change from baseline values will be performed using a rank-based ANCOVA model, with treatment group and randomization stratification factors as fixed factors, and the relevant baseline value as a covariate. Missing value will be imputed by LOCF method using available post-baseline data for visits up to week 24. P-value for difference from placebo will be provided.

Correlation of baseline TARC (measured value), Eotaxin-3, and IgE (measured value) with the following clinical endpoints will be explored using ANCOVA model. The model will include the below clinical endpoint as the dependent variable, with randomization stratification factors, the log10 transformed baseline biomarker value, treatment group, and treatment by baseline biomarker interaction as the predictor variables. Model coefficients and P-value will be provided to indicate significance of the correlation/association.

- Change from baseline to week 24 in DSQ total score
- Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 24
- Absolute change in EoE EREFS total score from baseline to week 24
- Absolute change in EoEHSS mean grade score from baseline to week 24
- Absolute change in EoEHSS mean stage score from baseline to week 24

Correlation of baseline TARC (measured value), Eotaxin-3, IgE (measured value), and positivity to at least one antigen-specific IgE (The threshold for positivity being ≥ 0.35 kU/L) with the histologic responder (histologic response of esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24) will be explored using the logistic model. The model will include the histologic responder/non-responder as the dependent variable, with randomization stratification factors, the log10 transformed baseline biomarker data, treatment group, and treatment by baseline biomarker interaction as the predictor variables. Model coefficients and P-value will be provided to indicate significance of the correlation/association.

Association of the DSQ score with the histology measures and EREFS score will be explored. Specifically, Pearson's correlation coefficient will be provided for the correlation of the following pairs within each treatment group:

- Total EoEHSS grade and stage scores (excluding lamina propria) vs. DSQ score at week 24
- Peak eos count vs. DSQ score at week 24
- Total EREFS score vs. DSQ score at week 24
- Change from baseline in total EoEHSS grade and stage scores (excluding lamina propria) vs. change from baseline in DSQ score at week 24
- Change from baseline in peak eos count vs. change from baseline in DSQ score at week 24
- Change from baseline in total EREFS score vs. change from baseline in DSQ score at week 24

All the above correlation/association analyses will be performed on the FAS for

- All observed data, regardless of the use of rescue treatment
- Observed data, with data set to missing for all time points subsequent to the use of rescue treatment

5.12. Analysis of Psychometric Validity of Patient Reported Outcome Measures

A series of analyses for assessing the psychometric validity of the DSQ, EoE-SQ and EoE-IQ will be performed with methods detailed in a separate Psychometric Analysis Plan (PAP). Results will be made available in a separate report.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the study baseline assessment for all measurements will be the latest available valid measurement taken prior to the first administration of study drug. If any randomized patients are not treated, the baseline will be the last value on or prior to the randomization. In addition, Part C baseline is defined as the last available valid measurement taken prior to the first dose of extended treatment in Part C. The baseline of DSQ is defined in Section 4.4.1.

The following rules specify the determination by both date/time information:

1. For AE, lab (including biomarker), PK and ADA data, both date and time of the measurement will be used to determine baseline by comparing with the first injection date and time.
2. For other data except AE, lab (including biomarker), PK or ADA, only date of the measurement will be used to determine baseline by comparing with the first injection date.

For re-screened patients, all data from the same patient will be used to derive baseline regardless of whether the data are from the screen failure subject ID or enrolled subject ID.

6.2. General Data Handling Conventions

For the laboratory safety variables and biomarker data, if the data are below the lower limit of quantification (LLOQ) / limit of linearity, half of the lower limit value (i.e., LLOQ/2) will be used for quantitative analyses. For data above the upper limit of quantification (ULOQ) / limit of linearity, the upper limit value (i.e., ULOQ) will be used for quantitative analyses.

6.3. Data Handling Convention for Missing Data

Missing data will not be imputed in listings. This section includes the methods for missing data imputation for some summary analyses, if necessary.

Adverse event

If the intensity of a TEAE is missing, it will be classified as “severe” in the frequency tables by intensity of TEAE. If the assessment of relationship of a TEAE to the study drug is missing, it will be classified as “related” in the frequency tables by relation to the study drug.

Adverse event start date

AE start date will be used for AE classification and analysis of AESIs. If AE start date is not complete, then the character variable will keep the original incomplete date, the numerical date variable will be imputed and an imputation flag will indicate which date component is missing.

If AE start day is missing, and AE start month and year are not missing: If AE start year is the same as first dose year and the AE start month is the same as the first dose month, then impute AE start day using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Otherwise impute the AE start day using the first day of the month. If this leads to a date before informed consent, the informed consent date will be used. Imputation flag is ‘D’.

If AE start month is missing, and AE start year is not missing: If AE start year is less than the first dose year, use the informed consent day and month. If AE start year is equal to the first dose year, use the first dose day and month. If this leads to a date after the AE end date, use AE end date instead. If AE start year is after the first dose year, use 01 January. Imputation flag is 'M'.

If AE start year is missing: Impute AE start date using the day of first dose. If this leads to a date after the AE end date, use AE end date instead. Imputation flag is 'Y'.

Adverse event end date

The general recommendation is not to impute AE end date. However, since AE end date will be used for the imputation of AE start date, in order to carry through the logic for programming, the following intermediate step will be used. Afterwards, only the original character/numeric date recorded in CRF will be kept in the final analysis dataset.

If AE end day is missing, and AE end month and year are not missing: Impute AE end date using the last day of the month. If this leads to a date after end of study follow up date, use the end of study date instead.

If AE end month is missing, and AE end year is not missing: Impute AE end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the end of study date instead.

If AE end year is missing: Impute AE end date using the end of study date.

Medication start and end date missing

To determine whether a medication is pre-treatment medication or concomitant medication or both, the missing medication start date is estimated as early as possible, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be calculated in medication listings.

Prior medication start date

If start day is missing, and start month and year are not missing: Impute the start day using the first day of the month. Imputation flag is 'D';

If start month is missing, and start year is not missing: Impute the day and month using 01 January. Imputation flag is 'M'.

If start year is missing: Impute start date using 2 years before informed consent date. Imputation flag is 'Y'.

A special note: for start date with year missing, the general principle is not to impute. However, in order to simplify the programming flow, the imputation is proposed to align with the protocol which specifies to collect up to 2 years prior medication. Since the start date of prior medication will not be used in any analysis, the rule will not impact the analysis result.

Prior medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date on or after first dose intake date, use first dose intake date -1 instead. Imputation flag is 'M'

If end year is missing: Impute end date using the first dose intake date -1. Imputation flag is 'Y'.

Concomitant medication start date

The imputation rule for concomitant medication start date is the same as AE start date.

Concomitant medication end date

If end day is missing, and end month and year are not missing: Impute end date using the last day of the month. If this leads to a date after end of study follow up date, use the last visit study date instead. Imputation flag is 'D'.

If end month is missing, and end year is not missing: Impute end date using 31 December as the day and month. If this leads to a date after end of study follow up date, use the last study visit date instead. Imputation flag is 'M'.

If end year is missing: Impute date using the end of last study visit date. Imputation flag is 'Y'.

Medication coding

Medications whose ATC level 4 cannot be coded will be summarized by setting ATC4=ATC2 in the table programs. However, these uncoded ATC level 4 records still need to be confirmed with study DM and study MD.

PCSV

Patients who had post-baseline PCSV but missing baseline value will be regarded as having treatment emergent PCSV.

6.4. Analysis Visit Windows

Data analyzed by-visit-analysis (efficacy [excluding daily diary data and data collected via biopsy/endoscopy procedures], laboratory data, visit sign, ECG, ADA) will be summarized by the study scheduled visits described Section 10.2, "Schedule of Event". The analysis visit windows will be exhaustive so that all available values obtained from unscheduled visits and early termination (ET) visit have the potential to be summarized.

No analysis visit windows will be applied for the study scheduled visits.

The following analysis visit windows will be used to map the unscheduled clinic visits and ET visit, based on the study day:

Visit No.	Visit	Targeted Study Days[a]	Analysis Window in Study Days
1	Screening	-85 to -29	≤ -29
2	Screening Endoscopy/Biopsy	-28 to -14	-28 to -1
3	Baseline	1	1
4	Week 1	8	[2, 11]

Visit No.	Visit	Targeted Study Days[a]	Analysis Window in Study Days
5	Week 2	15	[12, 22]
6	Week 4	29	[23, 43]
7	Week 8	57	[44, 71]
8	Week 12	85	[72, 99]
9	Week 16	113	[100, 127]
10	Week 20	141	[128, 155]
11	Week 24 (Part A end of treatment)	169	[156, 176][b]
Following windows only apply to patients who entered Part C and received at least 1 Part C dose			
12	Week 26	183	[177, 190][c]
13	Week 28	197	[191, 211]
14	Week 32	225	[212, 239]
15	Week 36	253	[240, 267]
16	Week 40	281	[268, 295]
17	Week 44	309	[296, 323]
18	Week 48	337	[324, 351]
19	Week 52 (Part C end of treatment)	365	[352, 379]
Following window applies to all patients			
20	12-week follow-up	Patients not entering Part C: 253	≥ 177
		Patients entering Part C: 449	≥ 380

[a] Study days are calculated from the day of 1st injection. Study day = (date of assessment – 1st injection date +1) when date of assessment ≥ 1st injection date; otherwise study day = (date of assessment – 1st injection date). If patient never received any dose of study drug, randomization date will be used in place of 1st injection date.

[b] If unscheduled or ET visit occurs in this window and it's after the first dose of Part C, it will be considered for Week 26. This rule also applies to Week 24 biopsy and endoscopy assessments.

[c] If unscheduled visit occurs in this window and it's before the first dose of Part C, it will be considered for Week 24.

In general, the following order will be used to select the record for analysis at given visit:

1. Scheduled visit
2. Early termination (ET) if scheduled visit not available
3. Unscheduled visit if both scheduled visit and ET visit are not available

If there are multiple measurements of the same test in the same window, the following rules will be used to select the analysis value:

- If multiple valid values of a variable exist within an analysis visit window, the closest from the target study day will be selected.
- If the difference is a tie, the value after the targeted study day will be used.
- If multiple available values of a variable exist within a same day, then the first value of the day will be selected.

Both scheduled and unscheduled measurements will be considered for determining abnormal/PCSV values from laboratory, vital sign or ECG as well as the baseline values.

For DSQ data (collected daily by eDiary), the analysis visit windows will be implemented following the procedures below:

Part A (diaries collected after the first injection in Part C will not be used for Part A analysis)

Step 1: Derive the study day

- If diary date ≥ 1st injection date in the study and < 1st injection date in Part C, then Part A diary study day = diary date – 1st injection date ***in the study*** +1;
- If diary date < 1st injection date in the study, Part A diary study day = diary date – 1st injection date ***in the study***

Step 2: Windows are defined as -14 to -1 = BL, 1 to 14 = week 2, 15 to 28 = week 4, etc, with 14-day intervals between visit windows, through 155 to 168 = week 24. For patients who never entered Part C, windows in the 12-week follow-up period will continue with the 14-day intervals as 169 to 182 = week 26, 183 to 196 = week 28, etc.

Part C (only applies to patients who received at least 1 dose of Part C study drug)

Step 1: Derive the study day,

- For diary date ≥ 1st injection date in Part C, Part C diary study day = diary date – 1st injection date ***in Part C*** +1;

Step 2: Windows are defined as 1 to 14 = week 26, 15 to 28 = week 28, etc, with 14-day intervals between visit windows, through 183 to 196 = week 52.

6.5. Statistical Technical Issues

None.

7. INTERIM ANALYSIS

No interim analysis is planned.

Primary analysis and final analysis are planned for Part A. The primary analysis will be performed when the last Part A patient has completed their end of Part A visit including patients who have terminated early in Part A. The assessments of primary, secondary, and exploratory efficacy endpoints through the end of Part A during the primary analysis will be the final (and only) analyses of these endpoints. Hence, there will be no need for alpha adjustment due to this primary analysis. The final analysis for Part A will occur when all patients who entered the 12-week follow-up period immediately from Part A completed the follow-up period.

Multiple steps of analyses will occur at the time when other study parts are completed and will be detailed in Part B SAP.

To maintain study integrity with respect to the post Part A visits and analyses, a dissemination plan will be written. This plan will clearly identify the team (including the statistician) that will perform the Part A analysis and all related activities, restrict other clinical team members and other Sponsor personnel from access to individual patient treatment allocation and site level analysis results, and ensure that the dedicated team will not participate in the data review or data decisions for the following post treatment analyses. However, the dedicated team can participate in the analysis following the final database lock.

8. SOFTWARE

All analyses will be done using SAS Version 9.4 or above.

9. REFERENCES

1. Barbie, DA, P Tamayo, JS Boehm, SY Kim, S E Moody, IF Dunn, AC Schinzel, P Sandy, E Meylan, C Scholl, S Frohling, EM Chan, ML Sos, K Michel, C Mermel, SJ Silver, BA Weir, JH Reiling, Q Sheng, PB Gupta, RC Wadlow, H Le, S Hoersch, BS Wittner, S Ramaswamy, DM Livingston, DM Sabatini, MMeyerson, RK Thomas, ES Lander, JP Mesirov, DE Root, DG Gilliland, T Jacks, and WC Hahn. Systematic Rna Interference Reveals That Oncogenic Kras-Driven Cancers Require Tbk1. Nature 462, no 7269. 2009 5 Nov: 108-12. PMID: 19847166
2. Charman CR, Venn AJ, and Williams, HC. The patient-oriented eczema measure. Arch Dermatol 2004; 140:1513-1519.
3. Collins MH, Martin LJ, Alexander ES, Todd Boyd J, Sheridan R, He H, et al.Newly developed and validated eosinophilic esophagitis histology scoring system and evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring. Dis Esophagus. 2017 Feb 1;30(3):1-8
4. Dellon ES, Katzka DA, Collins MH, Hamdani M, Gupta SK, Hirano I; MP-101-06 Investigators. Budesonide Oral Suspension Improves Symptomatic, Endoscopic, and Histologic Parameters Compared With Placebo in Patients With Eosinophilic Esophagitis. Gastroenterology. 2017 Mar;152(4):776-786.e5. doi: 10.1053/j.gastro.2016.11.021. Epub 2016 Nov 23. PMID: 27889574
5. Dellon, ES, Veerappan R, Selitsky SR, Parker JS, Higgins LL, Beitia RM,, Robert M. Genta RM , and Lash RH, MDA Gene Expression Panel is Accurate for Diagnosis and Monitoring Treatment of Eosinophilic Esophagitis in Adults. Clin Transl Gastroenterol. 2017 Feb 9;8(2):e74. doi: 10.1038/ctg.2017.2.
6. Greuter T, Bussmann C, Safroneeva E, Schoepfer AM, Biedermann L, Vavricka SR, Straumann A. Long-Term Treatment of Eosinophilic Esophagitis With Swallowed Topical Corticosteroids: Development and Evaluation of a Therapeutic Concept. Am J Gastroenterol. 2017 Oct;112(10):1527-1535.
7. Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut. 2013 Apr;62(4):489-95. PubMed PMID: 22619364.
8. Hudgens S, Evans C, Phillips E, Hill M. Psychometric validation of the Dysphagia Symptom Questionnaire in patients with eosinophilic esophagitis treated with budesonide oral suspension. J Patient Rep Outcomes. 2017;1(1):3. doi: 10.1186/s41687-017-0006-5. Epub 2017 Sep 12.
9. ICH. (1998, February 5). ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

10. Lucendo AJ, Arias A, Molina-Infante J. Efficacy of Proton Pump Inhibitor Drugs for Inducing Clinical and Histologic Remission in Patients With Symptomatic Esophageal Eosinophilia: A Systematic Review and Meta-Analysis. Clin Gastroenterol Hepatol. 2016 Jan;14(1):13-22.e1.
11. Rothenberg ME. Molecular, genetic, and cellular bases for treating eosinophilic esophagitis. Gastroenterology. 2015 May;148(6):1143-57.
12. Rubin, D.B. (1987) Multiple Imputation for Nonresponse in Surveys. John Wiley & Sons Inc., New York.
13. Spergel JM, Brown-Whitehorn TF, Cianferoni A, Shuker M, Wang ML, Verma R, Liacouras CA. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet.J Allergy Clin Immunol. 2012 Aug;130(2):461-7.e5.
14. Subramanian, A, P Tamayo, VK Mootha, S Mukherjee, BL Ebert, MA Gillette, A Paulovich, SL Pomeroy, TR Golub, ES Lander, and JP Mesirov. Gene Set Enrichment Analysis: A Knowledge-Based Approach for Interpreting Genome-Wide Expression Profiles. Proc Natl Acad Sci U S A 102, no. 43. 2005 25 Oct: 15545-50. PMID: 16199517
15. Sherrill JD, Kiran KC, Blanchard C, Stucke EM, Kemme KA, Collins MH, Abonia JP, Putnam PE, Mukkada VA, Kaul A, Kocoshis SA, Kushner JP, Plassard AJ, Karns RA, Dexheimer PJ, Aronow BJ, Rothenberg ME.Analysis and expansion of the eosinophilic esophagitis transcriptome by RNA sequencing. Genes Immun. 2014 Sep;15(6):361-9. doi: 10.1038/gene.2014.27.

10. APPENDIX

10.1. Summary of Statistical Analyses

Efficacy Analyses:

Endpoint	Analysis Populations	Primary Statistical Method	Supportive/Sensitive Statistical Method	Subgroup Analysis	Other Analyses
Primary Endpoints					
Proportion of patients achieving a histologic response of esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24	FAS	Cochran-Mantel-Haenszel test / MI for missing due to the COVID-19 pandemic, otherwise define missing as non-responder	Cochran-Mantel-Haenszel test on LOCF-MI, and on PPS	Yes	Histogram
Absolute change from baseline in the DSQ total score at week 24	FAS	MI+ANCOVA	ANCOVA with LOCF and WOCF	Yes	Line plot
Secondary Endpoints					
Secondary continuous variables	FAS	MI+ANCOVA for endpoints measured repeatedly (eg, DSQ); ANCOVA with WOCF-MI for endpoints measured only once post-baseline in Part A (eg, peak eos count)	ANCOVA with LOCF, LOCF-MI	Yes for key secondary efficacy	Line plot
Secondary binary variables	FAS	Cochran-Mantel-Haenszel test / MI for missing due to the COVID-19 pandemic, otherwise define missing as non-responder	Cochran-Mantel-Haenszel test on LOCF-MI	No	Histogram

Safety Analyses:

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Descriptive statistics and model-based analyses	No	No	No
Laboratory Measures	SAF	Descriptive Statistics	No	No	No
Vital sign	SAF	Descriptive Statistics	No	No	No
ECG	SAF	Descriptive Statistics	No	No	No

10.2. Schedule of Time and Events

Table 1: Parts A Schedule of Events – Screening Period and Placebo-controlled, Double-Blind Treatment Period

	Screening Period		24-Week Double-Blind Treatment Period								
Study Procedure	**Screening[1] V1**	**Screening Endoscopy/Biopsy[2] V2**	**Baseline V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**DB EOT V11[3]**
Week (W)				**W1**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24[3]**
Day (D)	**D-85 to D-29[1]**	**D-21[2]**	**D1**	**D8**	**D15**	**D29**	**D57**	**D85**	**D113**	**D141**	**D169**
Visit Window (Days [d])		**±7 d**		**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±7 d**
Screening[4]/Baseline:											
Informed consent and assent	X										
Inclusion/Exclusion criteria	X	X	X								
Med. history, Demographics	X										
Randomization[2a]			X[2a]								
Treatment:											
Training for self-injection[5]			X	X	X						
Administer study drug[6]			X	X	X	X	X	X	X	X	
Study drug dispensation[6]					X	X	X	X	X	X	
Study drug accountability						X	X	X	X	X	X
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	X
Efficacy:[7]											
DSQ PRO (daily)[8]	assessed by patient daily using eDiary										
PGIC[9]								X		X	X
PGIS[9]			X					X		X	X
EoE Impact Questionnaire [10]			X					X			X
EoE Symptom Questionnaire[10]			X					X			X
TNSS[11]			X					X			X
RQLQ(S)+12 [11]			X					X			X
ACQ-5[11]			X					X			X
POEM[11]			X					X			X
EoE-EREFS[2,12]		X[2, 2a, 4]									X[2, 2b]
Endoscopy with biopsies (histology, IHC, RNA) [2]		X[2, 2a, 4]									X[2, 2b]

	Screening Period		24-Week Double-Blind Treatment Period								
Study Procedure	**Screening[1] V1**	**Screening Endoscopy/Biopsy[2] V2**	**Baseline V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**DB EOT V11[3]**
Week (W)				**W1**	**W2**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24[3]**
Day (D)	**D-85 to D-29[1]**	**D-21[2]**	**D1**	**D8**	**D15**	**D29**	**D57**	**D85**	**D113**	**D141**	**D169**
Visit Window (Days [d])		**±7 d**		**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±3 d**	**±7 d**
Safety: [7]											
Vital signs[13]	X	X	X[13]	X[13]	X[13]	X[13]	X	X	X	X	X
Physical examination	X										X
ECG	X										X
Height	X										X[14]
Weight	X	X	X		X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing:[7]											
Hematology, Chemistry	X		X					X			X
Serology tests [15]	X										
Serum FSH	X										
Pregnancy test[16]	Serum	Urine	Urine			Urine	Urine	Urine	Urine	Urine	Urine
Urinalysis	X		X					X			X
PK and ADA:[7]											
PK sample			X					X			X
ADA sample			X					X			X
Biomarkers and Genomics:[7]											
Whole blood DNA (optional)			X								
Whole blood RNA (optional)	X		X								X
Eotaxin-3	X		X			X		X			X
TARC[17], Total IgE	X		X			X		X[17]			X
Allergen-specific IgE, IgG4	X		X			X		X			X
Future Biomarker Serum/Plasma	X		X			X		X			X

ADA = anti-drug antibody; DB EOT = end of double-blind treatment period; DSQ = Dysphagia Symptom Questionnaire; ECG = electrocardiogram; EoE-EREFS = Eosinophilic Esophagitis-Endoscopic Reference Score; IHC = immunohistochemistry; PGIC = Patient Global Impression of Change of Dysphagia; PGIS = Patient Global Impression of Severity of Dysphagia; POEM = Patient-Oriented Eczema Measure; PRO = patient-reported outcome; PK = pharmacokinetic; RQLQ(S)+12 = Rhinoconjunctivitis Quality of Life Questionnaire for patients aged 12+ years; TNSS = Total Nasal Symptom Score; V = visit

Table 2: Part C Schedule of Events – Extended Active Treatment Period

	28-Week Extended Active Treatment Period								
Study Procedure	**V11[1]**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**EOT V19**
Week (W)	**W24[1]**	**W26**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**
Day (D)	**D169**	**D183**	**D197**	**D225**	**D253**	**D281**	**D309**	**D337**	**D365**
Visit Window (Days [d])	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**
Treatment:[2]									
Administer study drug [3, 4]	X	X	X	X	X	X	X	X	
Study drug dispensation [4]	X	X	X	X	X	X	X	X	
Study drug accountability		X	X	X	X	X	X	X	X
Concomitant medications/procedures		X	X	X	X	X	X	X	X
Efficacy:[2]									
DSQ eDiary[5]	←---------- completed daily by patient ----------→								
PGIC[6]					X				X
PGIS[6]					X				X
EoE Impact Questionnaire[7]					X				X
EoE Symptom Questionnaire [7]					X				X
TNSS [8]					X				X
RQLQ(S)+12 [8]					X				X
POEM [8]					X				X
ACQ-5 [8]					X				X
EoE-EREFS [9, 10]									X[10, 10a]
Endoscopy with biopsies (histology, IHC, RNA)[10]									X[10, 10a]
Safety: [2]									
Vital signs [11]	X[11]	X[11]	X	X	X	X	X	X	X
Height [12]									X
Weight		X	X	X	X				X
Physical examination									X
ECG									X
Adverse events		X	X	X	X	X	X	X	X

	28-Week Extended Active Treatment Period								
Study Procedure	**V11[1]**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**EOT V19**
Week (W)	**W24[1]**	**W26**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**
Day (D)	**D169**	**D183**	**D197**	**D225**	**D253**	**D281**	**D309**	**D337**	**D365**
Visit Window (Days [d])	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**
Laboratory Testing:[2]									
Hematology, Chemistry					X				X
Pregnancy test [13]		Urine		Urine	Urine	Urine	Urine	Urine	Urine
Urinalysis					X				X
PK and ADA:[2]									
PK Sample				X					X
ADA sample				X					X
Biomarkers:[2]									
Whole blood RNA (optional)									X
Eotaxin-3		X		X					X
TARC[14], Total IgE		X[14]		X[14]					X
Allergen-specific IgE, IgG4		X		X					X
Future Biomarker Serum/Plasma		X		X					X

ADA = anti-drug antibody; DSQ = Dysphagia Symptom Questionnaire; ECG = electrocardiogram; EoE-EREFS = Eosinophilic Esophagitis-Endoscopic Reference Score; EOT = end of extended active treatment period; IHC = immunohistochemistry; POEM = Patient-Oriented Eczema Measure; PRO = patient reported outcome; PGA = physician global assessment; PGIC = Patient Global Impression of Change of Dysphagia; PGIS = Patient Global Impression of Severity of Dysphagia; PK = pharmacokinetic; RQLQ(S)+12 = Rhinoconjunctivitis Quality of Life Questionnaire for patients aged 12+ years; TNSS = Total Nasal Symptom Score; V = visit

Table 3: Follow-up Period, Early Termination Visit, and Unscheduled Visit

Study Procedure	12-Week Follow-Up EOS Visit	Early Termination during 12-Week Follow-Up[1]	Early Termination during Parts A, B, or C[1]	Unscheduled Visit before Rescue Treatment	Unscheduled Visit for Other Reasons
Week (W)	**12 weeks after EOT visit**				
Day (D)	**84 days after EOT visit**				
Visit Window (Days [d])	**±7 d**				
Concomitant medications/procedures	X	X	X	X	X
Efficacy:					
DSQ eDiary[2]	←completed daily by patient→		X	X	
PGIC[3]			X	X	
PGIS[3]			X	X	
EoE Impact Questionnaire [4]			X	X	
EoE Symptom Questionnaire [4]			X	X	
TNSS [5]			X	X	
RQLQ(S)+12 [5]			X	X	
ACQ-5 [5]			X	X	
POEM [5]			X	X	
EoE-EREFS [6, 7]			X [7, 7a]	X [8]	
Endoscopy with biopsies (histology, IHC, RNA)[7]			X [7, 7a]	X [8]	
Safety:					
Vital signs	X	X	X	X	
Height [9]			X		
Weight	X	X	X		
Physical examination			X		
ECG			X		
Adverse events	X	X	X	X	X
Laboratory Testing:					
Hematology, Chemistry	X	X	X		
Pregnancy test	Urine	Urine	Urine		
Urinalysis	X	X	X		

Study Procedure	12-Week Follow-Up EOS Visit	Early Termination during 12-Week Follow-Up[1]	Early Termination during Parts A, B, or C[1]	Unscheduled Visit before Rescue Treatment	Unscheduled Visit for Other Reasons
Week (W)	**12 weeks after EOT visit**				
Day (D)	**84 days after EOT visit**				
Visit Window (Days [d])	**±7 d**				
PK and ADA:					
PK Sample	X	X	X	X	
ADA	X	X	X	X	X
Biomarkers:					
Future Biomarker Serum/Plasma (optional)			X		

ADA = anti-drug antibody; DSQ = Dysphagia Symptom Questionnaire; ECG = electrocardiogram; EoE-EREFS = Eosinophilic Esophagitis-Endoscopic Reference Score; EOS = end of study (visit); EOT = end of treatment period; POEM = Patient-Oriented Eczema Measure; PRO = patient-reported outcome; PGA = physician global assessment; PGIC = Patient Global Impression of Change of Dysphagia; PGIS = Patient Global Impression of Severity of Dysphagia; PK = pharmacokinetic; RQLQ(S)+12 = Rhinoconjunctivitis Quality of Life Questionnaire for patients aged 12+ years; TNSS = Total Nasal Symptom Score

10.2.1. Footnotes for the Schedule of Events Tables

10.2.1.1. Footnotes for Table 1

1. For patients without a satisfactory prior endoscopy/biopsy (eg, histological criteria were not met, or the biopsy was not performed while patient was on at least 8 weeks of high-dose PPI treatment), the screening period will be extended for up to 12 weeks (day -85) to allow for at least 8 weeks of high-dose PPI treatment prior to the screening endoscopy/biopsies. For all other patients, the screening period will be shorter, with sufficient time to allow screening assessments and laboratory test results to be available prior to the baseline endoscopy/biopsies.
2. The endoscopy/EoE-EREFS/biopsy procedures should be performed after all other efficacy and safety assessments.

   2a. The baseline endoscopy with biopsies should be performed at approximately day -21±7 days to allow for availability of the intraepithelial eosinophil count result from the central pathology laboratory prior to day 1. For patients without a satisfactory prior historical endoscopy/biopsy, the baseline endoscopy/biopsies must be performed after at least 8 weeks of high-dose PPI. Patients may be randomized as soon as their endoscopy/biopsy results are available and DSQ eDiary entries are completed.

Note: Biopsy specimens from the stomach and/or duodenum will be obtained in all patients <18 years of age to rule out alternate etiologies. Stomach and/or duodenal biopsies will be obtained in adults only in the event of abnormal endoscopic findings (other than typical EoE findings) or clinical suspicion of alternate etiologies.

   2b. For patients who receive rescue treatment during the double-blind treatment period, the endoscopy/EoE-EREFS/biopsy procedures will be performed prior to the initiation of rescue treatment. Patients undergoing endoscopy/biopsy prior to rescue will not undergo the scheduled endoscopy/biopsy at week 24.

Note: All randomized patients found to have stomach and/or duodenal abnormalities at baseline will have follow-up stomach and/or duodenal biopsies at week 24 and week 52.

3. Assessments indicated for this week 24 (end of treatment) visit should be performed for all patients in Part A. For patients who will enter Part C, there are additional events listed in week 24 visit in Table 2 for Part C.
4. Patients may be re-screened once if they fail the screening evaluation, unless the reason for screen failure is related to histologic or clinical disease severity inclusion criteria. The baseline endoscopy with biopsy and EoE-EREFS scoring will not be repeated for re-screened patients. These results will continue to be valid baseline data. Re-screening must occur within 6 months of the screen failure.
5. Patients and/or caregivers will be trained on administration of study drug.
6. On scheduled in-clinic study visit days, study drug will be administered in the clinic (by the patient, site staff, or caregiver). Study drug will be provided for those doses scheduled to be administered at home before the next in-clinic visit. Doses of study

drug administered at home should be administered 1 week after the prior dose of study drug. Study drug administration that occurs in clinic should occur per the Schedule of Events in Tables 1 and 2. Patients will be closely monitored at the study site at visits 3 to 6 for a minimum of 30 minutes after the administration of study drug. In addition to the predose assessments, AEs and vital signs (body temperature, blood pressure, respiratory rate and heart rate) will be assessed at 30 minutes (±10 minutes) post-dose.

7. Assessments will be performed and blood samples will be collected before the administration of study drug.
8. DSQ eDiary will be completed once daily by the patients after their last meal of the day but before they go to bed. Site personnel should conduct regular checks of patient eDiary compliance.
9. Patient Global Impression of Change (PGIC) of Dysphagia and Patient Global Impression of Severity (PGIS) of Dysphagia will be completed by the patient via electronic questionnaire at the indicated site visits.
10. EoE Impact Questionnaire and EoE Symptom Questionnaire will be completed by the patient via electronic questionnaire at the indicated site visits.
11. Total Nasal Symptom Score (TNSS) and Rhinoconjunctivitis Quality of Life Questionnaire for patients aged 12+ years [RQLQ(S)+12] will be administered only to patients with a documented history of allergic rhinitis; Asthma Control Questionnaire-5 (ACQ-5) will be administered only to patients with a documented history of asthma; Patient-Oriented Eczema Measure (POEM) will be administered only to patients with a documented history of AD. TNSS, POEM, ACQ-5 and RQLQ(S)+12 will be completed via electronic questionnaire and at the indicated site visits. The questionnaires will be administered only to the subset of patients who fluently speak the language in which the questionnaire is presented (based on the availability of validated translations in participating countries).
12. EoE-EREFS should be completed before biopsies are performed.
13. At visits 3 through 6, vital signs (body temperature, blood pressure, respiratory rate, heart rate) should be taken predose and 30 minutes (±10 minutes) post-dose. Vital signs should be taken predose at all other indicated visits.
14. For adolescent patients only.
15. Includes HIV Ab, HBsAg, HBsAb, HBcAb, HCV Ab, and TB. Tuberculosis testing will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ECs.
16. Not required if post-menopausal status confirmed at screening. A negative result must be obtained prior to the randomization visit. In case of a positive urine test, the study treatment will be withheld and a serum pregnancy test to confirm the pregnancy should be performed as soon as possible. A confirmed pregnancy will lead to study drug discontinuation in all cases.
17. TARC analysis will occur only at visits 1, 3. 6, 11, and 19

10.2.1.2. Footnotes for Table 2

1. This visit is the same as the week 24 visit for Part A (Table 1), and all other assessments indicated for week 24 of Part A (Table 1) should be performed.
2. Study assessments will be performed and blood samples will be collected prior to administration of study drug.
3. Patients will be closely monitored at the study site at visits 11 and 12 for a minimum of 30 minutes after the administration of study drug. In addition to predose assessments, AEs and vital signs (body temperature, blood pressure, respiratory rate, and heart rate) will be assessed at 30 minutes (±10 minutes) post-dose.
4. On scheduled in-clinic study visit days, study drug will be administered in the clinic (by the patient, site staff, or caregiver). Study drug will be provided for those scheduled doses to be administered at home before the next in-clinic visit. Doses of study drug administered at home should be administered 1 week after the prior dose of study drug. Study drug administration that occurs in clinic should occur per the Schedule of Events in Table 1 and Table 2.
5. DSQ eDiary will be completed once daily by the patients after their last meal of the day but before they go to bed. Site personnel should conduct regular checks of patient eDiary compliance.
6. PGIC and PGIS will be completed by the patient via electronic questionnaire at the indicated site visits.
7. EoE Impact Questionnaire and EoE Symptom Questionnaire will be completed by the patient via electronic questionnaire at the indicated site visits.
8. TNSS and RQLQ(S)+12 will be administered only to patients with a documented history of allergic rhinitis; ACQ-5 will be administered only to patients with a documented history of asthma, and POEM will be administered only to patients with a documented history of AD. TNSS, POEM, ACQ-5 and RQLQ(S)+12 will be completed via electronic questionnaire and at the indicated site visits. The questionnaires will be administered only to the subset of patients who fluently speak the language in which the questionnaire is presented (based on the availability of validated translations in participating countries).
9. EoE-EREFS should be completed before biopsies are performed.
10. Endoscopy/EoE-EREFS/biopsy procedures should be performed after all other efficacy and safety assessments. Note: All randomized patients found to have stomach and/or duodenal abnormalities at baseline will have follow-up stomach and/or duodenal biopsies at weeks 24 and 52.

10a. For patients who receive rescue treatment, endoscopy/EoE-EREFS/biopsy procedures will be performed prior to initiation of rescue treatment. Patients undergoing endoscopy/biopsy prior to rescue will not undergo the scheduled endoscopy/biopsy at weeks 24 and 52.

11. At visits 11 and 12, vital signs (body temperature, blood pressure, respiratory rate, heart rate) should be taken predose and 30 minutes (±10 minutes) post-dose. Only predose vital signs are required at subsequent visits.
12. For adolescents only
13. In case of a positive urine pregnancy test, the study treatment will be withheld and a serum pregnancy test to confirm the pregnancy should be performed as soon as possible. A confirmed pregnancy will lead to study drug discontinuation in all cases.
14. TARC analysis will occur only at visits 1, 3, 6, 11, and 19.

10.2.1.3. Footnotes for Table 3

1. Patients who are withdrawn from study drug will be asked to complete the 12-week follow-up period and the end of study visit.
2. DSQ eDiary will be completed once daily by the patients after their last meal of the day but before they go to bed. Site personnel should conduct regular checks of patient eDiary compliance.
3. PGIC and PGIS will be completed by the patient via electronic questionnaire at the indicated site visits.
4. EoE Impact Questionnaire and EoE Symptom Questionnaire will be completed by the patient via electronic questionnaire at the indicated site visits.
5. TNSS and RQLQ(S)+12 will be administered only to patients with a documented history of allergic rhinitis; ACQ-5 will be administered only to patients with a documented history of asthma, and only in countries in which a valid translation is available; POEM will be administered only to patients with a documented history of AD. TNSS, POEM, ACQ-5 and RQLQ(S)+12 will be completed via electronic questionnaire and at the indicated site visits.
6. EoE-EREFS should be completed before biopsies are performed.
7. Endoscopy/EoE-EREFS/biopsy procedures should be performed after all other efficacy and safety assessments.

Note: All randomized patients found to have stomach and/or duodenal abnormalities at baseline will have follow-up stomach and/or duodenal biopsies at weeks 24 and 52 or ET visit.

7a. For patients who receive rescue treatment during the double-blind treatment period, endoscopy/EoE-EREFS/biopsy procedures will be performed prior to initiation of rescue treatment. Patients undergoing endoscopy/biopsy prior to rescue will not undergo the scheduled endoscopy/biopsy at weeks 24 and 52.

8. Endoscopy/EoE-EREFS/biopsy will be performed only if the Unscheduled Visit is for the purpose of administering rescue therapy.
9. For adolescents only.

10.3. Criteria for Potentially Clinically Significant Values (PCSV)

Where adolescent criteria (age >12 to <18) are different than adult criteria (>18), the adolescent criteria are provided in [parentheses] in the combined column. The criteria inside the "Combined" column will be used for display in the reporting outputs. Applicable criteria will be applied to parameters collected in the study to identify treatment-emergent PCSV cases.

Parameter	**Adults (≥18)**[a]	**Adolescents (≥12 to <18)** [a]	**Combined**
Clinical Chemistry			
ALT/SGPT	>3 and ≤ 5 ULN and baseline ≤ 3 ULN >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	>3 and ≤ 5 ULN and baseline ≤ 3 ULN >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	>3 and ≤ 5 ULN and baseline ≤ 3 ULN >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN
AST/SGOT	>3 and ≤ 5 ULN and baseline ≤ 3 ULN >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	>3 and ≤ 5 ULN and baseline ≤ 3 ULN >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN	>3 and ≤ 5 ULN and baseline ≤ 3 ULN >5 and ≤ 10 ULN and baseline ≤ 5 ULN >10 and ≤ 20 ULN and baseline ≤ 10 ULN >20 ULN and baseline ≤ 20 ULN
Alkaline Phosphatase	>1.5 ULN and baseline ≤ 1.5 ULN	≥1.5 ULN and baseline <1.5 ULN	>1.5 [≥1.5] ULN and baseline ≤ 1.5[<1.5] ULN
Total Bilirubin	>1.5 and ≤ 2 ULN and baseline ≤ 1.5 ULN >2 ULN and baseline ≤ 2.0 ULN	≥1.3 ULN and baseline < 1.3 ULN	>1.5 [≥1.3] and ≤ 2 ULN and baseline ≤ 1.5 [< 1.3] ULN >2 ULN and baseline ≤ 2.0 ULN
Conjugated Bilirubin[b]	(Direct Bilirubin >35% Total Bilirubin and Total Bilirubin >1.5 ULN) and (Direct Bilirubin ≤35% Total Bilirubin **or** Total Bilirubin ≤1.5 ULN) at baseline	(Direct Bilirubin >35% Total Bilirubin and Total Bilirubin ≥1.3 ULN) and (Direct Bilirubin ≤35% Total Bilirubin **or** Total Bilirubin <1.3 ULN) at baseline	(Direct Bilirubin >35% Total Bilirubin and Total Bilirubin >1.5 [≥1.3] ULN) and (Direct Bilirubin ≤35% Total Bilirubin **or** Total Bilirubin ≤1.5 [<1.3] ULN) at baseline
ALT and Total Bilirubin	(ALT>3 ULN and TBILI>2 ULN) and baseline (ALT ≤3 ULN **or** TBILI ≤2 ULN)	(ALT>3 ULN and TBILI>2 ULN) and baseline (ALT ≤3 ULN **or** TBILI ≤2 ULN)	(ALT>3 ULN and TBILI>2 ULN) and baseline (ALT ≤3 ULN **or** TBILI ≤2 ULN)
CPK	>3 and ≤ 10 ULN and baseline ≤ 3ULN >10 ULN and baseline ≤ 10ULN	≥3 ULN and baseline < 3ULN	>3 [≥3] and ≤ 10 ULN and baseline ≤ 3 [<3] ULN >10 ULN and baseline ≤ 10ULN

Parameter	**Adults (≥18)**[a]	**Adolescents (≥12 to <18)** [a]	**Combined**
Creatinine	≥150 µmol/L (Adults) and baseline < 150 µmol/L >=30% change from baseline and <100% change from baseline ≥100% change from baseline	≥132µmol/L and baseline < 132µmol/L (or ≥1.5 mg/dL and baseline <1.5 mg/dL) >=30% change from baseline	≥150 [≥132] µmol/L and baseline < 150 [<132] µmol/L >=30% change from baseline and <100% change from baseline ≥100% change from baseline
Uric Acid Hyperuricemia Hypouricemia	>408 µmol/L and <=408 µmol/L at baseline <120 µmol/L and >= 120 µmol/L at baseline	≥8.0 mg/dL and <8.0 mg/dl at baseline (or ≥476 µmol/L and <476 µmol/L at baseline ≤2 mg/dL and >2 mg/dL at baseline (or ≤119 µmol/L and baseline > 119 µmol/L)	>408 [≥476] µmol/L and ≤408 [<476] µmol/L at baseline <120 µmol/L and ≥ 120 µmol/L at baseline
Blood Urea Nitrogen	≥17 mmol/L and <17 mmol/L at baseline	≥7.14 mmol/L and <7.14 mmol/L at baseline	≥17 [≥7.14] mmol/L and <17 [<7.14] mmol/L at baseline
Chloride Hypochloremia Hyperchloremia	<80 mmol/L and baseline ≥ 80 mmol/L >115 mmol/L and baseline ≤ 115 mmol/L	<80 mmol/L and baseline ≥ 80 mmol/L ≥115 mmol/L and baseline < 115 mmol/L	<80 mmol/L and baseline ≥ 80 mmol/L >115 mmol/L and baseline ≤ 115 mmol/L
Sodium Hyponatremia Hypernatremia	≤129 mmol/L and baseline > 129 mmol/L ≥160 mmol/L and baseline <160 mmol/L	≤129 mmol/L and baseline >129 mmol/L ≥150 mmol/L and baseline <150 mmol/L	≤129 mmol/L and baseline > 129 mmol/L ≥160 [≥150] mmol/L and baseline <160 [<150] mmol/L
Potassium Hypokalemia Hyperkalemia	<3 mmol/L and baseline ≥ 3 mmol/L ≥5.5 mmol/L and baseline <5.5 mmol/L	≤3.5 mmol/L and baseline >3.5 mmol/L ≥5.5 mmol/L and baseline <5.5 mmol/L	<3 [≤3.5] mmol/L and baseline ≥ 3 [>3.5] mmol/L ≥5.5 mmol/L and baseline <5.5 mmol/L
Total Cholesterol	≥7.74 mmol/L and < 7.74 mmol/L at baseline	≥ 6.20 mmol/Land < 6.20 mmol/L at baseline	≥7.74 [≥6.20] mmol/L and < 7.74 [<6.20] mmol/L at baseline
Triglycerides	≥4.6 mmol/L and < 4.6 mmol/L at baseline	Fasted level ≥5.64 mmol/L and < 5.64 mmol/L at baseline	≥4.6 [≥5.64 fasted] mmol/L and < 4.6 [<5.64 fasted] mmol/L at baseline

Parameter	Adults (≥18)[a]	Adolescents (≥12 to <18) [a]	Combined
Glucose Hypoglycaemia Hyperglycaemia	(≤3.9 mmol/L and <LLN) and (>3.9 mmol/L or >=LLN) at baseline ≥11.1 mmol/L (unfasted) and <11.1 mmol/L (unfasted) at baseline; ≥7 mmol/L (fasted) and <7 mmol/L (fasted) at baseline	<2.7 mmol/L and ≥2.7 mmol/L at baseline (or < 50 mg/dL and ≥ 50 mg/dL at baseline) ≥10 mmol/L (unfasted) and < 10 mmol/L (unfasted) at baseline (or ≥180 mg/dl and <180 mg/dl at baseline); ; ≥7 mmol/L (fasted) and <7 mmol/L (fasted) at baseline (or ≥120 mg/dL and <120 mg/dL at baseline)	(≤3.9 [<2.7] mmol/L and <LLN) and (>3.9 [≥2.7] mmol/L or >=LLN) at baseline ≥11.1 [≥10] mmol/L (unfasted) and <11.1 [<10] mmol/L (unfasted) at baseline; ≥7 mmol/L (fasted) and <7 mmol/L (fasted) at baseline
HbA1c[b]	>8% and <= 8% at baseline	>6.5% and <= 6.5% at baseline	>8% [>6.5%] and ≤ 8% [≤6.5%] at baseline
Albumin	≤25 g/L and >25 g/L at baseline	≤25 g/L and >25 g/L at baseline	≤25 g/L and >25 g/L at baseline
CRP[b]	>2 ULN or >10 mg/L (if ULN not provided) and <=2 ULN or <=10 mg/L (if ULN not provided) at baseline	NONE	>2 ULN or >10 mg/L (if ULN not provided) and <=2 ULN or <=10 mg/L (if ULN not provided) at baseline (adults only)
Calcium total	NONE	<2 mmol/L and baseline ≥2 mmol/L (or ≤ 8 mg/dL and baseline >8 mg/dL) ≥2.9 mmol/L and baseline <2.9 mmol/L (or ≥11.6 mg/dL and baseline <11.6 mg/dL)	<2 mmol/L and baseline ≥2 mmol/L (adolescents only) ≥2.9 mmol/L and baseline <2.9 mmol/L (adolescents only)
LDL Cholesterol	NONE	≥4.91 mmol/L and <4.91 mmol/L at baseline (≥ 190 mg/dl and <190 mg/dl at baseline)	≥4.91 mmol/L and <4.91 mmol/L at baseline (adolescents only)

Parameter	Adults (≥18)[a]	Adolescents (≥12 to <18) [a]	Combined
Hematology			
WBC	<3.0 Giga/L and >=3.0 Giga/L at baseline (Non-Black); <2.0 Giga/L and >=2.0 Giga/L at baseline (Black) ≥16.0 Giga/L and < 16 Giga/L at baseline	<4.0 Giga/L and ≥4.0 Giga/L at baseline >13.5 Giga/L and ≤13.5 Giga/L at baseline	<3.0 Giga/L and >=3.0 Giga/L at baseline (Non-Black); <2.0 Giga/L and >=2.0 Giga/L at baseline (Black) [<4.0 Giga/L and ≥4.0 Giga/L at baseline] ≥16.0 [>13.5] Giga/L and < 16 [≤13.5] Giga/L at baseline
Lymphocytes	>4.0 Giga/L and <= 4.0 Giga/L at baseline	<0.6 Giga/L and ≥0.6 Giga/L at baseline >6.0 Giga/L and ≤6.0 Giga/L at baseline	<0.6 Giga/L and ≥0.6 Giga/L at baseline (adolescents only) >4.0 [>6.0] Giga/L and ≤4.0 [≤6.0] Giga/L at baseline
Neutrophils	<1.5 Giga/L and >=1.5 Giga/L at baseline (Non-Black); <1.0 Giga/L and >=1.0 Giga/L at baseline (Black)	<1.2 Giga/L and ≥1.2 Giga/L at baseline >ULN and baseline ≤ ULN	<1.5 Giga/L and >=1.5 Giga/L at baseline (Non-Black); <1.0 Giga/L and >=1.0 Giga/L at baseline (Black) [<1.2 Giga/L and ≥1.2 Giga/L at baseline] >ULN and baseline ≤ ULN (adolescents only)
Monocytes	>0.7 Giga/L <= 0.7 Giga/L at baseline	>1.2 Giga/L and <= 1.2 Giga/L at baseline	>0.7 [1.2] Giga/L <= 0.7 [1.2] Giga/L at baseline
Basophils	>0.1 Giga/L <= 0.1 Giga/L at baseline	NONE	>0.1 Giga/L <= 0.1 Giga/L at baseline (adults only)
Eosinophils	(>0.5 Giga/L and >ULN) and (<=0.5 Giga/L or <= ULN at baseline)	(>0.5 Giga/L and >ULN) and (<=0.5 Giga/L or <= ULN at baseline)	(>0.5 Giga/L and >ULN) and (<=0.5 Giga/L or <= ULN at baseline)
Hemoglobin	≤115 g/L and > 115 g/L at baseline for male; ≤95 g/L and> 95 g/L at baseline for Female. ≥185 g/L and <185 g/L at baseline for Male; ≥165 g/L and < 165 g/L at baseline for Female Decrease from Baseline ≥20 g/L	<100 g/L and >=100 g/L at baseline ≥200 g/L and <200 g/L at baseline	≤115 g/L and > 115 g/L at baseline for male; ≤95 g/L and> 95 g/L at baseline for Female. [<100 g/L and >=100 g/L at baseline] ≥185 g/L and <185 g/L at baseline for Male; ≥165 g/L and < 165 g/L at baseline for Female [≥200 g/L and <200 g/L at baseline] Decrease from Baseline ≥20 g/L

Parameter	**Adults (≥18)**[a]	**Adolescents (≥12 to <18)** [a]	**Combined**
Hematocrit	≤0.37 v/v and > 0.37 v/v at baseline for Male ; ≤0.32 v/v and > 0.32 v/v at baseline for Female ≥0.55 v/v and < 0.55 v/v at baseline for Male ; ≥0.5 v/v and < 0.5 v/v at baseline for Female	≤0.37 v/v and >0.37 v/v at baseline for Male; ≤0.33 v/v and >0.33 v/v at baseline for Female ≥0.52 v/v and <0.52 v/v at baseline for Male; ≥0.47 v/v and <0.47 v/v at baseline for Female	≤0.37 v/v and > 0.37 v/v at baseline for Male ; ≤0.32 [≤0.33] v/v and > 0.32 [>0.33] v/v at baseline for Female ≥0.55 [≥0.52] v/v and < 0.55 [<0.52] v/v at baseline for Male ; ≥0.5 [≥0.47] v/v and < 0.5 [<0.47] v/v at baseline for Female
RBC	<4 Tera/L and baseline ≥4 Tera/L For Male; <3 Tera/L and baseline ≥3 Tera/L for Female ≥7 Tera/L and baseline < 7 Tera/L for Male; ≥6 Tera/L and baseline < 6 Tera/L for Female	NONE	<4 Tera/L and baseline ≥4 Tera/L For Male; <3 Tera/L and baseline ≥3 Tera/L for Female ≥7 Tera/L and baseline < 7 Tera/L for Male; ≥6 Tera/L and baseline < 6 Tera/L for Female
Platelets	<100 Giga/L and ≥100 Giga/L at baseline ≥700 Giga/L and < 700 Giga/L at baseline	<100 Giga/L and ≥100 Giga/L at baseline >700 Giga/L and ≤ 700 Giga/L at baseline	<100 Giga/L and ≥100 Giga/L at baseline ≥700 Giga/L and < 700 Giga/L at baseline

Parameter	Adults (≥18)[a]	Adolescents (≥12 to <18) [a]	Combined
Urinalysis			
pH	≤4.6 and > 4.6 at baseline ≥8 and < 8 at baseline	NONE	≤4.6 and > 4.6 at baseline (adults only) ≥8 and < 8 at baseline (adults only)
Ketonuria	NONE	Presence and absence at baseline	Presence and absence at baseline (adolescents only)
Glycosuria	NONE	Presence and absence at baseline	Presence and absence at baseline (adolescents only)
Microscopic Hematuria	NONE	> 5 RBCs/ HPF and ≤5 RBCs/ HPF at baseline	> 5 RBCs/ HPF and ≤5 RBCs/ HPF at baseline (adolescents only)
Proteinuria	NONE	≥ 1+ and <1 at baseline	≥ 1+ and <1 at baseline (adolescents only)
Vital signs			
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	≤90 mmHg and decrease from baseline ≥20 mmHg ≥119 mmHg and increase from baseline ≥20 mmHg	≤95 mmHg [≤90 mmHg] and decrease from baseline ≥20mmHg ≥160 mmHg [≥119 mmHg] and increase from baseline ≥20 mmHg
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	≤54 mmHg and decrease from baseline ≥10 mmHg ≥78 mmHg and increase from baseline ≥10 mmHg	≤45 mmHg [≤54 mmHg] and decrease from baseline ≥10 mmHg ≥110 mmHg [≥78 mmHg] and increase from baseline ≥10 mmHg
Temperature	Rectal, ear: >100.4 °F/38.0 °C Oral: >99.5 °F/37.5 °C Axillary or skin infrared (temporal): >99 °F/37.2 °C	Rectal, ear: >100.4 °F/38.0 °C Oral: >99.5 °F/37.5 °C Axillary or skin infrared (temporal): >99 °F/37.2 °C	Rectal, ear: >100.4 °F/38.0 °C Oral: >99.5 °F/37.5 °C Axillary or skin infrared: >99 °F/37.2 °C

Parameter	Adults (≥18)[a]	Adolescents (≥12 to <18) [a]	Combined
Respiratory rate	<12 per minute and ≥12 per minute at baseline >20 per minute and ≤20 per minute at baseline	<12 per minute and ≥12 per minute at baseline >20 per minute and ≤20 per minute at baseline	<12 per minute and ≥12 per minute at baseline >20 per minute and ≤20 per minute at baseline
Weight	≥5% increase from baseline ≥5% decrease from baseline	≥5% weight loss from baseline	≥5% increase from baseline (adults only) ≥5% decrease from baseline
ECG			Ref.: CPMP 1997 guideline.
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm
PR	≥220 ms and increase from baseline ≥20 ms	≥200 ms and < 200 ms at baseline	≥220 ms and increase from baseline ≥20 ms [≥200 ms and < 200 ms at baseline]
QRS	≥120 ms & < 120 ms at baseline	≥110 ms & < 110 ms at baseline	≥120 [≥110] ms and < 120 [<110] ms at baseline
QTc Borderline Prolonged Additional	<u>Absolute values (ms)</u> Borderline: 431-450 ms and < 431ms at baseline for Male; 451-470 ms and < 451 ms at baseline for Female Prolonged: >450 to <500 ms and <= 450 ms at baseline for Male; >470 to <500 ms and <= 470 ms at baseline for Female Additional: ≥500 ms and < 500 ms at baseline <u>Increase from baseline</u> Borderline: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms	<u>Absolute values (ms)</u> Borderline: 431-450 ms and < 431ms at baseline for Male; 451-470 ms and < 451 ms at baseline for Female Prolonged: >450 to <500 ms and <= 450 ms at baseline for Male; >470 to <500 ms and <= 470 ms at baseline for Female Additional: ≥500 ms and < 500 ms at baseline <u>Increase from baseline</u> Borderline: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms	<u>Absolute values (ms)</u> Borderline: 431-450 ms and < 431ms at baseline for Male; 451-470 ms and < 451 ms at baseline for Female Prolonged: >450 to <500 ms and <= 450 ms at baseline for Male; >470 to <500 ms and <= 470 ms at baseline for Female Additional: ≥500 ms and < 500 ms at baseline <u>Increase from baseline</u> Borderline: Increase from baseline 30-60 ms Prolonged: Increase from baseline >60 ms

[a] The ULN is based upon central lab reference ranges. The reference range might be different for different age-groups. For the purpose of this study in a particular patient the reference range based upon age at baseline will be used as reference throughout the study for determining PCSVs.
[b] Lab parameters not collected in this study.

10.4. Search Criteria for TEAEs of Special Interest

AESI	Search Criteria
Anaphylactic reactions	For SMQ "anaphylactic reaction" An **algorithmic approach** will be used. A case must include either: 1. A narrow term (a term from Category **A**); 2. Patient with both a term from Category **B** AND a term from Category **C**; 3. Patient with a term from Category **D** AND {a term from Category **B** - OR a term from Category **C** } For bullets 2 and 3, the search terms that are included under the SMQ for a particular event need to have the same start date (for e.g. if search shows cough (category B term) occurring at day 3 and urticaria (category C term) occurring at day 7, this event is not adjudicated as anaphylactic reaction as this is inconsistent with the clinical presentation of anaphylaxis as an acute event with simultaneous involvement of 2 or more body systems. Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock
Systemic hypersensitivity reactions	Hypersensitivity: Narrow SMQ for hypersensitivity Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock
Helminthic infections	-HLT = Cestode infections -HLT = Helminthic infections NEC -HLT = Nematode infections -HLT = Trematode infections

10.5. Important Protocol Deviations that Exclude Patients from the Per Protocol Analysis Set

*Note: This is a preliminary list and the final list will be generated prior to database lock.

Category	Description of Protocol Deviation	Notes
Entered study even though entry criteria not satisfied	Inclusion #1: Male or female >= 12 years of age at screening (V1)	
Entered study even though entry criteria not satisfied	Inclusion #2: A documented diagnosis of EoE by endoscopic biopsy prior to screening, as demonstrated by intraepithelial eosinophilic infiltration (peak cell count >=15 eos/hpf) from >= 1 region	
Entered study even though entry criteria not satisfied	Inclusion #3: Baseline endoscopic biopsies with demonstration on central reading of intraepithelial eosinophilic infiltration (peak cell count >=15 eos/hpf) in at least 2 of the 3 biopsied regions	
Entered study even though entry criteria not satisfied	Inclusion #4: History (by patient report) of an average of at least 2 episodes of dysphagia (with intake of solids) per week in the 4 weeks prior to screening	
Entered study even though entry criteria not satisfied	Inclusion #5: At least 4 episodes of dysphagia in the 2 wks prior to baseline, documented via eDiary, at least 2 of which require liquids, coughing or gagging, vomiting or medical attention to relieve	
Entered study even though entry criteria not satisfied	Inclusion #7: Baseline DSQ score >=10	
Entered study even though entry criteria not satisfied	Inclusion #8: Able to understand and complete study-related questionnaires	
Entered study even though entry criteria not satisfied	Inclusion #9: Willing and able to comply with clinic visits and study-related procedures	
Entered study even though entry criteria not satisfied	Inclusion #10: ICF signed by study patient or legal representative. For <=12 yrs, parent/guardian must provide signed ICF (patients must also provide separate informed assent to enroll in the study)	

Category	Description of Protocol Deviation	Notes
Entered study even though entry criteria not satisfied	Exclusion #1: Body weight <= 40 kg	
Entered study even though entry criteria not satisfied	Exclusion #2: Prior participation in a dupilumab clinical trial, or past or current treatment with dupilumab	
Entered study even though entry criteria not satisfied	Exclusion #3: Initiation/change of food-elimination diet or reintroduction of previously eliminated food in 6 wks prior to screening. Patients on food-elimination diet must remain through entire study	
Entered study even though entry criteria not satisfied	Exclusion #4: Other causes of esophageal eosinophilia or the following conditions: hypereosinophilic syndrome and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	
Entered study even though entry criteria not satisfied	Exclusion #5: Active Helicobacter pylori infection	
Entered study even though entry criteria not satisfied	Exclusion #6: History of achalasia, Crohn's disease, ulcerative colitis, celiac disease, and prior esophageal surgery	
Entered study even though entry criteria not satisfied	Exclusion #7: Any esophageal stricture unable to be passed with a standard, diagnostic, 9 to10 mm upper endoscope or any critical esophageal stricture that requires dilation at screening	
Entered study even though entry criteria not satisfied	Exclusion #9: Treatment with swallowed topical corticosteroids within 8 weeks prior to baseline	
Entered study even though entry criteria not satisfied	Exclusion #10: Initiation, discontinuation, or change in the dosage of proton pump inhibitors, leukotriene inhibitors, nasal and/or inhaled corticosteroids within 8 wks prior to the baseline endoscopy	

Category	Description of Protocol Deviation	Notes
Entered study even though entry criteria not satisfied	Exclusion #11: Initiation, discontinuation, or change in the dosage regimen of SC immunotherapy (SCIT)	
Entered study even though entry criteria not satisfied	Exclusion #12: Treatment with sublingual immunotherapy (SLIT)	
Entered study even though entry criteria not satisfied	Exclusion #13: Treatment with oral immunotherapy (OIT) within 6 months prior to visit 1	
Entered study even though entry criteria not satisfied	Exclusion #14: The following 3 months prior to screening: immunosuppressant/immunomodulating drugs, including but not limited to systemic corticosteroids, omalizumab, cyclosporine, etc.	One time dosing of a corticosteroid as part of anesthetic dosing during Visit 2 biopsy will be allowed.
Entered study even though entry criteria not satisfied	Exclusion #15: Treatment with an investigational drug within 2 months or within 5 half-lives (if known), whichever is longer, prior to visit 1	
Entered study even though entry criteria not satisfied	Exclusion #16: Planned or anticipated use of any prohibited medications and procedures during the study	
Entered study even though entry criteria not satisfied	Exclusion #17: Planned or anticipated major surgical procedure during the study	
Entered study even though entry criteria not satisfied	Exclusion #19: Active parasitic infection or suspected parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization	
Entered study even though entry criteria not satisfied	Exclusion #20: Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, or antifungals within 2 weeks before baseline visit (pt may be re-screened after the infection)	
Entered study even though entry criteria not satisfied	Exclusion #21: Known or suspected immunodeficiency disorder, including history of invasive opportunistic infections (eg, tuberculosis [TB], non-tuberculous mycobacterial infections, histoplasmosis, li	

Category	Description of Protocol Deviation	Notes
Entered study even though entry criteria not satisfied	Exclusion #22: Known history of human immunodeficiency virus (HIV) infection	
Entered study even though entry criteria not satisfied	Exclusion #23: Established diagnosis of hepatitis B viral infection at the time of screening or positive for hepatitis B surface antigen (HBsAg) at the time of screening	
Entered study even though entry criteria not satisfied	Exclusion #24: Established diagnosis of hepatitis C viral (HCV) infection at the time of screening. Patients positive for hepatitis C Ab are eligible for the study only if HCV RNA is negative.	
Entered study even though entry criteria not satisfied	Exclusion #25: On current treatment for hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis, or hepatic failure, or has evidence of liver disease	
Entered study even though entry criteria not satisfied	Exclusion #26: Any of the following abnormal lab values at screening: 1) Platelets <100 ×103/μL 2) Neutrophils <1.5 × 103/μL 3) Serum creatinine > 1.5 ULN	
Entered study even though entry criteria not satisfied	Exclusion #27: Severe concomitant illness that, in the investigator's judgment, would adversely affect the patient's participation in the study (eg, short life expectancy, uncontrolled diabetes, etc)	
Entered study even though entry criteria not satisfied	Exclusion #28: History of malignancy within 5 years prior to screening, except completely treated in situ carcinoma of the cervix and completely treated non-metastatic squamous or basal cell carcinoma	
Entered study even though entry criteria not satisfied	Exclusion #29: History of alcohol or drug abuse within 6 months prior to screening	
Entered study even though entry criteria not satisfied	Exclusion #30: 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 under	

Category	Description of Protocol Deviation	Notes
Entered study even though entry criteria not satisfied	Exclusion #31: Patient or his/her immediate family is a member of the investigational team	
Entered study even though entry criteria not satisfied	Exclusion #32: Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study	
Entered study even though entry criteria not satisfied	Exclusion #33: Women of childbearing potential who are unwilling to practice highly effective contraception prior to the initial dose, during the study & for at least 12 wks after last dose	
Received an excluded concomitant treatment	Swallowed topical corticosteroids (may be used as rescue treatment for EoE) starting at V3 through Week 52 visit	Only if occurred during Part A
Received an excluded concomitant treatment	Systemic corticosteroids (may be used as rescue treatment for EoE) starting at V3 through Week 52 visit	Only if occurred during Part A
Received an excluded concomitant treatment	Systemic immunosuppressive/immunomodulating drugs) starting at V3 through Week 52 visit	Only if occurred during Part A
Received an excluded concomitant treatment	Treatment with an investigational drug (other than dupilumab) starting at V3 through Week 52 visit	Only if occurred during Part A
Received an excluded concomitant treatment	Initiation, discontinuation, or change in dosage regimen of: Proton pump inhibitors; Systemic leukotriene inhibitors; Nasal and/or inhaled corticosteroids starting at V3 through Week 52 visit	Only if occurred during Part A
Received an excluded concomitant treatment	Initiation of SCIT, or change in dose for those patients on a stable dose of SCIT post randomization starting at V3 through Week 52 visit	Only if occurred during Part A

Category	Description of Protocol Deviation	Notes
Received an excluded concomitant treatment	Use of SLIT starting at V3 through Week 52 visit	Only if occurred during Part A
Received an excluded concomitant treatment	Use of OIT starting at V3 through Week 52 visit	Only if occurred during Part A
Received an excluded concomitant treatment	Major elective surgical procedures starting at V3 through Week 52 visit	Only if occurred during Part A
Received an excluded concomitant treatment	Esophageal dilation (may be used as rescue procedure) starting at V3 through Week 52 visit	Only if occurred during Part A
Received an excluded concomitant treatment	Initiation or change of food-elimination diet regimen starting at V3 through Week 52 visit	Only if occurred during Part A
Received wrong treatment or incorrect dose	Kit unassigned in IVR administered to patient	Only if occurred during Part A
Received wrong treatment or incorrect dose	Incorrect Kit administered by site or subject (out of order)	Only if occurred during Part A
Received wrong treatment or incorrect dose	Patient given study drug but patient not randomized	Only if occurred during Part A
Other Treatment compliance	Patient was dosed with IP that had a temperature excursion and deemed unacceptable	Only if occurred during Part A

Category	Description of Protocol Deviation	Notes
Other Treatment compliance	Staff inappropriately unblinded to treatment assignment	Only if occurred during Part A
Other Treatment compliance	Treatment assignment inappropriately unblinded	Only if occurred during Part A
Other Treatment Compliance	IP not administered for 2 consecutive visits or more than 5 total visits for non safety reasons (including home dosing) during the course of double blinded period (part A/ part B)	
Other Treatment Compliance	IP for Part C dosed PRIOR to Biopsy collection at Visit 11/ Week 24	
Randomization Error	Mis-stratification of subject	
Randomization Error	Subject randomized twice in the same study part	
Randomization Error	IVRS assigned two randomization numbers to one patient in the same study part	
Visit not performed	Screening visit 1 not performed	
Visit not performed	Visit 2 (Endoscopy/Biopsy) not performed	
Visit not performed	Visit 3 (Baseline) Day 1 not performed	
Visit not performed	Visit 11 Day 169 not performed (EOT Part A/Part B)	
Visit not performed	Early Termination Visit not performed for subjects who early terminate before EOT part A/Part B (Exception: If reason is withdrew consent or lost to follow-up or death)	
Procedure not performed	EREFS not performed by an Investigator	Only if occurred during Part A
Procedure not performed	Missed DSQ assessment more than 6 times in a 14 day block after Visit 3	Only if occurred during Part A

Category	Description of Protocol Deviation	Notes
Procedure not performed	EoE-EREFS not performed at Visits 2, 11, 19 or ET	Only if occurred during Part A
Procedure not performed	Esophageal Biopsy Collection not performed at Visit 2	
Procedure not performed	Esophageal Biopsy Collection not performed at Visits 11, 19 or ET (if not rescued)	Only if occurred during Part A
Procedure not performed	Esophageal Biopsy not collected prior to Rescue Treatment	Only if occurred during Part A
Procedure not performed	Medical History not collected	
Procedure not performed	EoE Medical History not collected	
Procedure not performed	Physical Examination not performed at Visit 1	
Procedure not performed	Hematology not performed prior to Visit 3	
Procedure not performed	Chemistry not performed prior to Visit 3	
Procedure not performed	Serum Pregnancy testing not performed at Screening visit 1	
Procedure not performed	HIV Ab not performed prior to Visit 3	
Procedure not performed	HBsAg not performed prior to Visit 3	
Procedure not performed	HBcAb not performed prior to Visit 3	
Procedure not performed	TB not performed, if required, prior to Visit 3	
Procedure not performed	PGIS assessment not collected at baseline visit	

Category	Description of Protocol Deviation	Notes
Procedure performed outside of window	PGIS not collected on same day of V3 study drug administration	
Inadequate Informed Consent administration	Consent/Assent not collected	
Inadequate Informed Consent administration	Assent and/or ICF signed after screening or any study procedures	

10.6. EoE Histology Scoring System (EoEHSS) Feature Evaluation Per Colllins et al. 2017

Feature	Grade Score	Stage Score
Eosinophilic inflammation (EI)	0 = intraepithelial eosinophils not present 1 = PEC <15/HPF 2 = PEC 15-59/HPF 3 = PEC >60/HPF	0 = intraepithelial eosinophils 0-14/HPF, 1 = PEC ≥15/HPF in <33% of HPFs 2 = PEC ≥15/HPF in 33-66% of HPFs 3 = PEC ≥15/HPF in >66% of HPFs
Basal zone hyperplasia (BZH)	0 = BZH not present 1 = basal zone occupies >15% but <33% of total epithelial thickness 2 = basal zone occupies 33-66% of total epithelial thickness 3 = basal zone occupies >66% of total epithelial thickness	0 = BZH not present 1 = BZH (any grade >0) in <33% of epithelium 2 = BZH (any grade >0) in 33-66% of epithelium 3 = BZH (any grade >0) in >66% of epithelium
Eosinophil abscess (EA)	0 = groups or aggregates of eosinophils not present 1 = group of 4-9 eosinophils 2 = group of 10-20 eosinophils 3 = group of >20 eosinophils	0 = groups or aggregates of eosinophils not present 1 = EA (any grade >0) in <33% of epithelium 2 = EA (any grade >0) in 33-66% of epithelium 3 = EA (any grade >0) in > 66% of epithelium
Surface layering (SL)	0 = absent SL (fewer than 3 aligned eosinophils) 1 = SL of 3-4 eosinophils 2 = SL of 5-10 eosinophils 3 = SL of >10 eosinophils	0 = absent SL 1 = SL (any grade >0) in <33% of epithelium 2 = SL (any grade >0) in 33-66% of epithelium 3 = SL (any grade >0) in >66% of epithelium.
Dilated intercellular spaces (DIS)	0 = DIS not seen at any magnification 1 = intercellular bridges in DIS visible at 400X magnification only 2 = intercellular bridges in DIS visible at 200X magnification 3 = intercellular bridges in DIS visible at 100X magnification or lower	0 = DIS not seen at any magnification 1 = DIS (any grade >0) in <33% of epithelium 2 = DIS (any grade >0) in 33-66% of epithelium 3 = DIS (any grade >0) in >66% of epithelium
Surface epithelial alteration (SEA)	0 = SEA not present 1= SEA without eosinophils 2 = SEA with any eosinophils 3 = shed altered surface epithelium admixed with numerous eosinophils consistent with exudate	0 = SEA not present 1 = SEA (any grade >0) in <33% of epithelium 2 = SEA (any grade >0) in 33-66% of epithelium 3 = SEA (any grade >0) in >66% of epithelium

Feature	Grade Score	Stage Score
Dyskeratotic epithelial cells (DEC)	0 = DEC not present 1 = 1 DEC/HPF 2 = 2-5 DEC/HPF 3 = >5 DEC/HPF	0 = DEC not present 1 = DEC (any grade >0) in <33% of epithelium 2 = DEC (any grade >0) in 33-66% of epithelium 3 = DEC (any grade >0) in >66% of epithelium
Lamina propria fibrosis (LPF)	0 = LPF not present 1 = fibers are cohesive and interfiber spaces cannot be demarcated 2 = fiber diameter equals the diameter of a basal cell nucleus 3 = fiber diameter exceeds the diameter of a basal cell nucleus	0 = LPF not present 1 = LPF (any grade >0) in <33% of lamina propria 2 = LPF (any grade >0) in 33-66% of lamina propria 3 = LPF (any grade >0) in >66% of lamina propria

PEC = peak eosinophil count (quantity of eosinophils in the most inflamed high power field)

10.7. Gene Lists Comprising Each Transcriptome Endpoint

EoE diagnostic panel	Type 2 inflammation signature
CDH26	IL4
CDH20	IL13
CLDN10	[redacted]
CTNNAL1	IL4R
DSG1	IL5
CHL1	[redacted]
CXCL6	TSLP
CCL26	[redacted]
CXCL1	[redacted]
IL8	[redacted]
IL5	[redacted]
IL13	[redacted]
CCR3	[redacted]
CLC	CCL26
IL5RA	[redacted]
CRISP2	[redacted]
FLG	[redacted]
UPK1A	CCR3
SPINK7	[redacted]
CRISP3	[redacted]
ACPP	[redacted]
UPK1B	[redacted]
CA2	[redacted]
PHLDB2	CLC
MUC4	ALOX15
GCNT3	[redacted]
EPPK1	[redacted]
ZNF365	POSTN
CITED2	[redacted]
ARG1	CMA1
ALOX12	TPSAB1
IGJ	HRH1
TNFAIP6	[redacted]
CFB	[redacted]
HRH1	ARG1
CFI	[redacted]
APOBEC3A	
MMP12	
CD200R1	
HPGDS	
FCGR3A	
FCGR3B	
RUNX2	
ALOX15	
GRK5	
SAMSN1	
PMCH	
SLC16A6	
KCNJ2	
ANO1	
SLC26A4	
TPSAB1	
TPSB2	
CPA3	
CMA1	
NEFM	
NEFL	
PNLIPRP3	
ENDOU	

EoE diagnostic panel	**Type 2 inflammation signature**
CDA EML1 SUSD2 GPR160 TSPAN12 LRRC31 GLDC GYS2 IGFL1 MT1M CRYM UBD GRPEL2 RTP4 ACTG2 CTSC POSTN KRT23 COL8A2 IL32 IL4 MSRB3 CCL8 EPX EPB41L3 SYNPO2 COL1A2 TRIM2 SYNPO2L NCAM1 F3 TSLP H19 FKBP5 SLAMF7 PTGFRN	

10.8. List of Part A Subjects Affected by Electronic Handheld Device Navigation Malfunction

Subject ID	Asset Tag	Date of First Synchronization After 13Mar2020 Update Release	Date Device Updated
[redacted]	[redacted]	2020-03-14	16-Apr-2020
[redacted]	[redacted]	2020-03-13	14-Apr-2020
[redacted]	[redacted]	2020-03-15	30-Mar-2020
[redacted]	[redacted]	2020-03-13	30-Mar-2020
[redacted]	[redacted]	2020-03-14	31-Mar-2020
[redacted]	[redacted]	2020-03-14	31-Mar-2020
[redacted]	[redacted]	2020-03-13	13-Apr-2020
[redacted]	[redacted]	2020-03-13	31-Mar-2020
[redacted]	[redacted]	2020-03-13	01-Apr-2020
[redacted]	[redacted]	2020-03-14	06-Apr-2020
[redacted]	[redacted]	2020-03-13	15-Apr-2020
[redacted]	[redacted]	2020-03-14	03-Apr-2020
[redacted]	[redacted]	2020-03-13	07-Apr-2020
[redacted]	[redacted]	2020-03-13	02-Apr-2020
[redacted]	[redacted]	2020-03-18	07-Apr-2020
[redacted]	[redacted]	2020-03-16	07-Apr-2020

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