Clinical Development and Regulatory Affairs
Biostatistics and Data Management

REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION: FINAL

Clinical Study Protocol Title:

A Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Dupilumab in Pediatric Patients with Active Eosinophilic Esophagitis

Compound: Dupilumab (REGN668)

Protocol Number: R668-EE-1877 Amendment 3

Clinical Phase: Phase 3

Sponsor: Regeneron Pharmaceuticals, Inc.

Study Biostatistician: [redacted]

Clinical Trial Manager: [redacted]

Study Medical Director: [redacted]

Version/Date: Original Statistical Analysis Plan / January 27, 2022

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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VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

TABLE OF CONTENTS

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

LIST OF TABLES

LIST OF FIGURES

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Ab	Antibody
AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CCL	Chemokine (C-C motif) ligand
CMH	Cochran-Mantel-Haenszel (test)
COA	Clinical outcome assessment
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
DSQ	Dysphagia symptom questionnaire
eCRF	Electronic case report form
EDC	Electronic data capture
EDP	EoE diagnostic panel
eGFR	Estimated glomerular filtration rate
EoE	Eosinophilic esophagitis
EoE-EREFS	Eosinophilic Esophagitis-Endoscopic Reference Score
EoE-HSS	EoE Histology Scoring System
EOS	End of study (visit)
eos/hpf	Eosinophils/high power field
EOT	End of treatment
EPIT	Epicutaneous immunotherapy
ET	Early termination

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

EU	European Union
FAS	Full analysis set
FLG	Filaggrin
GIC	Global Impression of Change
GIS	Global Impression of Severity
ICF	Informed consent form
ICH	International Council for Harmonisation
IFN-γ	Interferon-gamma
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
IHC	Immunohistochemistry
IL	Interleukin
IL-4Rα	Interleukin-4 receptor alpha
IVRS/IWRS	Interactive voice/web response system
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing antibody
NES	Normalized Enrichment Scores
OIT	Oral immunotherapy
PCSV	Potentially clinically significant value
PEESS	Pediatric Eosinophilic Esophagitis Symptom Score
PEIS	Pediatric EoE Impact Scale
PESQ	Pediatric EoE Sign/Symptom Questionnaire
PK	Pharmacokinetic
PPI	Proton pump inhibitor
PT	Preferred term (MedDRA)
QOL	Quality of life
Q2W	Once every 2 weeks
QW	Once weekly

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

RBC	Red blood cell
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis software
SC	Subcutaneous
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
SOC	System organ class
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
Th2	Type 2 helper T cell
ULN	Upper limit of normal
WBC	White blood cell
WOCF	Worst observation carried forward

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

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 data analysis of R668-EE-1877.

This plan will be finalized prior to the data lock for the end of Part A of study R668-EE-1877, i.e., the last patient reaching the week 16 visit in Part A.

1.1. Background/Rationale

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease characterized by esophageal dysfunction and eosinophilic inflammation in the esophagus; it is thought to be triggered by an abnormal type 2 immune response to food allergens (Furuta, 2017) (Liacouras, 2011). Chronic esophageal inflammation leads to progressive remodeling, stricture formation, and fibrosis (Hirano, 2014) (Schoepfer, 2014) (Dellon, 2018). Although considered a rare disease, the current prevalence is estimated at 22.7 people per 100,000 worldwide (Arias, 2016) and appears to be on the increase (Dellon, 2014). Eosinophilic esophagitis has been reported in all ages; however, most cases are in children and adults younger than 50 years (Dellon, 2014) (Dellon, 2007) (Kapel, 2008) (Liacouras, 2011) (Spergel, 2009). Children under the age of 18 represent approximately 30% of the EoE patient population (Dellon, 2014) (Prasad, 2009). The primary clinical manifestations of EoE in both adults and children over 10 years of age are dysphagia and food impaction (Lucendo, 2017). Clinical features in younger children are non-specific in nature and vary significantly depending on the patient's age and ability of the patient to describe salient symptoms. Infants and toddlers are more likely to present with feeding difficulties, vomiting, or regurgitation with the potential for failure to thrive, whereas school-age children present with complaints of abdominal pain and heartburn (Iuliano, 2018). Older children with symptomatic EoE may also modify their dietary and eating behavior by taking small bites, chewing thoroughly, eating slowly, drinking copious fluids, and avoiding food consistencies that stick, which is highly suggestive of dysphagia, as this is a feeding behavior reported in adults as an attempt to prevent esophageal food impactions (Iuliano, 2018). These symptoms lead to substantially impaired quality of life (DeBrosse, 2011) (Falk, 2014) (Straumann, 2008) (Straumann, 2003). Endoscopic findings are related to the inflammation in the esophagus and consist of fixed or transient concentric rings, longitudinal furrows, white plaques, reduced mucosal vascularity, fragile or crepe-like mucosa, and strictures. Furrows and white plaques are likely the most common finding in children. Rings are not common in children, although rings and furrows are the most commonly seen in nearly half of adult patients (Singla, 2016). Some patients (particularly pediatric) may present with a normal-appearing esophagus, but still have histologically active EoE (Wechsler, 2018).

Current standard of care for children with EoE consists of food-elimination diets, off-label proton pump inhibitors (PPIs), off-label use of swallowed topical corticosteroids, and esophageal dilation. Esophageal dilation is frequently utilized to relieve dysphagia symptoms caused by esophageal strictures. Since strictures do not occur as commonly in children, esophageal dilation is not as commonly performed in children with EoE as compared to adults with EoE (Chehade, 2018) (Furuta, 2017). The standard therapies for EoE are limited by variable response rates, relapse after therapy cessation, and adverse effects on quality of life. These limitations lead to a significant unmet need for new treatments targeting key pathways driving EoE inflammation (Spergel, 2012)

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

(Greuter, 2017). Proton pump inhibitors can result in histologic remission in approximately 50% of patients with EoE (Lucendo, 2017) with the remaining patients unresponsive. Swallowed topical corticosteroids have been reported in clinical trials to induce partial clinical responses and histologic remission; however, they are not uniformly effective and may be associated with local fungal infections, as well as a risk of growth suppression and hypothalamic–pituitary–adrenal axis suppression following systemic absorption (Golekoh, 2016), limiting their use to short term.

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 immunoglobulin E (IgE) (Hamilton, 2014). Additionally, preclinical data demonstrate that treatment with dupilumab prevents infiltration of eosinophils into tissues.

Dupilumab was evaluated in adult patients with EoE in a phase 2, multicenter, double-blind, randomized, placebo-controlled study (R668-EE-1324), where substantial improvements in clinical, histologic, and endoscopic aspects of the disease were demonstrated (Hirano, 2019a). Dupilumab was well tolerated by the study patients, with safety data generally consistent with other dupilumab studies and with no new safety signals associated with use in the EoE patient population (Hirano, 2019b). These results support pursuing further development of dupilumab for the treatment of EoE in adult, adolescent, and pediatric patients. As such, a multi-part phase 3 trial evaluating the efficacy and safety of dupilumab in adult and adolescent patients with EoE (R668-EE-1774) was initiated. This study consists of three parts: Part A and Part B are 24-week treatment, randomized, double-blind, placebo-controlled study phases and Part C is a 28-week, extended active treatment phase that enrolls patients from Part A and Part B. The co-primary endpoints for the adult and adolescent study include both a validated symptom measurement utilizing the dysphagia symptom questionnaire (DSQ) and histologic evaluation. Part A of study R668-EE-1774 evaluating the once weekly (QW) regimen revealed a significant effect on both of the co-primary endpoints. In Part B of study R668-EE-1774, the dupilumab [redacted] mg weekly demonstrated a significant effect on both of the co-primary endpoints and clinically meaningful improvements in other secondary histological, endoscopic, molecular and other patient reported outcomes. Although dupilumab [redacted] mg Q2W dosing regimen showed significant improvement in the histologic primary endpoint over a 24-week treatment period, dupilumab [redacted] mg Q2W did not show improvement in EoE disease symptoms compared with placebo even though, the magnitude of improvements in all other secondary histologic, endoscopic, and molecular endpoints of EoE were similar to the ones observed with the dupilumab [redacted] mg QW dosing regimen. Histological and molecular evidence suggest that the disease has the same underlying pathogenesis across age groups and responds similarly to swallowed topical corticosteroid treatment regardless of age (Straumann, 2012). Therefore, for the pediatric trial, where symptoms are heterogeneous, success of the trial will be determined by histologic measures; however, symptom assessments will be evaluated through secondary and exploratory endpoints.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Study R668-EE-1877 is a randomized, 2-part, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in pediatric EoE patients aged ≥ 1 year to <12 years. Children with active EoE, aged ≥1 year to <12 years, who are PPI non-responsive as determined by esophageal histology, will be randomized 2:2:1:1 to receive either a higher exposure dupilumab dose regimen (n=30) or a lower exposure dupilumab dose regimen (n=30) (in a weight-tiered dosing schema) or a higher exposure-matched placebo (n=15) or a lower exposure-matched placebo (n=15) over 16 weeks (Figure 1). Primary efficacy will be assessed by a histological endpoint: proportion of patients with histologic remission (≤6 eos/hpf). A total sample size of 90 patients is based on the number of patients to inform the primary efficacy histological endpoint and to characterize the safety profile of dupilumab in pediatric patients with EoE.

1.2. Study Objectives

1.2.1. Primary Objectives

To demonstrate the efficacy of dupilumab treatment compared with placebo in pediatric patients aged ≥ 1 year to <12 years with active EoE based on histologic improvement meeting validated histologic criteria.

1.2.2. Secondary Objectives

The secondary objectives of the study are:

- To demonstrate the efficacy of dupilumab compared to placebo in pediatric patients with active EoE after 16 weeks of treatment as assessed by endoscopic visual measurements of disease activity using the Eosinophilic Esophagitis-Endoscopic Reference Score (EoE-EREFS) and histologic abnormalities as measured by the EoE Histology Scoring System (EoE-HSS)
- To evaluate the safety, tolerability, and immunogenicity of dupilumab treatment for up to 16 weeks in pediatric patients with active EoE
- To evaluate the effects of dupilumab on transcriptomic signatures associated with EoE and type 2 inflammation
- To study the effects of dupilumab on the type 2 inflammation gene expression signature
- To evaluate the concentration-time profile of functional dupilumab in serum in this population
- To assess efficacy of long-term (52 weeks) dupilumab treatment
- To assess safety, tolerability, and immunogenicity of long-term (52 weeks) dupilumab treatment
- To evaluate the impact of dupilumab treatment on EoE signs and symptoms

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

1.2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To explore impact of dupilumab treatment on health-related quality of life
- To explore impact of dupilumab on global impression of change and severity of disease
- To explore impact of dupilumab treatment on changes in weight and growth during the double-blind and extended active phases
- To conduct exploratory research to study EoE and dupilumab mechanism of action in pediatric patients, including predictive biomarker discovery and/or validation

1.2.4. Modifications from the Statistical Section in the Final Protocol

NA

1.2.5. Revision History for SAP Amendments

NA

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

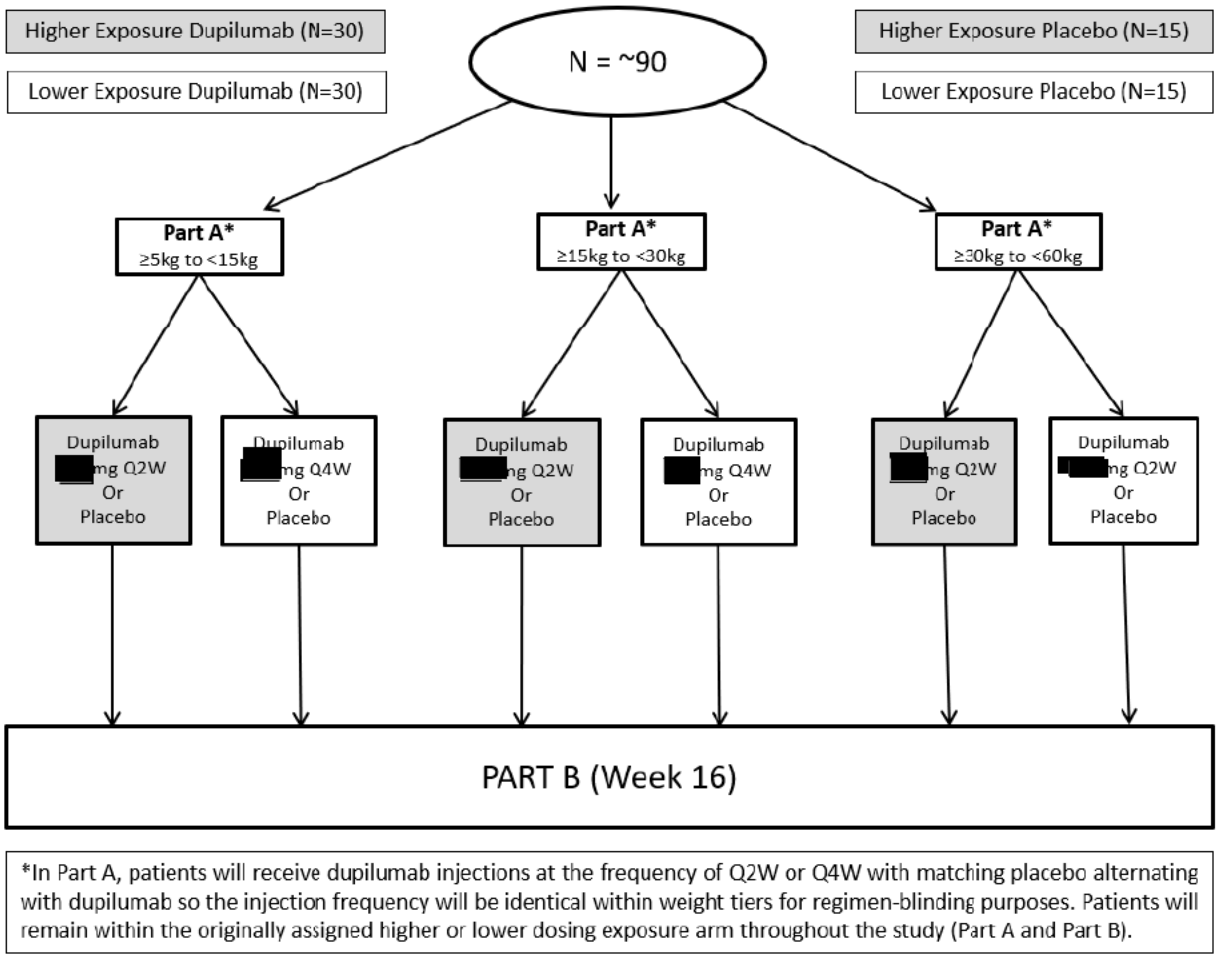
This is a phase 3, multicenter, randomized, 2-part, double-blind, placebo-controlled study investigating the efficacy, safety, tolerability, PK, and immunogenicity of dupilumab in pediatric patients (aged ≥1 to <12 years) with active EoE.

In Part A, approximately 90 patients aged ≥ 1 year to <12 years will be randomized in a 2:2:1:1 ratio to receive a higher exposure dosing regimen, a lower exposure dosing regimen of dupilumab, a higher exposure-matched placebo or a lower exposure-matched placebo for a 16-week treatment period according to a central randomization scheme provided by an IWRS to the designated study pharmacist (or qualified designee). Randomization will be stratified according to weight at baseline (≥5 kg to <15 kg, ≥15 kg to <30 kg, or ≥30 kg to <60 kg). The dosing of the placebo group will be matched with high exposure and low exposure dupilumab regimens in the respective weight tiers. Patients will remain within the originally assigned higher or lower dosing exposure arm throughout the study. At the end of Part A, eligible patients will be provided an option to enter into Part B, which is a 36-week extended active treatment period with dupilumab. All patients (Part A active and placebo) will receive dupilumab based on body weight at visit 8/week 16 per the higher- and lower-exposure dosing group to which they were assigned at randomization. Treatment assignment in Part B is managed by an IWRS to maintain blinding of treatment assignment. Since the objective of using the tiered body weight dose level approach is to maintain a uniform drug exposure, as patients grow over the course of the study if a patient's weight tier has increased at visit 12/week 32, the patient will be re-assigned to the corresponding extended active treatment regimen based on weight tier at visit 12/week 32. All patients will be followed up for an additional 12 weeks after completing Part B. Patients in Part A who are not entering Part B would enter a 12-week follow-up period immediately after Part A.

See Figure 1 and Figure 2 for Part A/Part B weight-tiered dosing regimens of study drug.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

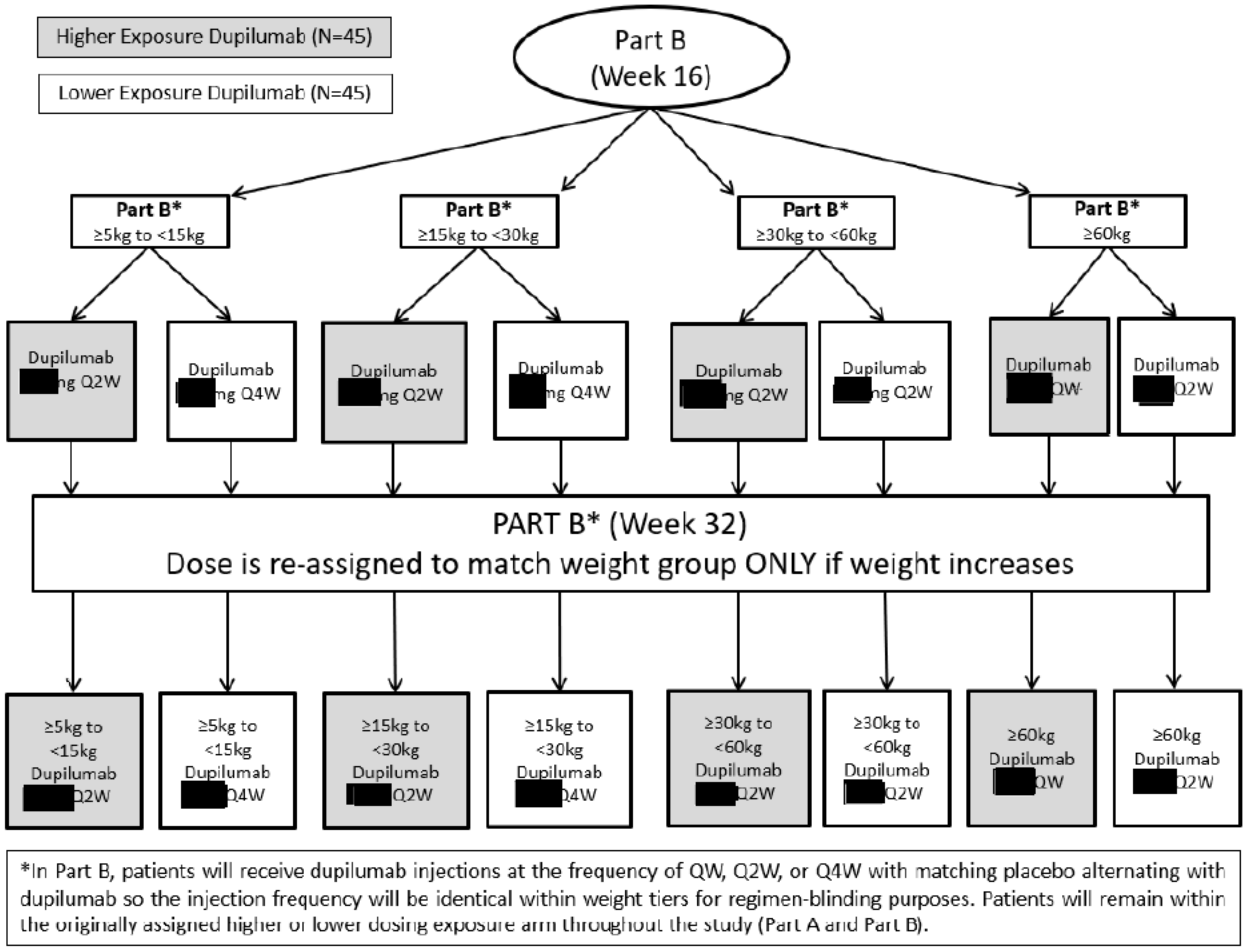
Figure 1: Part A Weight-Tiered Dosing Regimens of Study Drug



*In Part A, patients will receive dupilumab injections at the frequency of Q2W or Q4W with matching placebo alternating with dupilumab so the injection frequency will be identical within weight tiers for regimen-blinding purposes. Patients will remain within the originally assigned higher or lower dosing exposure arm throughout the study (Part A and Part B).

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Figure 2: Part B Weight-Tiered Dosing Regimens of Study Drug



*In Part B, patients will receive dupilumab injections at the frequency of QW, Q2W, or Q4W with matching placebo alternating with dupilumab so the injection frequency will be identical within weight tiers for regimen-blinding purposes. Patients will remain within the originally assigned higher or lower dosing exposure arm throughout the study (Part A and Part B).

2.2. Statistical Hypothesis

The following null hypothesis and alternative of the primary endpoint will be tested for the comparison of each dupilumab treatment group to placebo for Part A:

- Null hypothesis (H_0): The success rate (where success is achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 16) is equal between dupilumab groups (higher exposure group or lower exposure group) and placebo.
- Alternative hypothesis (H_1): The success rate differs at week 16 between dupilumab and placebo.

No formal hypothesis testing will be undertaken for Part B and hence there will be no adjustment for multiplicity for Part B.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

2.3. Sample Size and Power Considerations

The planned sample size is a total of approximately 90 patients (2:2:1:1 ratio, 30 patients in the higher exposure dupilumab group, 30 patients in the lower exposure dupilumab group, 15 patients in the higher exposure-matched placebo group, and 15 patients in the lower exposure-matched placebo group).

The assumptions used in the sample size calculation were based on Part A of the R668-EE-1774 study in adults and adolescents with EoE. Based upon the similarity of pathophysiology and expected similarity of histologic response between adults and pediatric patients, a similar proportion of responders at week 16 was assumed for sample size calculation. The lower exposure dupilumab group was assumed to have a similar treatment effect to the higher exposure dupilumab group. The treatment group difference observed in the R668-EE-1774 Part A adolescents was assumed for the sample size calculation for this study in children aged ≥1 year to <12 years. In Part A of R668-EE-1774, the proportions of patients achieving a peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24 were 59.5% and 5.1% for dupilumab and placebo, respectively. In Part A of R668-EE-1774, the proportions of adolescent patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24 were 36.4% and 0% for dupilumab and placebo, respectively. The treatment group difference observed in adolescents was approximately 36.5%. It is estimated that with a total number of 90 patients (30 patients in the higher exposure dupilumab group, 30 patients in the lower exposure dupilumab group, and 30 patients in the combined placebo group), at the 2-sided 5% significance level using Fisher's exact test, the study can provide 95% power to detect a treatment difference of 35.6% in the proportion of histologic responders (i.e., patients achieving peak esophageal intraepithelial eosinophil count ≤6 eos/hpf) at week 16 between placebo (5.1%) and each dupilumab treatment group (40.7%).

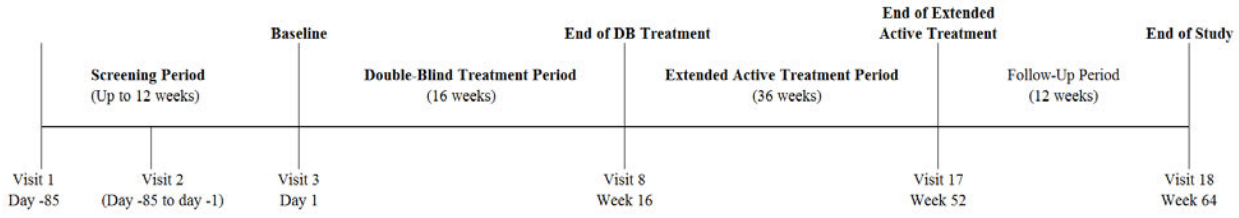
Sample size calculations were performed using nQuery Advisor 7.0.

2.4. Study Plan

Patients will undergo a screening period of up to 85 days, a double-blind 16-week treatment period (Part A), a 36-week extended active treatment period (Part B), and a 12-week follow-up period.

The study flow diagram is provided in Figure 3 Study Flow Diagram.

Figure 3 Study Flow Diagram



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

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Patients are required to have a documented diagnosis of EoE which may be established *either* by a prior historical biopsy, as demonstrated by intraepithelial eosinophilic infiltration (peak eosinophils/high power field ≥15 eos/hpf) (400×) from at least 1 esophageal region and performed after at least 8 weeks of treatment with an approved PPI regimen, *or* by biopsies performed after approximately 8 weeks of PPI treatment initiated prior to screening or during the screening period, which demonstrates ≥15 eos/hpf) (400×) from at least 2 of the 3 esophageal regions (proximal, mid, and distal); if the PPI regimen is stopped, biopsies must occur within 2 weeks of stopping the PPI. Patients who are on PPIs during the screening period and are eligible to enroll in the study, have the choice either to remain on the PPI regimen during the entire study or stop the PPI regimen prior to baseline and then must remain off PPIs during the entire study.

Biopsies will be obtained during endoscopy at screening visit 2, at the week 16 visit, and at the week 52 visit, or immediately prior to start of rescue medication or procedures. A total of at least 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 histology (needed for study inclusion criteria, as well as endpoint assessment) and the others for RNA extraction. Biopsies will be used for exploratory research to study EoE, dupilumab mechanism of action, and to identify or validate predictive biomarkers (efficacy and/or safety). Exploratory analyses of the biopsies may include but are not limited to immunohistochemistry [IHC] and RNA sequencing (or other methods for assessing RNA expression and RNAscope).

Patients may be re-screened if they fail the screening evaluation, unless the reason for screen failure is related to histologic inclusion criteria. The baseline endoscopy with biopsies 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.

Patients who permanently discontinue from study drug will be encouraged to remain in the study. Those who agree and do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.

At the end of the double-blind treatment period (week 16), eligible patients in Part A may enter Part B, which consists of 36-week extended active treatment. Patients who do not enter Part B will enter a 12-week follow-up period.

NOTE: If there are restrictions to the clinical study as a result of the COVID-19 pandemic, it may be necessary to adjust the visit schedule, convert in-person visits to telephone contacts, and postpone study procedures until the next available in clinic study visit. It is necessary that the randomization visit (visit 3) and the first visit of Part B occur in the clinic. Endoscopies with biopsies are required at approximately week 16 and week 52. If it is not possible to complete the endoscopies with biopsies due to COVID-19 restrictions and provided there are no specific safety concerns for the patient, patients may be allowed to continue their current study medication regimen until the endoscopies with biopsies can be performed. All temporary mechanisms utilized, and deviations from planned study procedures in response to COVID-19 will be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency. Once COVID-19 conditions resolve, all study visits and procedures should follow the schedule of events.

The study event table is presented in Section 11.2.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

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 Part A safety analysis set (SAF) is the basis for Part A safety analyses.

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

3.1. The Full Analysis Set (FAS)

For Part A, the FAS includes all randomized patients in Part A; it is based on the treatment allocated (as randomized). Efficacy endpoints in Part A (double-blind treatment period) will be analyzed using the FAS.

For Part B, the efficacy endpoints in Part B (extended active treatment period) will be summarized for all patients who received any study drug in Part B.

3.2. The Safety Analysis Set (SAF)

Part A:

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

Part B:

For safety analyses of Part B (extended active treatment period), only a subset of SAF (Part B SAF) will be included, which is defined as those patients who received at least 1 dose of Part B study drug.

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

- For a patient randomized to higher exposure dupilumab or lower exposure dupilumab, if the patient received all placebo injections in Part A, the actual treatment will be assigned as placebo.
- For a patient randomized to higher exposure dupilumab or lower exposure dupilumab, if the patient received at least one dupilumab injections in Part A, the actual treatment will be assigned as the planned treatment.
- For a patient randomized to placebo, if the patient received at least one dupilumab injections in Part A, the actual treatment will be assigned as lower exposure dupilumab.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

For safety summaries, the following analysis periods are defined:

- Part A 16-week treatment period is defined as:
  - For patients who entered Part B: Day 1 to the date of first dose of study drug for Part B Extended Active Treatment period (or week 16 visit if patient entered Part B but never received any Part B study drug)
  - For patients who did not enter Part B
    - Day 1 to week 16 visit if patients completed week 16 visit with a known visit date
    - Day 1 to study day 113 (+7 days) if patients had missing week 16 visit date, or to patients' last study participation date if patients did not complete week 16, whichever is earlier. For patients who received extended dosing in the double-blind treatment period due to the COVID-19 pandemic, and week 16 visit date is not available, 16-week treatment period will end on their last study participation date.
- Part B extended treatment period for patients who entered Part B is defined as:
  - The day after the first dose of study drug in Part B to the date of week 52 visit if patients completed week 52 with known visit date
  - The day after the first dose of study drug in Part B to study day 365 (+7 days) if patients had missing week 52 visit date, or to the last study participation date if patients did not complete week 52 visit, whichever is earlier. For patients who received extended dosing in the extended treatment period due to the COVID-19 pandemic, and week 52 visit date is not available, 36-week extended treatment period will end on their last study participation date
- Follow-up period is defined as:
  - For patients who entered Part B: the day after the end of Part B extended treatment period to the patient last study participation date
  - For patients who did not enter Part B: the day after the end of Part A 16-week treatment period to the last study participation date

The Part A and Part B SAFs will be the basis for the safety analyses for the Part A treatment period and Part B treatment period, respectively; however, for the analyses during 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 16 visit (for Part A SAF) or week 52 visit (for Part B SAF).

Due to COVID-19 pandemic, patients are allowed to extend their current assigned dose regimen of study drug (Part A and/or Part B) until endoscopy with biopsy can be performed at week 16 visit and/or week 52 visit. The safety data during the extended dosing period will also be presented in the corresponding analysis period.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

3.3. The Pharmacokinetic Analysis Set (PKAS)

The PK analysis population includes all patients who received any study drug and who had at least 1 non-missing result following the first dose of study drug. The PK analysis set is based on the actual treatment received (as treated) rather than as randomized.

3.4. The Immunogenicity Analysis Set

The ADA analysis set (AAS) includes all patients who received any amount of study drug (active or placebo [safety analysis set]) and had at least one non-missing anti-drug antibody result following the first dose of study drug or placebo. The ADA analysis set is based on the actual treatment received (as treated) rather than as randomized.

The NAb analysis set includes all treated patients who received any study drug (active or placebo), have at least one non-missing anti-drug antibody result following the first dose of study drug (active or placebo), and either tested negative at all ADA sampling times or tested positive for ADA with at least one non-missing NAb result after first dose of the study drug (active or placebo). Patients who are ADA negative are set to negative and included as such in the NAb analysis set.

3.5. 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 primary efficacy and safety analyses:

- Age group (years; ≥1- <6, ≥6 -<12; ≥1- <8, ≥8 -<12)
- Sex (Male, Female)
- Duration of EoE (years from start date of EoE to randomization date; <5, ≥5)
- Baseline weight group (≥5 - <15 kg, ≥15- <30 kg, ≥30- <60 kg)
- Prior use of swallowed topical steroids (STC) for the treatment of EoE (Yes, No)
- Inadequate response, intolerant and/or contraindicated to swallowed topical corticosteroids (STC) (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)

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Subgroups to be considered for primary efficacy endpoint only:

- Baseline BMI group (kg/m^2; overweight: ≥85 percentile of BMI for ≥2 years based on age and gender, ≥95 percentile of weight based on length (height), age and gender for <2 years, not overweight: not meeting the criteria of overweight) [based on CDC (Center for Disease Control and Prevention) chart]
- 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)

Subgroup to be considered for selected secondary efficacy endpoints only (details are in Section 5.6.4):

- Prior use of swallowed topical steroids (STC) for the treatment of EoE (Yes, No)

NOTE: The subgroup analysis may not be performed if the number of patients within the subgroup is <10% of overall sample size. The stratification factor is not included in the subgroup analysis of primary efficacy endpoint.

* The inadequate response, intolerant and/or contraindicated to STC subgroup is defined as

- Contraindicated to STC: patients never used STC for the treatment of EoE, and the reasons for never using STC were concomitant medical concern or contraindication (e.g., diabetes, immunomodulating treatment) or potential side-effect(s) from STC
- Inadequate response: patients had used STC for the treatment of EoE but the treatment with STC was not effective in relieving EoE symptoms
- Intolerant to STC: patients had used STC for the treatment of EoE and the treatment with STC was effective in relieving EoE symptoms, with the reasons for stopping STC for EoE being concomitant medical concern or contraindication or side effect(s)

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

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; 1-<6 years, 6-<12 years; 1-<8 years, ≥8-<12 years), Sex (Male, Female), Ethnicity with grouping (Hispanic or Latino, Not-Hispanic or Latino), Race with grouping (White, Black or African American, Asian, Other), Country, Baseline weight as a continuous variable and with grouping (kg; ≥5-<15 kg, ≥15- <30 kg, ≥30-<60 kg), Height/length (cm), and calculated BMI (kg/m^2; overweight, not overweight) [see the BMI grouping definition in Section 3.5].
- Baseline disease characteristics
  - Pediatric EoE Sign Questionnaire (PESQ-C [caregiver version]) (details of PESQ-C are in Section 4.4.2)
    - Proportion of days with 1 or more EoE signs for PESQ-C
    - Proportion of total segments within a day (night, morning, afternoon, evening) with 1 or more EoE signs for PESQ-C
    - Number of sign-free days during the 14-day period preceding baseline visit for PESQ-C
  - Pediatric EoE Symptom Questionnaire (PESQ-P [patient version]) (details of PESQ-P are in Section 4.4.2)
    - Proportion of days with 1 or more EoE symptoms for PESQ-P
    - Proportion of total segments within a day (night, morning, afternoon, evening) with 1 or more EoE symptoms for PESQ-P
    - Number of symptom-free days during the 14-day period preceding baseline visit for PESQ-P
  - Pediatric Eosinophilic Esophagitis Symptom Score (PEESSv2.0 [caregiver version])
  - Global Impression of Severity (GIS-P [patient version], GIS-C [caregiver version], GIS-Clin [clinician version]) (details of GIS-P, GIS-C and GIS-Clin are in Section 4.4.3)
  - Pediatric EoE Impact Scale (PEIS-C [caregiver version] and PEIS-P [patient version]) (details of PEIS-C and PEIS-P are in Section 4.4.3)
  - Duration of EoE as a continuous variable and with grouping (years; <5, ≥5)
  - Age at EoE onset as a continuous variable and with grouping (years; <5, ≥5)
  - Peak esophageal intraepithelial eosinophil count (eos/hpf) of three regions (proximal, mid, and distal)

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

- Mean stage score from the EoE-HSS summed over three regions (proximal, mid, and distal)
- Mean grade score from the EoE-HSS summed over three regions (proximal, mid, and distal)
- Prior use of STC for EoE (Yes, No)
- Effectiveness of prior use of STC for EoE (Yes, No)
- Inadequate response, intolerant and/or contraindicated to STC (Yes or No)
- Prior esophageal dilations (Yes, No)
- Number of prior esophageal dilations
- Patients treated with PPI at randomization (Yes, No)
- Patient on food elimination diet in past (Yes, No)
- Patient on food elimination diet at screening (Yes, No)
- Historical esophageal biopsy showing ≥15 (eso/hpf [400 ×]) after 8 weeks of high-dose PPI (Yes, No)
- Prior use of STC for EoE and prior esophageal dilation (Yes, No)
- EREFS total score
- Baseline serum total immunoglobulin E (IgE) as a continuous variable and with grouping (IU/mL; <100, ≥100)
- Baseline blood peripheral EOS as a continuous variable and with grouping (Giga/L; <0.15, ≥0.15; <0.30, ≥0.30; <0.50, ≥0.50)

4.2. Medical History

Medical history will be coded using MedDRA. The same MedDRA version will be used for Part A and Part A patients' data in Part B within the scope of DBL. Information related to EoE medical history and comorbid atopic conditions include diagnosis of EoE, atopic dermatitis, asthma, allergic rhinitis, allergic conjunctivitis, chronic rhinosinusitis, nasal polyps, food allergy, hives, contact dermatitis, 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 has ever been on a food elimination diet in the past, type of food elimination, and reason for elimination of specific food.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

4.3. Pre-Treatment/Concomitant Medication/Procedures

Medications/Procedures will be recorded from the day of informed consent until the end-of-study (EOS) visit. Medications will be coded using WHO Drug Dictionary (WHODRUG). Medications of interest include PPIs and swallowed topical/systemic corticosteroids for the treatment of EoE.

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

Concomitant medications/procedures (CM/CP): medications taken or procedures performed following the first dose of study drug through the EOS visit. This includes medications or procedures 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 3.2):

- CMs/CPs taken during the Part A 16-week double-blind treatment period
- CMs/CPs taken during the Part B 36-week extended active treatment period
- CMs/CPs taken during the 12-week follow-up period

Prohibited concomitant medications/procedures during the study:

Treatment with the following concomitant medications is prohibited through week 52 and may result in temporary or permanent discontinuation of study drug:

- Swallowed topical corticosteroids (may be used as rescue treatment of EoE)
- Systemic corticosteroids (may be used as rescue treatment of EoE)
  - NOTE: One-time use of a corticosteroid as a part of the anesthetic preparation used during each endoscopy procedure is allowed
- Systemic immunosuppressive/immunomodulating drugs (including, but not limited to, mepolizumab, omalizumab, cyclosporine, mycophenolate-mofetil, azathioprine, methotrexate, IFN-γ, or other immunomodulatory biologics)
- Treatment with an investigational drug (other than dupilumab)
- Initiation, discontinuation, or change in dosage regimen after baseline of the following medications (stable doses of these medications are allowed):
  - Proton pump inhibitors
  - Systemic leukotriene inhibitors
- Initiation, discontinuation, or change in dosage regimen of nasal and/or inhaled corticosteroids within 8 weeks prior to visit 2, visit 8, or visit 17 endoscopies with biopsies
- Initiation of SCIT, or change in dose for those patients on a stable dose of SCIT, within 1 year prior to screening
- Sublingual immunotherapy (SLIT)
- OIT
- Epicutaneous immunotherapy (EPIT)

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

- Treatment with a live (attenuated) vaccine, e.g.:
  - Chickenpox (varicella)
  - FluMist-influenza
  - Intranasal influenza
  - Measles (rubeola)
  - Measles-mumps-rubella combination
  - Measles-mumps-rubella-varicella combination
  - Mumps
  - Oral polio (Sabin)
  - Oral typhoid
  - Rubella
  - Smallpox (vaccinia)
  - Yellow fever
  - Bacille Calmette-Guerin
  - Rotavirus
  - Varicella zoster (shingles)

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 director (or medical monitor) before database locks with documented procedures.

Rescue treatments (including both medications and procedures): If medically necessary (e.g., for treatment of intolerable EoE symptoms), rescue medications (systemic and/or swallowed topical corticosteroids) or emergency esophageal dilations are allowed for study patients. An endoscopy with biopsy will be performed prior to the initiation of rescue therapy. Patients who undergo an endoscopy with biopsy due to initiation of rescue therapy will not undergo the subsequent scheduled endoscopy/biopsy at week 16 and/or week 52. Patients who receive rescue treatment during the double-blind period of the study will not be eligible for the 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

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

and will be asked to return to the clinic for all remaining study visits for the double-blind treatment period and the follow-up period and participate in all assessments for these visits except for endoscopy/biopsy, as noted above. For the purpose of primary endpoint efficacy analyses, patients who receive rescue treatment during the study will be considered treatment failures.

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 duodenum will be obtained at visit 2 in all patients to rule out alternate etiologies of esophageal eosinophilia. Gastric biopsy samples should include 2 samples from the antrum and 2 samples from the body. Duodenal biopsy samples should include 2 bulb samples and 2 from another portion of the duodenum. All randomized patients found to have stomach and/or duodenal abnormalities at baseline will have follow-up stomach and/or duodenal biopsies at week 16 and week 52.

4.4. Efficacy Variable

4.4.1. Primary Efficacy Variable

The primary endpoint is:

- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf (400×) at week 16

Peak esophageal intraepithelial eosinophil count

Peak esophageal intraepithelial eosinophil count will be measured from esophageal biopsies. Biopsies will be obtained by endoscopy at the second screening visit (visit 2), at week 16, and at week 52 visits, and immediately prior to start of rescue medication or rescue procedure and during the early termination visits. A total of at least 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 histology (needed for study inclusion criteria, as well as endpoint assessment) and the others for RNA extraction. 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. Biopsy samples for histopathological analyses will be sent to a central pathology laboratory for processing and analysis. If required by the investigator institution, biopsy samples will be processed and analyzed by the local laboratory, and the processed specimen will be sent to the central pathology laboratory for central reading. The peak esophageal intraepithelial eosinophil count at each visit is the maximum of the quantities of eosinophils in the most inflamed high power fields (hpfs) across the 3 regions. For example, if 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 will be considered as 4/hpf for week 16. 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.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

4.4.2. Secondary Efficacy Variable(s)

The secondary endpoints are:

- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf at week 16
- Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 16
- Absolute change in mean EoE grade score from the EoE-HSS from baseline to week 16
- Absolute change in mean EoE stage score from the EoE-HSS from baseline to week 16
- Absolute change in EoE-EREFS from baseline to week 16
- Change from baseline to week 16 in the proportion of days with 1 or more EoE signs as measured by the PESQ-C (for patients aged ≥1 to <12 years)
- Number of sign-free days during the 14-day period preceding week 16 as measured by the PESQ-C (for patients aged ≥1 to <12 years)
- Change from baseline to week 16 in the proportion of total segments within a day (night, morning, afternoon, evening) with 1 or more EoE signs as measured by the PESQ-C (for patients aged ≥1 to <12 years)
- Change from baseline to week 16 in the proportion of days with 1 or more EoE symptoms as measured by the PESQ-P (for patients aged ≥8 to <12 years)
- Number of symptom-free days during the 14-day period preceding week 16 as measured by the PESQ-P (for patients aged ≥8 to <12 years)
- Change from baseline to week 16 in the proportion of total segments within a day (night, morning, afternoon, evening) with 1 or more EoE symptoms as measured by the PESQ-P (for patients aged ≥8 to <12 years)
- Change in total score from baseline to week 16 as measured by the PEESSv2.0 (caregiver version) (for patients aged ≥1 to <12 years)
- Normalized Enrichment Scores (NES) for the relative change from baseline to week 16 in the EoE diagnostic panel (EDP) transcriptome signature
- NES for the relative change from baseline to week 16 in the type 2 inflammation transcriptome signature

NOTE: All the above primary and secondary endpoints assessed at week 16 for Part A will be assessed at week 52 for Part B (except for PEESSv2.0 [caregiver version]) as secondary endpoints and summarized with descriptive statistics based on the treatment assignment in the double-blind treatment period as well as the extended active treatment assignment for patients previously in the placebo group.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Eosinophilic Esophagitis Histology Scoring System (EoE-HSS)

The EoE-HSS is a recently validated histologic scoring system that measures other histological abnormalities in addition to the density of eosinophilic infiltration. It has been confirmed in adults to have external reliability and this scoring system is highly responsive to treatment (Collins, 2017) (Warners, 2018). Eosinophilic esophagitis grade and stage scores evaluate 8 features: eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, dilated intercellular spaces, surface epithelial alteration, dyskeratotic epithelial cells, and lamina propria fibrosis (absent/present). Assessment of lamina propria fibrosis may not be possible if the esophageal biopsy specimens do not contain adequate amounts of subepithelium lamina propria; in this case it will not be included in the overall EoE grade and stage scores.

Histology results will be interpreted by a pathologist at a central pathology reading center who will be blinded to the treatment assignment. Severity (grade) and extent (stage) of abnormalities will be scored using a 4-point scale (0 normal; 3 maximum change). The detailed scoring scheme for each feature is provided in Section 11.5. The mean grade or mean stage score from EoE-HSS is the ratio of the sum of the assigned score for each evaluated feature divided by the maximum possible score (maximum value is 24). For example, if each of 8 features has maximum grade of 3 for a biopsy, the mean grade score is 1 (24/24). If one feature is not evaluated, the maximum possible score is reduced by 3. Maximum possible score reduction may occur when lamina propria fibrosis is not present. If all other features are evaluable, the maximum possible score for a biopsy lacking lamina propria fibrosis is reduced from 24 to 21 because of 7 evaluated features. Both mean grade and mean stage scores will be determined for biopsies from 3 esophageal regions (proximal, mid, and distal). The algorithm of the calculation of mean grade and mean stage scores is as follows.

- The mean grade and mean stage scores summed over the 3 regions is the final score used in the primary analysis of the associated endpoints. An example table is provided below to illustrate the calculation of mean grade and mean stage scores. For example, the mean grade 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).
- If a mean score is available from at least 1 of the 3 regions, the sum of available mean scores will be used as final mean score. For example, if the mean grade score is 0.33 and 0.33 from the proximal and mid regions but missing from distal region, the final mean grade score will be 0.66 (0.33+0.33).

Feature	Esophageal region		
	Proximal	Mid	Distal
Eosinophilic inflammation	3	3	3
Basal zone hyperplasia	2	3	3
Eosinophil abscess	2	2	3
Surface layering	0	0	0
Dilated intercellular spaces	0	0	0
Surface epithelial alteration	0	0	0
Dyskeratotic epithelial cells	0	0	0
Lamina propria fibrosis	Missing due to absence	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

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Eosinophilic Esophagitis-Endoscopic Reference Score (EoE-EREFS)

The EoE esophageal characteristics will be analyzed based on the EoE-EREFS, a validated scoring system for inflammatory and remodeling features of disease using both overall scores and scores for each individual characteristic (Hirano, 2013). The EoE-EREFS utilizes a composite score using standardized methodology to assess clinical signs of EoE disease. Imaging should be collected for EoE-EREFS analysis and scoring by a centralized reading center. The proximal and distal esophageal regions will be scored separately; the score for each region ranges from 0 to 9 and the overall score ranges from 0 to 18. 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 score for each region is the sum of assigned scores for each of the above 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 the score is available only from 1 of the 2 regions, that available score is used as total score. For example, if score is 8 from the proximal region and missing from the distal region, the total score is 8.

In addition to the major features above, data for the following minor features will be assessed by the investigator:

- 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 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 screening visit 2, week 16, and week 52 or ET visits by centralized reading center. For patients who receive rescue treatment, endoscopy/imaging for EoE-EREFS/biopsy procedures will be performed prior to initiation of rescue treatment.

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, 2017). 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 (Regeneron unpublished data). The gene lists comprising the EDP and type 2 transcriptomes can be found in Section 11.6.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

A Normalized Enrichment Score (NES) is a way to generate a single numerical value to represent a complex gene expression signature. Changes in the NES score represents the overall changes in the expression of that molecular phenotype. A NES score 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 (Barbie, 2009) (Subramanian, 2005). NES of the relative change from baseline to week 16 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.

Pediatric EoE Sign/Symptom Questionnaire (PESQ)

The PESQ has a patient version (PESQ-P) and a caregiver version (PESQ-C).

PESQ-P is a patient-reported outcome measure intended to be completed independently by EoE patients ≥8 to <12 years of age.

- The PESQ-P measures of the symptoms of EoE and will be collected using an electronic diary (eDiary). Patients are asked to complete the eDiary every day just before they go to bed for the night. The symptoms measured by the PESQ-P include stomach pain, heartburn, acid reflux, regurgitation, vomiting, food refusal, and trouble swallowing food.
  - [redacted]
- Patient-reported information on the occurrence of EoE symptoms during the day or during one or more segments of the day will be used for the derivation of PESQ-P-based endpoints. [redacted]

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Symptoms	PESQ-P	
	Occurrence (Yes/No)	Symptoms occurred during time period of day [1]
Stomach pain	✓	✓
Heartburn (Burning feeling in chest)	✓	✓
Acid reflux (Acid coming up from stomach into throat)	✓	✓
Regurgitation (Food came up from stomach into mouth [but did not throw up])	✓	✓
Vomiting (Threw up)	✓	✓
Food refusal (Refused to eat a meal)	✓	✓ [3]
Trouble swallowing food	✓	✓ [3]
Food got stuck in throat [2]	✓	✓ [3]

[1] Time periods include "Last night", "This morning", "This afternoon", or "This evening" (except refused to eat a meal and trouble swallowing food).
[2] Patients are only asked if 'food got stuck in the throat' if they indicate that they had trouble swallowing food.
[3] [redacted]

PESQ-C is an observer-reported outcome measure intended to be completed independently by caregivers of all pediatric EoE patients in the study.

- The PESQ-C measures the signs of EoE and will be collected via an eDiary. Caregivers of all patients are asked to complete the eDiary every day after the patient has gone to bed for the night. The signs measured by the PESQ-C include stomach pain, heartburn, acid reflux, regurgitation, vomiting, food refusal, and trouble swallowing food.

[redacted]

[redacted]

- Caregiver-reported information on the occurrence of EoE signs during the day or during one or more segments of the day will be used for the derivation of PESQ-C-based endpoints. [redacted]

Signs [1]	**PESQ-C**	
	Occurrence (Yes/No)	Signs occurred during time period of day [2]
Stomach pain	✓	✓
Heartburn (Burning feeling in chest)	✓	✓
Acid reflux (Acid coming up from stomach into throat)	✓	✓
Regurgitation (Food came up from stomach into mouth [but did not throw up])	✓	✓
Vomiting (Threw up)	✓	✓
Food refusal (Refused to eat a meal)	✓	✓ [4]
Trouble swallowing food	✓	✓ [4]
Food got stuck in throat [3]	✓	✓ [4]

[1] For symptoms that are not directly observable by the caregiver (e.g., heartburn), caregivers may infer their occurrence through patient verbalizations, "Observers should only be asked to rate signs and behaviors that are observable, or verbalizations made by the pediatric patient on how he or she is feeling" (FDA Guidance Document, 2020).

[2] Time periods include "Last night", "This morning", "This afternoon", or "This evening" (except refused to eat a meal and trouble swallowing food).

[3] Caregivers are only asked if 'food got stuck in the throat' if they indicate that the patient had trouble swallowing food.

[4] [redacted]

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

[redacted]

Pediatric Eosinophilic Esophagitis Symptom Score (PEESS)

The Pediatric Eosinophilic Esophagitis Symptom Score (PEESS) version 2.0 (caregiver version) is a caregiver-reported outcomes measure which assesses the frequency and severity of EoE symptoms among pediatric patients (Franciosi, 2011). The PEESSv2.0 (caregiver version) consists of 20 items and has a one-month recall period. Each item has a 0-4 scale, which is transformed to 0-100 as follows: 0 = 0, 1 = 25, 2 = 50, 3 = 75, 4 = 100. The mean total PEESSv2.0 score is computed as the sum of all the item scores over the number of items answered. The total score should not be calculated if more than 50% of the total items are missing. The total PEESSv2.0 (caregiver version) score ranges from 0 to 100; higher scores indicate greater symptom burden of among pediatric EoE patients. This questionnaire will be collected on paper at baseline visit 3, week 16, or ET visit before follow-up or unscheduled visit before rescue treatment.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

4.4.3. Exploratory Variable(s)

The exploratory endpoints are:

- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤1 eos/hpf at week 16
- Percent change in total score of Pediatric EoE Impact Scale (caregiver version) (PEIS-C) from baseline to week 16 (for patients aged ≥1 to <12 years)
- Percent change in total Pediatric EoE Impact Scale (patient version) (PEIS-P) score from baseline to week 16 (for patients aged ≥8 to <12 years)

NOTE: Total score of PEIS-C or PEIS-P refers to averaging the scores of each of the individual questions, not totaling the scores from each of the individual questions.

- Change in GIC-patient, caregiver, and clinician version score

NOTE: Change in GIC for different questionnaires refers to the question itself asking the overall change of patient's/caregiver's EoE condition, not the change from baseline (the GIC is not administered at baseline).

- Change in GIS-patient, caregiver, and clinician version score
- Change from baseline in body weight for age percentile at week 16
- Change in body mass index for age z-score from baseline to week 16 for patients ≥2 years of age
- Change in weight for age z-score from baseline to week 16
- Change in weight for height z-score from baseline to week 16
- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 16 and achieving absolute change from baseline to week 16 in the proportion of days with 1 or more EoE signs as measured by PESQ-C
- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 16 and achieving percent change from baseline to week 16 in the proportion of days with 1 or more EoE signs as measured by PESQ-C
- Absolute change from baseline to week 16 in EREFS (excluding stricture)
- Absolute change from baseline to week 16 in EREFS inflammation sub-score
- Absolute change from baseline to week 16 in EREFS remodeling sub-score

NOTE: All the above exploratory endpoints assessed at week 16 will be assessed at week 52 as exploratory endpoints and summarized with descriptive statistics based on the treatment assignment in the double-blind treatment period as well as the extended active treatment assignment for patients previously in the placebo group.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Pediatric EoE Impact Scale (PEIS)

The Pediatric EoE Impact Scale (PEIS) has a patient version (PEIS-P) and a caregiver version (PEIS-C).

PEIS-P is a patient-reported outcome measure intended to be completed independently by pediatric EoE patients ≥8 to <12 years of age. The PEIS-P will assess the impact of EoE on the patient during the past 1 week. Response to each item below (except item 5) is on a 5-point scale (0 = "Never", 1 = "Almost never", 2 = "Sometimes", 3 = "Almost always", 4 = "Always"). Response to item 5 is on a 6-point scale (0 = "Never", 1 = "Almost never", 2 = "Sometimes", 3 = "Almost always", 4 = "Always", 5 = "Not applicable - I did not go to school during the past 7 days"). The PEIS-P average score is the sum of non-missing responses divided by the number of items with non-missing responses (note: response of "Not Applicable - I did not go to school during the past 7 days" is considered as missing response and not be counted in the average score). The average score could range from 0 to 4.

Item No.	Question
1	During the past 7 days, how often were you worried because of your EoE?
2	During the past 7 days, how often did you feel sad because of your EoE?
3	During the past 7 days, how often were you embarrassed in front of other people because of your EoE?
4	During the past 7 days, how often did you have difficulty sleeping at night because of your EoE?
5	During the past 7 days, how often did you have difficulty concentrating at school because of your EoE?
6	During the past 7 days, how often did you have difficulty playing with your friends because of your EoE?

PEIS-C is intended to be completed independently by caregivers of pediatric EoE patients ≥1 to <12 years of age. The PEIS-C will assess the impact of the pediatric patient's EoE on caregiver anxiety, social and professional activities, activities of daily living, and relationships during the past 1 week. Response to each item (except item 4 and 4a) is on a 5-point scale (0 = "Not at all", 1 = "Very little", 2 = "A little", 3 = "Very much", 4 = "Extremely"). If response to item 4 is "No", items 4a and 4b will be skipped and considered as missing response. The PEIS-C average score is the sum of non-missing responses divided by the number of items with non-missing responses (note: response to item 4a is not included in the score calculation). The average score could range from 0 to 4.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Item No.	Question
1	During the past 7 days, how worried were you because of your child's EoE?
2	During the past 7 days, how sad were you because of your child's EoE?
3	During the past 7 days, how much did your child's EoE limit your social activities?
4	Are you currently employed (working for pay)? (*If "Yes", go to question 4a and then 4b. If "No", go to Question 5*)
4a	During the past 7 days, how many days did you miss work because of your child's EoE
4b	During the past 7 days, how much did your child's EoE limit your productivity while you were working?
5	During the past 7 days, how much did your child's EoE limit your everyday activities (for example: house chores, going shopping)?
6	During the past 7 days, how much did your child's EoE cause problems with your personal relationships?

Global Impression of Change (GIC)

The GIC has a patient version (GIC-P), a caregiver version (GIC-C), and a clinician version (GIC-Clin).

- The GIC-P is a single-item patient-reported outcome measure intended to be completed independently by pediatric EoE patients ≥8 to <12 years of age. The GIC-P will assess the patient's impression about the overall change (improvement or worsening) in his/her EoE condition since study treatment initiation.
- The GIC-C is a single-item observer-reported outcome measure intended to be completed independently by caregivers of pediatric EoE patients ≥1 to <12 years of age. The GIC-C will assess the caregiver's impression about the overall change (improvement or worsening) in the pediatric patient's EoE condition since study treatment initiation.
- The GIC-Clin is a single-item observer-reported outcome measure intended to be completed independently by study investigator-physician of all pediatric EoE patients in the study. The GIC-Clin will assess the study investigator's/clinician's impression about the overall change (improvement or worsening) in the pediatric patient's EoE condition since study treatment initiation.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

The GIC-P, GIC-C, GIC-Clin score could range from 1 to 7.

Questionnaire	Question	Response (score)
GIC-P	Since you started getting the study injection, how would you describe the overall change in your eosinophilic esophagitis (EoE)?	A lot better (1)
		Somewhat better (2)
		A little better (3)
		No change (4)
		A little worse (5)
		Somewhat worse (6)
		A lot worse (7)
GIC-C	Since your child started getting the study injection, how would you describe the overall change in your child's eosinophilic esophagitis (EoE)?	Very much improved (1)
		Much improved (2)
		Minimally improved (3)
		No change (4)
		Minimally worse (5)
		Much worse (6)
		Very much worse (7)
GIC-Clin	Since your patient started getting the study injection, how would you describe the overall change in your patient's eosinophilic esophagitis (EoE)?	Very much improved (1)
		Much improved (2)
		Minimally improved (3)
		No change (4)
		Minimally worse (5)
		Much worse (6)
		Very much worse (7)

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Global Impression of Severity (GIS)

The GIS has a patient version (GIS-P), a caregiver version (GIS-C), and a clinician version (GIS-Clin).

- The GIS-P is a single-item patient-reported outcome measure intended to be completed independently by pediatric EoE patients ≥8 to <12 years of age. The GIS-P will assess the patient's impression about the overall severity of his/her EoE condition during the past 1 week.
- The GIS-C is a single-item observer-reported outcome measure intended to be completed independently by caregivers of pediatric EoE patients ≥1 to <12 years of age. The GIS-C will assess the caregiver's impression about the overall severity of the pediatric patient's EoE condition during the past 1 week.
- The GIS-Clin is a single-item observer-reported outcome measure intended to be completed independently by study investigator-physician of all pediatric EoE patients in the study. The GIS-Clin will assess the study investigator's/clinician's impression about the overall severity of the pediatric patient's EoE condition during the past 1 week.

The GIS-P, GIS-C, and GIS-Clin score could range from 1 to 4.

Questionnaire	**Question**	**Response (score)**
GIS-P	During the past 7 days, how bad was your eosinophilic esophagitis (EoE)?	Not bad (1)
		A little bad (2)
		Bad (3)
		Very bad (4)
GIS-C	During the past 7 days, how severe was your child's eosinophilic esophagitis (EoE)?	Mild (1)
		Moderate (2)
		Severe (3)
		Very severe (4)
GIS-Clin	Overall, how severe is your patient's eosinophilic esophagitis (EoE)?	Mild (1)
		Moderate (2)
		Severe (3)
		Very severe (4)

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Body Weight and Body Mass Index (BMI) Z-scores and Percentiles

Body weight for age z-score, body weight for age percentile, body weight for height/length z-score, and BMI for age z-score at each visit will be calculated based on the growth charts from Centers for Disease Control and Prevention (CDC) for ages 0 to 20 years (for ages 2 to <12 years) and World Health Organization (WHO) growth charts for ages 0 to <2 years (for ages 1 to <2 years). These charts included a set of smoothed percentiles along with CDC LMS (Lambda-Mu-Sigma) parameters to allow the calculation of other percentiles or z-scores (Flegal, 2013). To obtain the z-score for body weight or BMI, the following equation will be used $Z = [(X/M)^{L}-1]/(L\times S)$ for $L\neq 0$; $Z = \ln(X/M)/S$ for $L = 0$, where X is the measured body weight or BMI at each visit and L, M, and S values are from CDC table. The corresponding percentile can be obtained from standard normal distribution. The following CDC growth charts will be used. The growth chart is provided in half month intervals for age.

- Weight-for-age chart (weight in kilograms) for birth to 36 months population by sex and age
- Weight-for-age chart for 2 to 20 years population in kilograms by sex and age
- Weight-for-stature chart (weight in kilograms) by sex and stature (stature in centimeters)
- BMI for age charts for 2 to 20 years population by sex and age

For example, to obtain the weight for age z-score of a 24-month-old male who weighs 14.5 kg, the corresponding L, M, and S values in weight-for-age charts for 2 to 20 years population are -0.20615245, 12.6707633, 0.108125811, respectively. By applying the above LMS method equation z-score is 1.23 and the corresponding percentile is 89%.

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

The EREFS (excluding stricture), inflammation sub-score, and remodeling sub-score 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 sub-score	Edema + Exudates + Furrows	0 - 5	0 -10
Remodeling sub-score	Rings + Stricture	0 - 4	0 - 8

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

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 using the Medical Dictionary for Regulatory Activities (MedDRA).

The definition of adverse events and serious adverse events are provided in protocol Section 10.2.1 and Section 10.2.2. Pre-treatment AE and treatment-emergent AE (TEAE) are defined as follows:

- Pre-treatment signs and symptoms (pre-treatment AEs) are AEs that developed or worsened in severity during the pre-treatment period.
- TEAEs are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the treatment-emergent period.
  - TEAEs for part A treatment period are defined as TEAEs with onset date during the Part A treatment period.
  - TEAEs for part B extended active treatment period are defined as TEAEs with onset during the Part B extended treatment period.
  - TEAEs for follow-up period are defined as TEAEs with onset during the follow-up period.

4.5.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) for this study include the following:

- Anaphylactic reactions
- Systemic hypersensitivity reactions
- Helminthic infections
- Any severe type of conjunctivitis or blepharitis
- Keratitis
- Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)
- Severe injection site reactions
- Herpes simplex infection
- Arthralgia

For detailed definition of these AESIs, please see Section 11.4.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

4.5.3. Laboratory Safety Variables

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory. Samples will be collected predose at time points according to visit schedule (Section 11.2). Tests will include:

Blood Chemistry

Sodium	Creatinine
Potassium	Blood urea nitrogen (BUN)
Chloride	Aspartate aminotransferase (AST)
Carbon dioxide	Alanine aminotransferase (ALT)
Calcium	Alkaline phosphatase
Glucose	Lactate dehydrogenase (LDH)
Albumin	Estimated glomerular filtration rate (eGFR)
Total protein, serum	Total and indirect bilirubin

Hematology

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

Urinalysis

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

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

Other Laboratory Tests

- Pregnancy testing will be performed for all WOCBP. Serum or urine pregnancy testing will be performed at time points listed in visit schedule (Section 11.2).
- Tuberculosis testing will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics boards.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

4.5.4. Vital Signs

Vital signs, including heart rate, blood pressure, respiration rate, and body temperature will be collected predose and 30 minutes post-dose at time points listed in the schedule of events in Section 11.2. 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. Body weight in kg and height in cm (or length for patients <2 years of age) will be measured at the time points listed in the schedule of events table in Section 11.2. Body mass index will be programmatically calculated based on the weight and height data.

4.5.5. Physical Examination Variables

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

A thorough and complete physical examination will be performed at the screening visit 1, baseline visit 3, week 16, week 52, ET visit before follow-up or unscheduled visit before rescue treatment.

4.6. Pharmacokinetic Variables

The PK variable is the concentration of functional dupilumab in serum and time for individual patients. Serum samples for measuring functional dupilumab concentrations will be collected at time points according to Section 11.2.

4.7. Immunogenicity Variables

The immunogenicity variables include ADA status, NAb status, and titer at nominal sampling time/visit. Serum samples for ADA will be collected at the clinic visits specified in Section 11.2. Samples positive in the dupilumab ADA assay will be further characterized for ADA titers and for the presence of NAb against dupilumab.

4.8. Biomarker Variables

Biomarkers to be analyzed in this study are:

- Serum total IgE
- Eotaxin-3

Serum/plasma samples for measurements of biomarkers to study the pharmacodynamic activity of dupilumab in EoE patients will be collected at time points according to Section 11.2.

4.9. Clinical Outcome Assessments for Psychometric Validity Assessment

The measurement properties of the PESQ-C and PESQ-P (as described in Section 4.4.2) will be evaluated using anchor-based methods and qualitative insights from the week 16 exit interviews. The details of the analyses are specified in the R668-EE-1877 psychometric analysis plan.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

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.

All data will be summarized by the following treatment groups in each study period:

- Part A
  - Higher exposure dupilumab dose regimen
  - Lower exposure dupilumab dose regimen
  - Combined dupilumab group (for safety analysis only)
  - Placebo
- Part B
  - Higher exposure dupilumab dose regimen/Higher exposure dupilumab dose regimen
  - Lower exposure dupilumab dose regimen/Lower exposure dupilumab dose regimen
  - Combined dupilumab group (for safety analysis only)
  - Placebo/Higher exposure dupilumab dose regimen
  - Placebo/Lower exposure dupilumab dose regimen
  - Placebo/Combined dupilumab group (for safety analysis only)
  - Total (for safety analysis only)

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 will be provided for Part B SAF patients.

5.2. Medical History

Medical history will be summarized by primary System Organ Class (SOC) and Preferred Term (PT) for each treatment group and for study total based on the FAS. The table will be sorted by decreasing frequency of SOC followed by PT based on the overall incidence across treatment groups.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

5.3. Prior/Concomitant Medications/Procedures

Number and proportion of patients taking prior/concomitant medications, prohibited medications/procedures, and rescue medications/procedures will be summarized for each treatment group and study total, based on study period specific FAS, by ATC Level 2 and ATC Level 4, sorted by decreasing frequency of ATC Level 2 and ATC Level 4 in the combined dupilumab treatment group. Patients will be counted once in each medication class linked to the medication.

Number and proportion of patients taking PPIs for the treatment of EoE will be summarized by PPI therapy name. In addition, number and proportion of patients taking swallowed topical/systemic corticosteroids for the treatment of EoE will be summarized for swallowed topical corticosteroids and systemic corticosteroids by ATC Level 2 and ATC Level 4, respectively.

Number and proportion of patients undergoing prior/concomitant procedures will be summarized for each treatment group and study total, based on the study period specific FAS, by SOC and PT, and sorted by decreasing frequency of SOC and PT in the combined dupilumab treatment group.

Separate summaries will be provided for Part A and Part B concomitant medications/procedures.

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 (including COVID-19 related reasons)
- The total number of patients who discontinued the study in Part A, and the reasons for discontinuation (including COVID-19 related reasons)
- Number of patients who entered into Part B
- The total number of patients who discontinued the study treatment in Part B, and the reasons for discontinuation (including COVID-19 related reasons)
- The total number of patients who discontinued the study in Part B, and the reasons for discontinuation (including COVID-19 related reasons)
- Number of patients who entered 12-week follow-up period from Part A and Part B, respectively

Summary table of important protocol deviations in each study treatment period will be provided.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

5.5. Extent of Study Treatment Exposure

5.5.1. Exposure to Investigational Product

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

> (Date of last study drug injection in the respective study period – date of first study drug injection in the respective study part) + 14

NOTE: exposure will be calculated based on the last study drug injection date and first study drug injection date regardless of temporary dosing interruption or dosing extension due to COVID-19. For patients with extended dosing due to COVID-19, the duration of exposure may exceed 16 weeks for Part A or 36 weeks for Part B as study design.

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 the number of patients, mean, standard deviation, median, Q1, Q3, minimum, and maximum. These summaries will be provided for Part A and Part B separately.

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

- Part A: ≥ 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, with an increment of 1 week for each subsequent category.
- Part B: ≥ 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, ≥175 days, ≥182 days, ≥189 days, ≥196 days, ≥203 days, ≥210 days, ≥217 days, ≥224 days, ≥231 days, ≥238 days, ≥245 days, ≥252 days, with an increment of 1 week for each subsequent category.

For patients who received at least 1 dose of study drug, the total duration of exposure to study drug during the study (throughout Part A and Part B) is calculated as:

> (Date of last study drug injection in the study – date of first study drug injection) + 14

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

> (Date of last study visit – date of first study injection) + 1

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

The duration of observation period will be summarized descriptively using number of patients, mean, standard deviation, median, Q1, Q3, minimum, and maximum. In addition, the number (n) and proportion (%) of patients with observation periods will be presented by specific time periods. The time periods of interest are specified as follows:

- Part A: ≥ 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, with an increment of 1 week for each subsequent category.
- Part B: ≥ 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, ≥176 days, ≥183 days, ≥190 days, ≥197 days, ≥204 days, ≥211 days, ≥218 days, ≥225 days, ≥232 days, ≥239 days, ≥246 days, ≥253 days, with an increment of 1 week for each subsequent category.

5.6. Analyses of Efficacy Variables

The analyses of efficacy variables are described in the subsections below and summarized in Section 11.1. The intercurrent events, strategies, and the corresponding missing data handling approaches for the primary estimand of interest for the primary endpoint are provided in Table 1 .

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Table 1: Summary of Primary Estimand for Primary Endpoint and Secondary Endpoints in Part A

Endpoint Category	Estimands			
	Endpoint(s)	**Population**	**Intercurrent event(s) strategy and missing data handling**	**Population-level summary/Analysis**
Primary Endpoint	Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf (400×) at week 16	FAS	The intercurrent events will be handled as follows: • Treatment discontinuation: data collected after the patient discontinued treatment will be included in the analysis (treatment policy strategy) • Initiation of treatment with systemic and/or swallowed topical corticosteroids drugs and dilation: patients will be considered as non-responders after such event (composite variable strategy) Note: the composite strategy will be considered if a patient receives rescue medication any time during the study. Missing data handling: patients with a missing value for the primary endpoint at week 16 due to study discontinuation or other reasons will be considered non-responders. Missing data due to COVID-19 will be imputed by multiple imputation (MI).	Cochran-Mantel-Haenszel (CMH) test adjusting for the randomization stratification factor (baseline weight group) will be utilized. The estimated proportion of the treatment difference between dupilumab groups and placebo, and its 2-sided 95% confidence intervals will be provided based on the CMH test.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Endpoint Category	Estimands			
	Endpoint(s)	**Population**	**Intercurrent event(s) strategy and missing data handling**	**Population-level summary/Analysis**
Secondary Endpoints	Binary endpoints (e.g., proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf at week 16)	FAS	The intercurrent events strategy and missing data handling methods will be the same with the primary endpoint.	The primary analysis method will be the same as for the primary endpoint.
	Continuous endpoints that are scheduled to be measured repeatedly post-baseline up to week 16 (e.g., change in the proportion of days with 1 or more EoE signs from baseline to week 16 as measured by the PESQ-C)	FAS	The intercurrent events will be handled as follows: • Treatment discontinuation: data collected after the patient discontinued treatment will be included in the analysis (treatment policy strategy) • Initiation of treatment with systemic and/or swallowed topical corticosteroids drugs and dilation: data after such events will be assigned by the worst observed value (composite variable strategy) Missing data handling: patients with a missing value at week 16 due to AE/lack of efficacy will be imputed using WOCF method, and MI approach will be used for the missing data due to other reasons.	Continuous secondary efficacy endpoints at week 16 will be analyzed using an analysis of covariance (ANCOVA) model with treatment groups, randomization stratification factor, and relevant baseline measurement as a covariate included in the model. The least square (LS) means and difference in LS means between dupilumab groups and placebo will be presented.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Endpoint Category	Estimands			
	Endpoint(s)	**Population**	**Intercurrent event(s) strategy and missing data handling**	**Population-level summary/Analysis**
	Continuous endpoints that are scheduled to be measured only once post-baseline up to week 16 (e.g., absolute change in EoE-EREFS from baseline to week 16)	FAS	The intercurrent events will be handled as follows: • Treatment discontinuation: data collected after the patient discontinued treatment will be included in the analysis (treatment policy strategy) • Initiation of treatment with systemic and/or swallowed topical corticosteroids drugs and dilation: data after such events will be assigned by the worst observed value (composite variable strategy) Missing data handling: patients with a missing value due to COVID-19 will be imputed using MI approach, and WOCF method will be used for missing not due to COVID-19. WOCF method refers to missing values at week 16 will be imputed with patient's baseline value or the available post-baseline value, whichever is worse.	

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

5.6.1. Analysis of Primary Efficacy Variable

The primary analysis of proportion of patients achieving a histologic response of peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 16 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 factor (baseline weight group [≥5 - <15 kg, ≥15- <30 kg, ≥30-<60 kg]). The randomization stratification of baseline weight group may be pooled to ensure the sufficient sample size of each stratum. Estimates of treatment difference and its 95% confidence interval will be presented along with the p-values.

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

To account for the use of rescue treatment, patients will be considered as non-responder for all time points subsequent to the use of rescue treatment in the primary analysis.

If week 16 biopsy is performed after the date when the first dose of Part B study drug is administered, patients will be considered as non-responder in the analysis.

Due to COVID-19 restrictions, patients may postpone the week 16 visit until an in-clinic visit can be done for biopsy. Before the biopsy procedure could be performed, study drug would be shipped to patients directly to enable them to extend their current assigned dose regimen of study drug. The data from those delayed week 16 visits will be used in the primary analysis as long as the patients keep the extended dosing before biopsy.

Missing data at week 16 will be handled according to the reasons for missingness as follows:

- If the peak esophageal intraepithelial eosinophil count at week 16 is missing due to COVID-19 pandemic, the data will be imputed by multiple imputation (MI) using a seed number of 6681877 for 10 times based on patients who have non-missing eosinophil counts at week 16. The MI will utilize the regression method with treatment group, randomization stratification factor, baseline eosinophil count as covariates and week 16 eosinophil count as response variable in the regression model. The imputed week 16 eosinophil counts 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 16 due to reasons not related to the COVID-19 pandemic (e.g., discontinuation from study), the patient will be classified as a non-responder at week 16.

Each of the imputed complete datasets will be analyzed by the CMH test. Statistical inference obtained from all imputed data will be combined using Rubin's formula (Ratitch, 2013).

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Sensitivity analyses

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

1. **Tipping point analysis approach**: To assess the robustness of analysis results under MNAR (missing not at random) assumption, a delta-adjusting pattern-mixture approach for tipping point analysis (Ratitch, 2013) will be conducted for the primary endpoint. The impact from missing data due to study discontinuation or other reasons on the comparisons in proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 16 between each dupilumab group and placebo control group will be examined, by adjusting for stratification factor:
    - A series of analyses will be performed by applying a specified sequence of different values of shift parameter to the 3 treatment groups for the data imputation: in the placebo group, different values (>0) of shift parameter will be subtracted from the imputed peak eosinophil count; in each of dupilumab group, different values (<0) of shift parameter will be added to the imputed peak eosinophil count. The imputed peak eosinophil count which is negative will be replaced by 0. Patients who achieve peak eosinophil count of ≤6 eos/hpf will be derived based on the imputed peak eosinophil count after shifting.
    - For each combination of different values of shift parameter applied to the 3 treatment groups, 10 multiple imputed datasets will be generated using a seed number of 6681877. Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf will be analyzed using CMH test. The results obtained from 10 multiple imputed datasets will be combined using Rubin's formula (Ratitch, 2013) for statistical inference, i.e., p-value and treatment difference between active treatment groups and placebo group.
    - A "tipping point" will be identified when the result is no longer statistically significant (i.e., p-value >0.05).
2. **Worst observation carried forward - multiple imputation (WOCF-MI) approach**: Data after rescue treatment or the missing peak esophageal intraepithelial eosinophil count at week 16 due to AE/lack of efficacy will be imputed with patient's baseline value or the available post-baseline value up to week 16, whichever is worse, i.e., WOCF. The missing data due to other reasons will be imputed by MI using a seed number of 6681877 for 10 times based on patients who have non-missing eosinophil counts at week 16. The imputed week 16 eosinophil counts will determine whether that patient will be classified as a responder or non-responder. The 10 complete datasets after the imputations will be analyzed using CMH test. The results from the 10 analyses will be combined using the SAS MIANALYZE procedure (Ratitch, 2013).

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

5.6.2. Analysis of Secondary Efficacy Variables

Binary endpoints at week 16

Secondary efficacy endpoints that measure binary responses at week 16 will be analyzed in the same fashion as the primary endpoint, including the method to handle missing data.

Continuous endpoints at week 16

Continuous secondary efficacy endpoints at week 16 will be analyzed using an analysis of covariance (ANCOVA) model for the FAS with treatment groups, randomization stratification factor, and relevant baseline measurement as a covariate included in the model. For endoscopy/biopsy-based endpoints (i.e., esophageal intraepithelial eos count, EoE-EREFS, EoE-HSS), if week 16 endoscopy/biopsy is performed after the date when the first dose of Part B study drug is administered, data from that endoscopy/biopsy will be set to missing in the analysis.

To account for the use of rescue treatment, data will be set to missing for all time points subsequent to the use of rescue treatment.

For continuous efficacy data that are scheduled to be measured repeatedly post-baseline up to week 16 (e.g., change in the proportion of days with 1 or more EoE signs from baseline to week 16 as measured by the PESQ-C), missing data will be imputed by the pattern-mixture approach. Specifically, the WOCF-MI approach, where the WOCF approach will be used for imputing the missing data due to rescue treatment/AE/lack of efficacy, and the MI approach will be used for the missing data due to other reasons (e.g., missing PESQ-C data due to less than 8 diary entries for the 14-day period). MI will follow the steps below using a seed number of 6681877 in both steps:

- Step 1: Use the Markov Chain Monte Carlo (MCMC) method to fill in the intermittent missing values so that a monotone missing pattern will be formed.
- Step 2: For each of the imputed datasets with monotone missing pattern in Step 1, the remaining missing data will be imputed using regression method with treatment group, randomization stratification factor, relevant baseline measurement as a covariate, and the post-baseline measurements up to week 16 as response variable.
- Step 3: Each of the 40 imputed datasets will be combined with the dataset imputed by WOCF approach, and then analyzed using the ANCOVA.
- Step 4: The results from the 40 analyses on the complete datasets will be combined to generate a valid overall statistical inference using Rubin's formula (Ratitch, 2013). The least square (LS) means and difference in LS means between dupilumab groups and placebo will be presented.

The cumulative distribution function (CDF) of the absolute change from baseline in the proportion of days (or total segments within a day) with 1 or more EoE signs as measured by the PESQ-C at week 16 and from baseline in the proportion of days (or total segments within a day) with 1 or more EoE symptoms as measured by the PESQ-P at week 16 will be graphed to present the between-treatment-group differences at each level of the change.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

For continuous efficacy data that are scheduled to be measured only once post-baseline up to week 16 (e.g., absolute change in EoE-EREFS from baseline to week 16), a hybrid approach WOCF-MI will be used to handle missing data. That is, missing values at week 16 due to reasons not related to COVID-19 pandemic will be imputed with patient's baseline value or the available post-baseline value, whichever is worse, i.e., a WOCF approach, and missing values at week 16 due to COVID-19 pandemic will be imputed using MI as described in the primary analysis of the primary endpoint of histologic response in Section 5.6.1. 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.

The primary analysis of EoE-EREFS will be based on centralized readings.

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 16 between the dupilumab and placebo groups is statistically significant. Missing NES data will be imputed by Last Observation Carried Forward (LOCF) approach. P-values will be reported.

Secondary endpoints in Part B

Secondary endpoints at week 52 (Part B) will be analyzed descriptively at given visits for treatment received in Part B as well as by treatment group as in Part A (double-blind treatment period). No missing values will be imputed.

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 patients 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 B 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 3). Part B baseline is the last available valid measurement taken prior to or on the date of the first dose of extended active treatment period (scheduled to be administered at week 16 visit).

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

5.6.3. Adjustment for Multiple Comparison

The following multiplicity adjustment approach, a hierarchical procedure, will be used to control the overall Type-1 error rate at 0.05 for the primary endpoint and the secondary endpoints across the 2 dupilumab dose regimens versus placebo in Part A only. Each hypothesis will be formally tested only if the preceding one is significant at the 2-sided 0.05 significance level. The hierarchical testing order is shown in the below table (all comparisons are with the placebo).

	Endpoints	Dupilumab	
		Higher Exposure Dupilumab	Lower Exposure Dupilumab
Primary endpoint	Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 16	1	10
Secondary endpoints	Proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf at week 16	2	11
	Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 16	3	12
	Absolute change in mean EoEHSS grade score from the EoE-HSS from baseline to week 16	4	13
	Absolute change in mean EoEHSS stage score from the EoE-HSS from baseline to week 16	5	14
	NES for the relative change from baseline to week 16 in the type 2 inflammation transcriptome signature	6	15
	NES for the relative change from baseline to week 16 in the EoE diagnostic panel (EDP) transcriptome signature	7	16
	Absolute change in EoE EREFS from baseline to week 16	8	17
	Change from baseline to week 16 in the proportion of days with 1 or more EoE signs as measured by the PESQ-C (for patients aged ≥1 to <12 years)	9	18

5.6.4. Subgroup Analysis

Subgroups described in Section 3.5 will be summarized for the primary efficacy endpoint (as listed in Section 4.4.1) and the below selected secondary endpoints. Treatment difference and its 95% confidence interval in subgroups of patients will be presented in forest plots. The stratification factor (baseline weight group) will not be included in the subgroup analysis when applying the CMH test and ANCOVA.

- Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 16
- Absolute change in mean EoEHSS grade score from the EoE-HSS from baseline to week 16
- Absolute change in mean EoEHSS stage score from the EoE-HSS from baseline to week 16
- Absolute change in EoE EREFS from baseline to week 16

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

5.6.5. Analysis of Exploratory Efficacy Variables

The exploratory efficacy endpoints at week 16 or week 52 will be analyzed descriptively.

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.

The CDF of the proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 16 and achieving absolute/percent change from baseline to week 16 in the proportion of days with 1 or more EoE signs as measured by PESQ-C will be graphed to present the between-treatment-group differences at each level of the change.

5.7. Analysis of Safety Data

The analysis of safety and tolerance will be performed on the SAF, as defined in Section 3.2.

The safety analysis will be based on the reported AEs and other safety information (clinical laboratory evaluations and vital signs).

Thresholds for Potential Clinically Significant Values (PCSV) in laboratory variables and vital signs are defined in Section 11.3. 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 B, baseline for Part B PCSVs is the last available valid measurement taken prior to the first dose of extended active treatment in Part B (scheduled to be administered at week 16 visit).

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 treatment group for each study period. For safety variables/summaries involving baseline values, e.g., absolute change from baseline or shift table, study period specific baseline will be utilized. 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 B and follow-up period will use Part B baseline (i.e., the last available valid measurement prior to the first dose of extended active treatment in Part B).

5.7.1. Adverse Events

The number and proportion of patients reporting TEAEs will be summarized for Part A 16-week double-blind treatment period, Part B 36-week extended active treatment period, and 12-week follow-up period, as described in Section 3.2.

AE incidence tables will be presented by treatment group for the SAF as well as subgroups defined for safety analysis (Section 3.5). TEAE summaries will present the number (n) and percentage (%) of patients experiencing an TEAE by SOC and PT, sorted by decreasing frequency of SOC and PT for the combined dupilumab treatment group. Multiple occurrences of AEs of the same PT (or SOC) in the same patient will be counted only once for that PT (or SOC). For tables presenting severity of events, the worst severity will be chosen for patients 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 3.2.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

An overall summary of TEAEs will be provided with number (n) and percentages (%) of patients with any:

- TEAE
- Serious TEAE
- TEAE of special interest (AESI)
- TEAE with fatal outcome
- TEAE leading to permanent treatment discontinuation

Detailed summaries of all TEAEs in each treatment group will include:

- TEAEs
  - TEAEs by primary SOC/PT
  - TEAEs by primary SOC/PT with incidence of PT ≥5% in any treatment group
  - TEAEs by severity and by primary SOC/PT
  - TEAEs related to study medication as assessed by the investigator by primary SOC/PT
  - TEAEs of special interest by AESI category (see Section 11.4) and primary SOC/PT
- Serious TEAEs by SOC/PT
- TEAEs leading to permanent discontinuation of study treatment by primary SOC/PT
- TEAEs with fatal outcome by primary SOC/PT

The number and proportion of patients with injection site reaction by PT will be summarized.

5.7.2. Clinical Laboratory Measurements

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

- Descriptive statistics of laboratory result and change from baseline by visit
- The number (n) and percentage (%) of patients with treatment-emergent PCSVs. This summary will be provided on the subgroup of SAF patients who did not meet the PCSV criterion at the 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

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

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. This summary will be provided on the subgroup of SAF patients who did not meet the PCSV criterion at the 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

5.7.4. Physical Exams

Abnormal status will be tabulated 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 profiles. Plots of concentration vs time will be provided as both non-log and semi-log. When plotted as non-log, concentrations less than LLOQ will be set to zero (0). When plotted as semi-log, for concentrations less than LLOQ, LLOQ/2 will be imputed.
- Graphical presentations of individual functional dupilumab concentration in serum vs actual sampling time profiles. When plotted as non-log, concentrations less than LLOQ will be set to zero (0). When plotted as semi-log, for concentrations less than LLOQ, LLOQ/2 will be imputed.
- Assessment of the impact of anti-drug antibodies on functional dupilumab concentrations in serum

No formal statistical analysis will be performed.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

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 status, ADA category, and maximum titer observed in patients in the ADA analysis set.

The ADA status of each patient may be classified as one of the following:

- Positive
- Pre-existing - If the baseline sample is positive and all post baseline ADA titers are reported as less than 4-fold the baseline titer value
- Negative - If all samples are found to be negative in the ADA assay

The ADA category of each positive patient is classified as:

- Treatment-boosted - A positive result at baseline in the ADA assay with at least one post baseline titer result ≥ 4-fold the baseline titer value
- Treatment-emergent - A negative result or missing result at baseline with at least one positive post baseline result in the ADA assay. Patients that are treatment-emergent will be further categorized as follows:
  - Persistent - A positive result in the ADA assay detected in at least 2 consecutive post baseline samples separated by at least a 12-week post baseline period (based on nominal sampling time), with no ADA-negative results in-between, regardless of any missing samples
  - Indeterminate - A positive result in the ADA assay at the last collection time point only, regardless of any missing samples
  - Transient - Not persistent or indeterminate, regardless of any missing samples

The maximum titer category of each patient is classified as:

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

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

The following listings will be provided by treatment group and ADA titer level:

- Number (n) and percent (%) of ADA-negative patients
- Number (n) and percent (%) of patients with pre-existing immunoreactivity
- Number (n) and percent (%) of treatment-emergent ADA positive patients
  - 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

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

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.

- Negative: Samples tested negative in the ADA assay, or samples positive in the ADA assay but tested negative in the NAb assay.
- Positive: Samples tested positive in the NAb assay.

5.10. Association of Immunogenicity with Exposure, Safety and Efficacy

The analyses in this section will only be performed if the incidence of treatment emergent ADA positive is sufficient to make meaningful conclusions (i.e., more than 5% in any treatment group).

5.10.1. Association of immunogenicity with exposure

Potential association between immunogenicity 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 category, maximum titer category, and NAb status on individual patient drug concentration profile.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

5.10.2. Immunogenicity and Safety/Efficacy

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

- TEAE
- Serious TEAE
- TEAE leading to permanent treatment discontinuation
- Injection site reaction (HLT= "Injection site reaction")
- Hypersensitivity (AESI category "Hypersensitivity")
- Anaphylaxis (SMQ: Anaphylactic Reaction [Narrow])

Potential association between immunogenicity variables and 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 Positive
  - Treatment-emergent
  - Treatment-boosted
- Maximum post-baseline titer category
- NAb positive

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. Biomarker values after the first rescue treatment used are set to missing (censoring), then LOCF approach will be used to impute the missing data at each visit for Part A analysis, and all observed values will be used for Part B analysis.

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.

Correlation of baseline Eotaxin-3 and total IgE (measured value) with the histologic responder (histologic response of peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 16) will be explored using the logistic model. The model will include the histologic responder/non-responder as the dependent variable, with randomization stratification factor, 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. Patients are considered non-responders after the rescue treatment is used. In addition, patients with missing peak eosinophil count at week 16 are considered as non-responders.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

5.12. Analysis of Psychometric Validity of Clinical Outcome Assessment Measures

Results of psychometric analysis of the PESQ-C and PESQ-P will be summarized in a clinical outcome assessment (COA) dossier. Evidence of content validity and measurement properties of relevant COAs will be submitted to the Agency.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

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 Baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of investigational product. If any randomized patients are not treated, the baseline will be the last value on or prior to the randomization. Part B baseline is defined as the last available valid measurement taken prior to the first dose of extended treatment in Part B.

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

1. The date and time of first injection will be used to determine the baseline for the AE, vital sign, lab (including biomarker), PK, and ADA data.
2. Only the date of first injection will be used to determine the baseline for other data except AE, vital sign, lab (including biomarker), PK, or ADA.

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 patient ID or enrolled patient ID.

6.2. General Data Handling Convention

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 TEAEs. 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’.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

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 01January. 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.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

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 data management and study medical director.

PCSV

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

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

6.4. Visit Windows

Data analyzed by-visit-analysis (efficacy [excluding daily diary data], laboratory data, vital sign, ADA) will be summarized by the study scheduled visits described in study protocol and SAP Section 11.2, "Schedule of Time and Events".

The analysis visit windows will be created per study Schedule of Events table for each parameter and will be applied if the data from the study scheduled visits are unavailable. The following general rules will be applied to unscheduled visit and/or early termination (ET) visit mapping for each parameter:

1. If ET visit falls in an analysis window which has no missing value of this parameter, ET visit will be mapped to the next scheduled visit.
2. If both ET visit and unscheduled visit of the same parameter are available in the same analysis visit window, only ET visit will be mapped.
3. If multiple unscheduled visits of the same parameter are available in the same analysis visit window, the unscheduled visits will be mapped using the following rules:
   a. The closest unscheduled visit from the target day will be selected.
   b. If multiple unscheduled visits occur on the same day, the first unscheduled visit will be utilized.
4. If unscheduled visit is greater than 4 weeks apart from the target day of the scheduled visit, the unscheduled visit will not be mapped.

Unscheduled visit and early termination (ET) visit will be mapped per the analysis visit windows for Part A and Part B (Table 2-6) based on the study day and visit of each parameter, respectively. The analysis visit windows may be applied to the scheduled assessments for PEIS, GIC and GIS.

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

Table 2 Analysis Visit Window for Efficacy Endpoints in Part A

Visit from SOE	Target Study Day in Part A	Analysis Visit Window based on Study Day[a] in Part A		
		Histology endpoints, Transcriptome endpoints, EOE-EREFS, PEIS-P, PEIS-C, PEESS	GIC-P, GIC-C, GIC-Clin	GIS-P, GIS-C
Baseline	1	≤1		≤1
Week 12	85		[2, 99]	[2, 99]
Week 16 (Part A end of treatment)	113	≥2 [b]	≥100 [b]	≥100 [b]

a. Study days are calculated from the day of 1st injection of Part A. Study day = (date of assessment – 1st injection date + 1) when date of assessment is on or after the 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 visit or ET visit occurs in this window, and it is after the first dose of Part B, it will be considered as part of Part B visits.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Table 3 Analysis Visit Window for Safety and Biomarkers in Part A

Visit from SOE	Target Study Day in Part A	Analysis Visit Window based on Study Day[a] in Part A				
		Vital Signs	Physical Examination	Laboratory, PK, Eotaxin-3	ADA	Serum total IgE
Baseline	1	≤1	≤1	≤1	≤1	≤1
Week 2	15	[2, 22]				
Week 4	29	[23, 43]		[2, 71]		≥2[b]
Week 8	57	[44, 71]				
Week 12	85	[72, 99]				
Week 16 (Part A end of treatment)	113	≥100[b]	≥2[b]	≥72[b]	≥2[b]	

a. Study days are calculated from the day of 1st injection of Part A. Study day = (date of assessment – 1st injection date + 1) when date of assessment is on or after the 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 visit or ET visit occurs in this window, and it is after the first dose of Part B, it will be considered as part of Part B visits.

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

Table 4 Analysis Visit Window for Efficacy Endpoints in Part B

Visit from SOE	Target Study Day in Part B	Analysis Visit Window based on Study Day[a] in Part B	
		Histology endpoints, Transcriptome endpoints, EOE-EREFS	PEIS-P, PEIS-C, GIC-P, GIC-C, GIC-Clin, GIS-P, GIS-C, GIS-Clin
Baseline of Part B	1	≤1	≤1
Week 32	113		[2, 183]
Week 52 (Part B end of treatment)	253	≥2	≥184

a. Study days are calculated from the day of 1st injection of Part B. Study day = (date of assessment – 1st injection date + 1) when date of assessment is on or after the 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.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Table 5 Analysis Visit Window for Safety and Biomarker Endpoints in Part B

Visit from SOE	Target Study Day in Part B	Analysis Visit Window based on Study Day[a] in Part B		
		Vital Signs	Physical Examination, Urinalysis, Serum total IgE, Eotaxin-3	Hematology, Chemistry, PK, ADA
Baseline of Part B	1	≤1	≤1	≤1
Week 20	29	[2, 43]		
Week 24	57	[44, 71]		
Week 28	85	[72, 99]		
Week 32	113	[100, 127]		[2, 183]
Week 36	141	[128, 155]		
Week 40	169	[156, 183]		
Week 44	197	[184, 211]		
Week 48	225	[212, 239]		
Week 52 (Part B end of treatment)	253	≥240	≥2	≥184

a. Study days are calculated from the day of 1st injection of Part B. Study day = (date of assessment – 1st injection date + 1) when date of assessment is on or after the 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.

12-week follow-up period after Part A/Part B end of treatment

Table 6 Analysis Visit Window for 12-week Follow-up Period after Part A/Part B End of Treatment

Visit from SOE	Target Study Day after EOT Visit[a]	Analysis Window based on Study Day[a] after EOT
Week 64 EOS Visit (Patient not entering Part B)	85 (relative to week 16 visit)	≥2[b]
Week 64 EOS Visit (Patient entering Part B)	85 (relative to week 52 visit)	≥2[b]

a. Study days are calculated from the day of week 16 visit for patients not entering Part B or the day of week 52 visit for patients entering Part B. Study day = (date of assessment – week 16/week 52 visit +1) when date of assessment is on or after week 16/week 52 visit. If patient does not complete week 16/week 52 visit, week 64 visit will be not applicable for this patient.

b. If unscheduled visit occurs after Part A/Part B EOT visit, and patient enters follow-up period, 1) the study day is ≤42 (6 weeks after Part A/Part B EOT visit), it will be considered for week 16/week 52 visit; 2) the study day is >42, it will be considered for EOS visit.

For PESQ-P and PESQ-C 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 B will not be used for Part A analysis)

Step 1: Diary study day derivation

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

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Step 2: Analysis visit windows are defined as Day -14 to Day -1 = BL, Day 1 to Day 14 = week 2, Day 15 to Day 28 = week 4, etc., with 14-day intervals between visit windows, through Day 99 to Day 112 = week 16. For patients who never entered Part B, analysis windows in the 12-week follow-up period will continue with 14-day intervals as Day 113 to Day 126 = week 18, Day 127 to Day 140 = week 20, etc.

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

Step 1: Diary study day derivation

- For diary date ≥ 1st injection date of study Part B, Part B diary study day = diary date – 1st injection date ***in Part B*** + 1;
- For diary date < 1st injection date of study Part B, Part B diary study day = diary date – 1st injection date in Part B.

Step 2: Analysis visit windows are defined as Day -14 to Day -1 = Part B BL, Day 1 to Day 14 = week 18, Day 15 to Day 28 = week 20, etc., with 14-day intervals between visit windows, through Day 239 to Day 253 = week 52. For patients who entered 12-week follow-up period after Part B, analysis windows will continue with 14-day intervals as Day 254 to Day 267 = week 54, Day 268 to Day 281 = week 56, etc.

6.5. Statistical Technical Issues

None.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

7. INTERIM ANALYSIS

No interim analysis is planned.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

8. TIMING OF STATISTICAL ANALYSIS

The primary analysis will be performed when the last patient has completed the last 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. Available Part B data will also be analyzed and evaluated, including assessment of secondary endpoints at week 52. The final analysis will occur when all patients who enter the 12-week follow-up period immediately from Part A or Part B completed the follow-up period.

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 Part A unblinded 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 Part A unblinded 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.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

9. SOFTWARE

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

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

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VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

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VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

11. APPENDIX

11.1. Summary of Statistical Analyses

11.1.1. Summary of Efficacy Analyses

Endpoint	Analysis Populations	Primary Statistical Method	Supportive/Sensitive Statistical Method	Subgroup Analysis	Other Analyses
Primary Endpoint					
Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf (400×) at week 16	FAS	Cochran-Mantel-Haenszel test/Missing as non-responder	Cochran-Mantel-Haenszel test with tipping point analysis approach and WOCF-MI approach, respectively	Yes [1]	Histogram
Secondary Endpoints					
Secondary continuous variable	FAS	ANCOVA with WOCF-MI approach for endpoints measured repeatedly (e.g., change from baseline in the proportion of days with 1 or more EoE signs as measured by the PESQ-C); ANCOVA with WOCF-MI approach for endpoints measured only once post-baseline up to week 16 (e.g., percent change in peak eosinophil count from baseline to week 16)	NA	No	Line plot except EoE-EREFS endpoint; Bar chart for EoE-EREFS endpoint
Secondary binary variable	FAS	Cochran-Mantel-Haenszel test/Missing as non-responder	NA	No	Histogram

[1] Note: The subgroup analysis may not be performed if the number of patients within the subgroup is <10% of overall sample size. The stratification factor is not included in the subgroup analysis of primary efficacy endpoint.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

11.1.2. Summary of Safety Analyses

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Descriptive statistics	No	TEAEs by Primary SOC/PT only [1]	No
Laboratory Measures	SAF	Descriptive statistics	No	No	No
Vital sign	SAF	Descriptive statistics	No	No	No

[1] Note: The subgroup analysis may not be performed if the number of patients within the subgroup is <10% of overall sample size.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

11.2. Schedule of Time and Events

Table 7: Schedule of Events – Screening and Double-Blind Treatment Period

Study Procedure	Screening Period		Part A: 16-Week Double-Blind Treatment Period					
	Screening[1, 3] V1	Screening[2] V2	Baseline V3	V4	V5	V6	V7	DB EOT[4] V8
Week (W)				W2	W4	W8	W12	W16
Day (D)	D-85 to D-1		D1	D15	D29	D57	D85	D113
Visit Window (Days [d])				±7 d	±3 d	±3 d	±3 d	+7 d
Screening/Baseline:								
Inclusion/Exclusion	X		X					
Informed Consent/Assent	X							
Informed consent/assent for optional genomic sub-study	X							
Informed consent/assent for optional future biomedical research sub-study	X							
Med History/Demographics	X							
Age in months	X	X	X	X	X	X	X	X
Randomization			X					
Treatment:								
Training for SC Injection[5]			X	X				
Administer Study Drug[6]			X	X	X	X	X	
Con Medications/Procedures	X	X	X	X	X	X	X	X
Efficacy:								
Weight, Height (or length for patients <2 years of age)	X		X	X	X	X	X	X
Pediatric EoE Sign/Symptom Questionnaire:[7] Patient version (PESQ-P) Caregiver version (PESQ-C)	◄ (Daily Diary) ►							
Pediatric EoE Impact Scale:[7] Patient version (PEIS-P) Caregiver version (PEIS-C)			X					X
Global Impression of Change:[8] Patient version (GIC-P) Caregiver version (GIC-C) Clinician version (GIC-Clin)							X	X
Global Impression of Severity:[8] Patient version (GIS-P) Caregiver version (GIS-C) Clinician version (GIS-Clin)			X				X	X

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Study Procedure	Screening Period		Part A: 16-Week Double-Blind Treatment Period					
	Screening[1, 3] V1	Screening[2] V2	Baseline V3	V4	V5	V6	V7	DB EOT[4] V8
Week (W)				**W2**	**W4**	**W8**	**W12**	**W16**
Day (D)	**D-85 to D-1**		**D1**	**D15**	**D29**	**D57**	**D85**	**D113**
Visit Window (Days [d])				**±7 d**	**±3 d**	**±3 d**	**±3 d**	**+7 d**
Pediatric Eosinophilic Esophagitis Symptom Score: [15] Caregiver version (PEESSv2.0)			X					X
Endoscopy with Biopsies and EoE-EREFS[2, 9]		X[2a]						X[2,2b]
Exit Interview [16]								X
Safety[10]:								
Vital Signs[11]	X		X[11]	X[11]	X	X	X	X
Physical Examination	X		X					X
Adverse Events	X	X	X	X	X	X	X	X
Laboratory Testing[10, 12]:								
Hematology	X		X		X			X
Chemistry	X		X		X			X
Pregnancy test (WOCBP)[13]	Serum		Urine	Urine	Urine	Urine	Urine	Urine
Urinalysis[14]	X							
PK and ADA Samples[10]:								
Functional dupilumab PK sample			X		X			X
Anti-dupilumab antibody sample			X					X
Biomarkers and Genomics:								
Serum Total IgE			X		X			
Eotaxin-3			X		X			X
Optional pharmacogenetics DNA samples (cheek swab)			X					

ADA = anti-drug antibody; EoE-EREFS = Eosinophilic Esophagitis-Endoscopic Reference Score; EOS = end of study; EOT = end of treatment; PRO = patient-reported outcome; ET = early termination; PEESS = Pediatric Eosinophilic Esophagitis Symptom Score; PESQ-P = Pediatric EoE Sign/Symptom Questionnaire (patient version); PESQ-C = Pediatric EoE Sign/Symptom Questionnaire (caregiver version); PEIS-P = Pediatric EoE Impact Scale (patient version); PEIS-C = Pediatric EoE Impact Scale (caregiver version); GIC-P = Global Impression of Change (patient version); GIC-C = Global Impression of Change (caregiver version); GIC-Clin = Global Impression of Change (clinician version); GIS-P = Global Impression of Severity (patient version); GIS-C = Global Impression of Severity (caregiver version); GIS-Clin = Global Impression of Severity (clinician version)

Table 8: Schedule of Events – Extended Active Treatment Period and 12-Week Follow-Up Period

Study Procedure	Part B: 36-Week Extended Active Treatment Period										Follow-Up Period
	V8[1]	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18 End of Study
Week (W)	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W64
Day (D)	D113	D141	D169	D197	D225	D253	D281	D309	D337	D365	D449
Visit Window (Days [d])	+7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	+7 d	±7 d
Screening for Part B:											
Inclusion/Exclusion	X										
Treatment:											
Administer Study Drug[4a, 4b]	X	X	X	X	X	X	X	X	X		
Con Meds/Procedures	X	X	X	X	X	X	X	X	X	X	X
Efficacy:											
Age in months	X	X	X	X	X	X	X	X	X	X	X
Weight, Height (or length for patients <2 years of age)[2]	X[4b]	X	X	X	X[4b]	X	X	X	X	X	X
Pediatric EoE Sign/Symptom Questionnaire:[5] Patient version (PESQ-P) Caregiver version (PESQ-C)	← (Daily Diary)										X
Pediatric EoE Impact Scale:[5] Patient version (PEIS-P) Caregiver version (PEIS-C)	X				X					X	X
Global Impression of Change:[6] Patient version (GIC-P) Caregiver version (GIC-C) Clinician version (GIC-Clin)	X				X					X	X
Global Impression of Severity:[6] Patient version (GIS-P) Caregiver version (GIS-C) Clinician version (GIS-Clin)	X				X					X	X
Pediatric Eosinophilic Esophagitis Symptom Score:[11] Caregiver version (PEESSv2.0)	X										
Endoscopy with Biopsies and EoE-EREFS[7,7a]	X[7,7a]									X[7,7a]	

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Study Procedure	Part B: 36-Week Extended Active Treatment Period										Follow-Up Period
	V8[1]	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18 End of Study
Week (W)	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W64
Day (D)	D113	D141	D169	D197	D225	D253	D281	D309	D337	D365	D449
Visit Window (Days [d])	+7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	+7 d	±7 d
Safety:											
Vital Signs[2,3,8]	X[8]	X	X	X	X	X	X	X	X	X	X
Physical Examination[2]	X									X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Hematology[2]	X				X					X	X
Chemistry[2]	X				X					X	X
Pregnancy test (WOCBP)[2,9]	urine	urine	urine	urine	urine	urine	urine	urine	urine	urine	urine
Urinalysis[2,10]	X									X	X
PK and ADA Samples:											
Functional dupilumab PK sample[2]	X				X					X	X
Anti-dupilumab antibody sample[2]	X				X					X	X
Biomarkers:											
Serum total IgE[2]	X									X	
Eotaxin-3[2]	X									X	

ADA = anti-drug antibody; EoE-EREFS = Eosinophilic Esophagitis-Endoscopic Reference Score; EOS = end of study; EOT = end of treatment; PEESS = Pediatric Eosinophilic Esophagitis Symptom Score; PRO = patient-reported outcome; PESQ-P = Pediatric EoE Sign/Symptom Questionnaire (patient version); PESQ-C = Pediatric EoE Sign/Symptom Questionnaire (caregiver version); PEIS-P = Pediatric EoE Impact Scale (patient version); PEIS-C = Pediatric EoE Impact Scale (caregiver version); GIC-P = Global Impression of Change (patient version); GIC-C = Global Impression of Change (caregiver version); GIC-Clin = Global Impression of Change (clinician version); GIS-P = Global Impression of Severity (patient version); GIS-C = Global Impression of Severity (caregiver version); GIS-Clin = Global Impression of Severity (clinician version)

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Table 9: Schedule of Events - Early Termination Visits and Unscheduled Visits

Study Procedure	ET[1] (Before Follow-up)	ET[1] (During Follow-up)	Unscheduled Visit (before Rescue Treatment)	Unscheduled Visit (For Other Reasons)
Treatment:				
Con Meds/Procedures	X	X	X	X
Efficacy:				
Age in months	X	X	X	X
Weight, Height (or length for patients <2 years of age)	X	X	X	
Pediatric EoE Sign/Symptom Questionnaire:[2] Patient version (PESQ-P) Caregiver version (PESQ-C)	← (Daily Diary)	→ X	X	
Pediatric EoE Impact Scale:[2] Patient version (PEIS-P) Caregiver version (PEIS-C)	X	X	X	
Global Impression of Change:[3] Patient version (GIC-P) Caregiver version (GIC-C) Clinician version (GIC-Clin)	X	X	X	
Global Impression of Severity:[3] Patient version (GIS-P) Caregiver version (GIS-C) Clinician version (GIS-Clin)	X	X	X	
Pediatric Eosinophilic Esophagitis Symptom Score:[6] Caregiver version (PEESSv2.0)	X		X	
Endoscopy with Biopsies with EoE-EREFS[4]	X[4, 4a]		X[4b]	
Safety:				
Vital Signs	X	X	X	
Physical Examination	X		X	
Adverse Events	X	X	X	X

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Study Procedure	ET[1] (Before Follow-up)	ET[1] (During Follow-up)	Unscheduled Visit (before Rescue Treatment)	Unscheduled Visit (For Other Reasons)
Laboratory Testing:				
Hematology	X	X		
Chemistry	X	X		
Pregnancy test (WOCBP)	urine	urine		
Urinalysis[5]	X	X		
PK and ADA Samples:				
Functional dupilumab PK sample	X	X		
Anti-dupilumab antibody sample	X	X		
Biomarkers:				
Serum total IgE			X	
Eotaxin-3			X	

ADA = anti-drug antibody; EoE-EREFS = Eosinophilic Esophagitis-Endoscopic Reference Score; EOS = end of study; EOT = end of treatment; PEESS = Pediatric Eosinophilic Esophagitis Symptom Score; PRO = patient reported outcome; PESQ-P = Pediatric EoE Sign/Symptom Questionnaire (patient version); PESQ-C = Pediatric EoE Sign/Symptom Questionnaire (caregiver version); PEIS-P = Pediatric EoE Impact Scale (patient version); PEIS-C = Pediatric EoE Impact Scale (caregiver version); GIC-P = Global Impression of Change (patient version); GIC-C = Global Impression of Change (caregiver version); GIC-Clin = Global Impression of Change (clinician version); GIS-P = Global Impression of Severity (patient version); GIS-C = Global Impression of Severity (caregiver version); GIS-Clin = Global Impression of Severity (clinician version); WOCBP = Women of childbearing potential

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Footnotes for the Schedule of Events Tables

Footnotes for Table 7

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 PPI treatment), the screening period will be extended for up to 12 weeks (day -85) to allow for at least 8 weeks of 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/imaging for EoE-EREFS/biopsy procedures should be performed after all other efficacy and safety assessments.

   2a. The baseline esophageal endoscopy with biopsies and the stomach and/or duodenum endoscopies with biopsies should be performed with sufficient time 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 PPI. Patients may be randomized as soon as their endoscopy/biopsy results are confirmed, and all other eligibility criteria are met.

   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 subsequent scheduled endoscopy/biopsy at week 16 and/or week 52.
3. Patients may be re-screened 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.
4. Assessments indicated for this week 16 (end of treatment) visit should be performed for all patients. For patients who will enter extended treatment, there are additional events listed for the week 16 visit in Table 8.
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) after all assessments are completed. Study drug administered at the study sites by site staff will be performed only by injection personnel who will not perform any clinical assessment/procedures. Study drug will be provided/dispensed for those doses scheduled to be administered at home before the next in-clinic visit. Study drug administration that occurs in clinic should occur per the Schedule of Events in Table 7 and Table 8. Parents (or caregivers) will return the study kit box (for prefilled syringes) at each subsequent in-clinic visit. Parents (or caregivers) who prefer to have the clinic staff administer study drug may choose to have injections administered in the clinic.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

7. The PESQ-P will be completed daily by patients ≥8 to <12 years of age (determined at the time of screening visit 1) just before going to bed for the night. The PESQ-C will be completed daily by caregivers of patients ≥1 to <12 years of age (determined at the time of screening visit 1) after the patients go to bed for the night. The PESQ-P and PESQ-C will be completed via an electronic diary (diary) and site personnel should conduct regular checks of patient and caregiver diary compliance. The PEIS-P and PEIS-C will be completed during site visits as indicated in the Schedule of Events table by the patients and caregivers, respectively.
8. The GIS-P, GIS-C, GIS-Clin and the GIC-P, GIC-C, and GIC-Clin will be completed by patients during site visits (≥8 to <12 years of age determined at the time of screening visit 1), caregivers (of patients ≥1 to <12 years of age determined at the time of screening visit 1), and study investigator/clinician, respectively.
9. EoE-EREFS imaging will be analyzed and scored by a central reading center. Minor esophageal features will be assessed by the investigator.
10. Assessments will be performed, and blood samples will be collected before the administration of study drug. In the event of suspected SAEs, such as anaphylaxis or hypersensitivity, functional dupilumab PK sample and anti-dupilumab antibody sample may be collected at or near the event.
11. Patients will be closely monitored at the study site at visits 3 and 4 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. Vital signs should be taken predose at all other indicated visits.
12. Tuberculosis testing will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ECs.
13. A negative result must be obtained prior to the randomization visit for all females post-menarche. 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.
14. Urinalysis is only required for patients aged ≥6 to <12 years.
15. The Pediatric Eosinophilic Esophagitis Symptom Score (PEESS) version 2.0 will be completed by caregivers of patients ≥1 to <12 years of age (determined at the time of screening visit 1).
16. Exit interviews will be conducted by a trained interviewer via telephone within 14 days of completing Week 16/Visit 8. These interviews will be completed with caregivers. Patients aged ≥8 to <12 years old (determined at the time of screening visit 1] may also join a portion of the exit interview).

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Footnotes for Table 8

1. This visit is the same as the week 16 visit for the double-blind study portion (Table 7), and all other assessments indicated for week 16 (Table 7) should be performed. Endoscopy with biopsies at visit 8/week 16 must be completed prior to administration of study drug for Part B Extended Active Treatment.
2. Study assessments will be performed, and blood samples will be collected prior to administration of study drug. In the event of suspected SAEs, such as anaphylaxis or hypersensitivity, functional dupilumab PK sample and anti-dupilumab antibody sample may be collected at or near the event.
3. 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. 4a. Study drug administration will continue through week 50.

   4b. Weight assessed at visit 8 / week 16 and visit 12 / week 32 will be used to determine weight-tiered dose for the 36-week extended active treatment period. If weight has increased at visit 12 such that the patient meets a larger weight tier, weight-tiered dosing will be re-assigned according to the patient's weight at this visit. If weight is the same or decreased at visit 12, then weight-tiered dosing will remain as originally assigned at visit 8 / week 16. The patient will remain within the original exposure dosing assignment (higher exposure group or lower exposure group). On scheduled in-clinic study visit days, study drug will be administered in the clinic (by the patient, site staff, or caregiver). Study drug administered at the study sites by site staff will be performed only by injection personnel who will not perform any clinical assessment/procedures. Study drug will be provided for those scheduled doses to be administered at home before the next in-clinic visit. Parents (or caregivers) will return the study kit box (for prefilled syringes) at each subsequent in-clinic visit. Study drug administration that occurs in clinic should occur per the Schedule of Events table. Parents (or caregivers) who prefer to have the clinic staff administer study drug may choose to have injections administered in the clinic.
5. The PESQ-P will be completed daily by patients ≥8 to <12 years of age (determined at the time of screening visit 1) just before going to bed for the night. The PESQ-C will be completed daily by caregivers of patients ≥1 to <12 years of age (determined at the time of screening visit 1) after the patients go to bed for the night. The PESQ-P and PESQ-C will be completed via an electronic diary (diary) and site personnel should conduct regular checks of patient and caregiver diary compliance. The PEIS-P and PEIS-C will be completed during site visits as indicated in the Schedule of Events table by the patients and caregivers, respectively.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

6. The GIS-P, GIS-C, GIS-Clin and the GIC-P, GIC-C, and GIC-Clin will be completed during site visits by patients (≥8 to <12 years of age determined at the time of screening visit 1), caregivers (of patients ≥1 to <12 years of age determined at the time of screening visit 1), and study investigator/clinician, respectively.
7. Endoscopy/imaging for EoE-EREFS/biopsy procedures should be performed after all other efficacy and safety assessments. Minor esophageal features will be assessed by the investigator.

   7a. 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 16 and 52.
8. 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 at visit 8.
9. 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.
10. Urinalysis is only required for patients aged ≥6 to <12 years.

11. The Pediatric Eosinophilic Esophagitis Symptom Score (PEESS) version 2.0 will be completed by caregivers of patients ≥1 to <12 years of age (determined at the time of screening visit 1).

Footnotes for Table 9

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. The PESQ-P will be completed daily by patients ≥8 to <12 years of age (determined at the time of screening visit 1) just before going to bed for the night. The PESQ-C will be completed daily by caregivers of patients ≥1 to <12 years of age (determined at the time of screening visit 1) after the patients go to bed for the night. The PESQ-P and PESQ-C will be completed via an electronic diary (diary) and site personnel should conduct regular checks of patient and caregiver diary compliance. The PEIS-P and PEIS-C will be completed during site visits as indicated in the Schedule of Events table by the patients and caregivers, respectively.
3. The GIS-P, GIS-C, GIS-Clin and the GIC-P, GIC-C, and GIC-Clin will be completed during site visits as indicated by patients (≥8 to <12 years of age determined at the time of screening visit 1), caregivers (of patients ≥1 to <12 years of age determined at the time of screening visit 1), and study investigator/clinician, respectively.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

4. EoE-EREFS imaging will be analyzed and scored by a central reading center. Minor esophageal features will be assessed by the investigator.

   4a. For patients who receive rescue treatment, endoscopy/imaging for 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 16 and 52.

   4b. Endoscopy/imaging for EoE-EREFS/biopsy will be performed only if the unscheduled visit is for the purpose of administering rescue therapy.

5. Urinalysis is only required for patients aged ≥6 to <12 years

The Pediatric Eosinophilic Esophagitis Symptom Score (PEESS) version 2.0 will only be completed by caregivers of patients >1 to <12 years of age (determined at the time of screening visit 1) an early termination and/or unscheduled visit before rescue visit(s) performed prior to visit 8 / week 16. There is no requirement to perform PEESS after visit 8 / week 16.

11.3. Criteria for Potentially Clinically Significant Values (PCSV)

Where criteria for ≥6 to <12 years are different from criteria for ≥1 to <6 years, the children criteria are provided in the [brackets] in the combined column. The criteria inside the "Combined" column will be used for display purpose in the reporting outputs. Applicable criteria will be applied to parameters collected in the study to identify treatment-emergent PCSV cases.

Parameter	≥6 to <12 years	≥1 to <6 years	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

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Parameter	≥6 to <12 years	≥1 to <6 years	Combined
Alkaline Phosphatase (ALP)	≥1.5 ULN and baseline < 1.5 ULN	≥1.5 ULN and baseline < 1.5 ULN	≥1.5 ULN and baseline < 1.5 ULN
Total Bilirubin	≥1.3 ULN and baseline < 1.3 ULN	≥1.3 ULN and baseline < 1.3 ULN	≥1.3 ULN and baseline < 1.3 ULN
Conjugated Bilirubin	(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 ≥1.3 ULN) and (Direct Bilirubin ≤35% Total Bilirubin or Total Bilirubin <1.3 ULN) at baseline	(Direct Bilirubin >35% Total Bilirubin and Total Bilirubin ≥1.3 ULN) and (Direct Bilirubin ≤35% Total Bilirubin or Total Bilirubin <1.3 ULN) at baseline
(ALT or AST) and Total Bilirubin (TBILI)	((ALT >3 ULN or AST>3 ULN) and TBILI>2 ULN) and ((ALT ≤3 ULN and AST ≤3 ULN) or TBILI ≤2 ULN) at baseline	((ALT >3 ULN or AST>3 ULN) and TBILI>2 ULN) and ((ALT ≤3 ULN and AST ≤3 ULN) or TBILI ≤2 ULN) at baseline	((ALT >3 ULN or AST>3 ULN) and TBILI>2 ULN) and ((ALT ≤3 ULN and AST ≤3 ULN) or TBILI ≤2 ULN) at baseline
Creatinine	≥90 µmol/L and baseline < 90 µmol/L ≥30% change from baseline	≥1 to <4 years: >62 µmol/L and ≤ 62 µmol/L at baseline ≥4 to <6 years: >71 µmol/L and ≤ 71 µmol/L at baseline	≥90 [≥1 to <4 years: >62; ≥4 to <6 years: >71] µmol/L and baseline < 90 [≥1 to <4 years: ≤ 62; ≥4 to <6 years: ≤ 71] µmol/L ≥30% change from baseline (≥6 to <12 years only)
Albumin	≤25 g/L and >25 g/L at baseline	NA	≤25 g/L and >25 g/L at baseline (≥6 to <12 years only)
Blood Urea Nitrogen (BUN)	≥7.14 mmol/L and <7.14 mmol/L at baseline	≥6.4 mmol/L and <6.4 mmol/L at baseline	≥7.14 [≥6.4] mmol/L and <7.14 [<6.4] mmol/L at baseline
Chloride	<80 mmol/L and ≥ 80 mmol/L at baseline ≥115 mmol/L and <115 mmol/L at baseline	≤80 mmol/L and >80 mmol/L at baseline ≥115 mmol/L and <115 mmol/L at baseline	<80 [≤80] mmol/L and baseline ≥ 80 [>80] mmol/L ≥115 mmol/L and baseline <115 mmol/L
Sodium	<129 mmol/L and ≥ 129 mmol/L at baseline ≥150 mmol/L and < 150 mmol/L at baseline	≤129 mmol/L and >129 mmol/L at baseline ≥150 mmol/L and <150 mmol/L at baseline	<129 [≤129] mmol/L and baseline ≥ 129 [>129] mmol/L ≥150 mmol/L and baseline < 150 mmol/L

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Parameter	≥6 to <12 years	≥1 to <6 years	Combined
Potassium	≤3.5 mmol/L and > 3.5 mmol/L at baseline ≥5.5 mmol/L and < 5.5 mmol/L at baseline	≤3.5 mmol/L and >3.5 mmol/L at baseline ≥5.5 mmol/L and <5.5 mmol/L at baseline	≤3.5 mmol/L and baseline > 3.5 mmol/L ≥5.5 mmol/L and baseline < 5.5 mmol/L
Calcium total	<2.0 mmol/L and ≥2.0 mmol/L at baseline ≥2.9 mmol/L and <2.9 mmol/L at baseline	≤2.0 mmol/L and >2.0 mmol/L at baseline ≥2.9 mmol/L and <2.9 mmol/L at baseline	<2.0 [≤2.0] mmol/L and ≥2.0 [>2.0] mmol/L at baseline ≥2.9 mmol/L and <2.9 mmol/L at baseline
Glucose	Hypoglycaemia: <2.7 mmol/L and ≥2.7 mmol/L at baseline Hyperglycaemia: ≥10.0 mmol/L (unfasted) and < 10.0 mmol/L (unfasted) at baseline; ≥7.0 mmol/L (fasted) and <7.0 mmol/L (fasted) at baseline	Hypoglycaemia: <2.7 mmol/L and ≥2.7 mmol/L at baseline Hyperglycaemia: ≥10.0 mmol/L (unfasted) and < 10.0 mmol/L (unfasted) at baseline; ≥7.0 mmol/L (fasted) and <7.0 mmol/L (fasted) at baseline	Hypoglycaemia: <2.7 mmol/L and ≥2.7 mmol/L at baseline Hyperglycaemia: ≥10.0 mmol/L (unfasted) and < 10.0 mmol/L (unfasted) at baseline; ≥7.0 mmol/L (fasted) and <7.0 mmol/L (fasted) at baseline
Hematology			
WBC	<5.0 Giga/L and ≥5.0 Giga/L at baseline >17.0 Giga/L and ≤17.0 Giga/L at baseline	**≥1 to <2 years**: <4.0 Giga/L and ≥ 4.0 Giga/L at baseline >20.0 Giga/L and ≤20.0 Giga/L at baseline **≥2 to <6 years:** <3.0 Giga/L and ≥ 3.0 Giga/L at baseline >16.0 Giga/L and ≤ 16.0 Giga/L at baseline	<5.0 [≥1 to <2 years: <4.0; ≥2 to <6 years: <3.0] Giga/L and ≥5.0 [≥1 to <2 years: ≥ 4.0; ≥2 to <6 years: ≥ 3.0] Giga/L at baseline >17.0 [≥1 to <2 years: >20.0; ≥2 to <6 years: >16.0] Giga/L and ≤17.0 [≥1 to <2 years: ≤20.0; ≥2 to <6 years: ≤ 16.0] Giga/L at baseline
Lymphocytes (ALC)	<1.0 Giga/L and ≥1.0 Giga/L at baseline >8.0 Giga/L and ≤8.0 Giga/L at baseline	<1.0 Giga/L and ≥ 1.0 Giga/L at baseline >10.5 Giga/L and ≤10.5 Giga/L at baseline	<1.0 Giga/L and ≥1.0 Giga/L at baseline >8.0 [>10.5] Giga/L and ≤8.0 [≤10.5] Giga/L at baseline
Neutrophils	<1.2 Giga/L and ≥1.2 Giga/L at baseline >ULN and baseline ≤ ULN	<1.2 Giga/L and ≥ 1.2 Giga/L at baseline	<1.2 Giga/L and ≥1.2 Giga/L at baseline >ULN and baseline ≤ ULN (≥6 to <12 years 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)

Parameter	≥6 to <12 years	≥1 to <6 years	Combined
Monocytes	>0.7 Giga/L and ≤ 0.7 Giga/L at baseline	NA	>0.7 Giga/L and ≤ 0.7 Giga/L at baseline (≥6 to <12 years only)
Hemoglobin	<100 g/L and ≥100 g/L at baseline or any decrease ≥ 20 g/L ≥200 g/L and <200 g/L at baseline	**≥1 to <2 years:** <90 g/L and ≥ 90 g/L at baseline or any decrease ≥ 20 g/L **≥2 to <6 years:** <100 g/L and ≥ 100 g/L at baseline or any decrease ≥ 20 g/L	<100 [≥1 to <2 years: < 90] g/L and ≥100 [≥1 to <2 years: ≥ 90] g/L at baseline or any decrease ≥ 20 g/L ≥200 g/L and <200 g/L at baseline (≥6 to <12 years only)
Hematocrit	< 32% and ≥ 32% at baseline >47% and ≤ 47% at baseline	**≥1 to <2 years:** < 29% and ≥ 29% at baseline > 42% and ≤ 42% at baseline **≥2 to <6 years:** < 32% and ≥ 32% at baseline > 47% and ≤ 47% at baseline	< 32% [≥1 to <2 years: < 29%] and ≥ 32% [≥1 to <2 years: ≥ 29%] at baseline >47% [≥1 to <2 years: > 42%] and ≤ 47% [≥1 to <2 years: ≤ 42%] at baseline
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
Urinalysis			
Ketonuria	Presence and absence at baseline	NA	Presence and absence at baseline (≥6 to <12 years only)
Glycosuria	Presence and absence at baseline	NA	Presence and absence at baseline (≥6 to <12 years only)
Microscopic Hematuria	>5 RBCs/hpf and ≤5 RBCs/hpf at baseline	NA	>5 RBCs/ hpf and ≤5 RBCs/ hpf at baseline (≥6 to <12 years only)
Proteinuria	≥ 1+ and <1+ at baseline	NA	≥ 1+ and <1+ at baseline (≥6 to <12 years only)
Vital Signs			
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	**≥1 to <3 years**: ≤63 bpm and decrease from baseline ≥20 bpm ≥140 bpm and increase from baseline ≥20 bpm **≥3 to <6 years**: ≤59 bpm and decrease from baseline ≥20 bpm ≥140 bpm and increase from baseline ≥20 bpm	≤50 [≥1 to 3 years: ≤63; ≥3 to <6 years: ≤59] bpm and decrease from baseline ≥20 bpm ≥120 [≥140] bpm and increase from baseline ≥20 bpm

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Parameter	≥6 to <12 years	≥1 to <6 years	Combined
SBP	≤80 mmHg and decrease from baseline ≥20 mmHg ≥120 mmHg and increase from baseline ≥ 20 mmHg	**≥1 to <3 years**: ≤70 mmHg and decrease from baseline ≥20 mmHg ≥116 mmHg and increase from baseline ≥20 mmHg **≥3 to <6 years**: ≤70 mmHg and decrease from baseline ≥20 mmHg ≥121 mmHg and increase from baseline ≥20 mmHg	≤80 [≤70] mmHg and decrease from baseline ≥20 mmHg ≥120 [≥1 to 3 years: ≥116; ≥3 to <6 years: ≥121] mmHg and increase from baseline ≥ 20 mmHg
DBP	≤48 mmHg and decrease from baseline ≥10 mmHg ≥72 mmHg and increase from baseline ≥ 20mmHg	**≥1 to <3 years**: ≤34 mmHg and decrease from baseline ≥10 mmHg ≥77 mmHg and increase from baseline ≥10 mmHg **≥3 to <6 years**: ≤34 mmHg and decrease from baseline ≥10 mmHg ≥83 mmHg and increase from baseline ≥10 mmHg	≤48 [≤34] mmHg and decrease from baseline ≥10 mmHg ≥72 [≥1 to 3 years: ≥77; ≥3 to <6 years: ≥83] mmHg and increase from baseline ≥ 20 mmHg [≥ 10 mmHg]
Temperature	Rectal, ear (Tympanic): >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 (Tympanic): >102.2 °F/39.0 °C Oral or pacifier: >102.2°F/39.0°C Axillary or skin infrared (temporal): >102.2°F/39.0°C	Rectal, ear (Tympanic): >100.4 °F/38.0 °C [>102.2 °F/39.0 °C] Oral: >99.5 °F/37.5 °C [>102.2°F/39.0°C] Axillary or skin infrared (temporal): >99 °F/37.2 °C [>102.2°F/39.0°C]
Respiratory rate	<16 per minutes and ≥16 per minute at baseline >30 per minute and ≤30 per minute at baseline	<20 per minute and ≥20 per minute at baseline >34 per minute and ≤34 per minute at baseline	<16 [<20] per minute and ≥16 [≥ 20] per minute at baseline >30 [> 34] per minute and ≤30 [≤ 34] per minute at baseline
Weight	≥5 % weight loss from baseline	≥5 % weight loss from baseline	≥5 % weight loss from baseline

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

11.4. Search Criteria for TEAEs of Special Interest

AESI Category	Search Criteria
Anaphylactic reactions	Narrow SMQ for anaphylactic reaction
Systemic hypersensitivity reactions	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
Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)	HLT = Eosinophilic disorders PT = Eosinophil count increased Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock.
Any severe type of conjunctivitis or blepharitis	Broad CMQ conjunctivitis PTs 1. Conjunctivitis 2. Conjunctivitis allergic 3. Conjunctivitis bacterial 4. Conjunctivitis viral 5. Atopic keratoconjunctivitis 6. Blepharitis 7. Dry eye 8. Eye irritation 9. Eye pruritus 10. Lacrimation increased 11. Eye discharge 12. Foreign body sensation in eyes 13. Photophobia 14. Ocular hyperaemia 15. Conjunctival hyperaemia 16. Xerophthalmia Blepharitis PTs 1. Blepharitis allergic 2. Bacterial blepharitis AND Serious AE= "Yes" OR Severity= "severe"
Keratitis	Narrow SMQ for corneal disorders
Severe injection site reactions	HLT=Injection Site Reactions AND Serious AE= "Yes" OR Severity= "severe"
Herpes simplex infection	HLT=Herpes viral infections
Arthralgia	PT=Arthralgia

Note: The search criteria are meant to assist the process of identification of TEAE of Special Interest/TEAE Syndrome. However, since these criteria might not be exhaustive in some cases or may not be specific in other cases, an additional blinded review of all PTs in the database may be performed by the medical monitor, based on medical judgement, to identify any TEAE of Special Interest/TEAE Syndrome that might have been missed by the criteria or to identify any TEAE may been inaccurately assigned as AESI by the algorithmic search.

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

11.5. EoE Histology Scoring System (EoE-HSS) Feature Evaluation Per Collins 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

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

Feature	Grade Score	Stage Score
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
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)

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

11.6. Gene Lists Comparising Each Transcriptome Endpoint

EoE diagnostic panel	Type 2 inflammation signature
CDH26	IL4
CDH20	IL13
CLDN10	IL13RA1
CTNNAL1	IL4R
DSG1	IL5
CHL1	IL33
CXCL6	TSLP
CCL26	IL25
CXCL1	CCL11
IL8	CCL13
IL5	CCL17
IL13	CCL18
CCR3	CCL24
CLC	CCL26
IL5RA	IL1RL1
CRISP2	FCER1A
FLG	FCER2
UPK1A	CCR3
SPINK7	CCR4
CRISP3	SIGLEC8
ACPP	HDC
UPK1B	PTGDS
CA2	PTGDR2
PHLDB2	CLC
MUC4	ALOX15
GCNT3	MUC5B
EPPK1	MUC5AC
ZNF365	POSTN
CITED2	DPP4
ARG1	CMA1
ALOX12	TPSAB1
IGJ	HRH1
TNFAIP6	GATA1
CFB	GATA3
HRH1	ARG1
CFI	STAT6
APOBEC3A	
MMP12	
CD200R1	
HPGDS	
FCGR3A	
FCGR3B	
RUNX2	
ALOX15	
GRK5	
SAMSN1	
PMCH	
SLC16A6	

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

EoE diagnostic panel	Type 2 inflammation signature
KCNJ2	
ANO1	
SLC26A4	
TPSAB1	
TPSB2	
CPA3	
CMA1	
NEFM	
NEFL	
PNLIPRP3	
ENDOU	
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	

VV-RIM-00185218-1.0 Approved - 01 Feb 2022 GMT-5:00

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STATISTICAL ANALYSIS PLAN
VERSION: AMENDMENT 1

Clinical Study Protocol Title:

A Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Dupilumab in Pediatric Patients with Active Eosinophilic Esophagitis

Compound:	Dupilumab (REGN668)
Protocol Number:	R668-EE-1877 Amendment 3
Clinical Phase:	Phase 3
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
Clinical Trial Manager:	[redacted]
Study Medical Director:	[redacted]
Version/Date:	Amendment 1/ June 2, 2022

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

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.

See appended electronic signature page

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VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

TABLE OF CONTENTS

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

LIST OF TABLES

LIST OF FIGURES

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Ab	Antibody
AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CCL	Chemokine (C-C motif) ligand
CMH	Cochran-Mantel-Haenszel (test)
COA	Clinical outcome assessment
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
DSQ	Dysphagia symptom questionnaire
eCRF	Electronic case report form
EDC	Electronic data capture
EDP	EoE diagnostic panel
eGFR	Estimated glomerular filtration rate
EoE	Eosinophilic esophagitis
EoE-EREFS	Eosinophilic Esophagitis-Endoscopic Reference Score
EoE-HSS	EoE Histology Scoring System
EOS	End of study (visit)
eos/hpf	Eosinophils/high power field
EOT	End of treatment
EPIT	Epicutaneous immunotherapy
ET	Early termination

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

EU	European Union
FAS	Full analysis set
FLG	Filaggrin
GIC	Global Impression of Change
GIS	Global Impression of Severity
ICF	Informed consent form
ICH	International Council for Harmonisation
IFN-γ	Interferon-gamma
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
IHC	Immunohistochemistry
IL	Interleukin
IL-4Rα	Interleukin-4 receptor alpha
IVRS/IWRS	Interactive voice/web response system
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel-Haenszel
NAb	Neutralizing antibody
NES	Normalized Enrichment Scores
OIT	Oral immunotherapy
PCSV	Potentially clinically significant value
PEESS	Pediatric Eosinophilic Esophagitis Symptom Score
PEIS	Pediatric EoE Impact Scale
PESQ	Pediatric EoE Sign/Symptom Questionnaire
PK	Pharmacokinetic
PPI	Proton pump inhibitor
PT	Preferred term (MedDRA)
QOL	Quality of life
Q2W	Once every 2 weeks

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

QW	Once weekly
RBC	Red blood cell
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis software
SC	Subcutaneous
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
SOC	System organ class
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
Th2	Type 2 helper T cell
ULN	Upper limit of normal
WBC	White blood cell
WH	Wilson-Hilferty
WOCF	Worst observation carried forward

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

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 data analysis of R668-EE-1877.

This plan will be finalized prior to the data lock for the end of Part A of study R668-EE-1877, i.e., the last patient reaching the week 16 visit in Part A.

1.1. Background/Rationale

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease characterized by esophageal dysfunction and eosinophilic inflammation in the esophagus; it is thought to be triggered by an abnormal type 2 immune response to food allergens (Furuta, 2017) (Liacouras, 2011). Chronic esophageal inflammation leads to progressive remodeling, stricture formation, and fibrosis (Hirano, 2014) (Schoepfer, 2014) (Dellon, 2018). Although considered a rare disease, the current prevalence is estimated at 22.7 people per 100,000 worldwide (Arias, 2016) and appears to be on the increase (Dellon, 2014). Eosinophilic esophagitis has been reported in all ages; however, most cases are in children and adults younger than 50 years (Dellon, 2014) (Dellon, 2007) (Kapel, 2008) (Liacouras, 2011) (Spergel, 2009). Children under the age of 18 represent approximately 30% of the EoE patient population (Dellon, 2014) (Prasad, 2009). The primary clinical manifestations of EoE in both adults and children over 10 years of age are dysphagia and food impaction (Lucendo, 2017). Clinical features in younger children are non-specific in nature and vary significantly depending on the patient's age and ability of the patient to describe salient symptoms. Infants and toddlers are more likely to present with feeding difficulties, vomiting, or regurgitation with the potential for failure to thrive, whereas school-age children present with complaints of abdominal pain and heartburn (Iuliano, 2018). Older children with symptomatic EoE may also modify their dietary and eating behavior by taking small bites, chewing thoroughly, eating slowly, drinking copious fluids, and avoiding food consistencies that stick, which is highly suggestive of dysphagia, as this is a feeding behavior reported in adults as an attempt to prevent esophageal food impactions (Iuliano, 2018). These symptoms lead to substantially impaired quality of life (DeBrosse, 2011) (Falk, 2014) (Straumann, 2008) (Straumann, 2003). Endoscopic findings are related to the inflammation in the esophagus and consist of fixed or transient concentric rings, longitudinal furrows, white plaques, reduced mucosal vascularity, fragile or crepe-like mucosa, and strictures. Furrows and white plaques are likely the most common finding in children. Rings are not common in children, although rings and furrows are the most commonly seen in nearly half of adult patients (Singla, 2016). Some patients (particularly pediatric) may present with a normal-appearing esophagus, but still have histologically active EoE (Wechsler, 2018).

Current standard of care for children with EoE consists of food-elimination diets, off-label proton pump inhibitors (PPIs), off-label use of swallowed topical corticosteroids, and esophageal dilation. Esophageal dilation is frequently utilized to relieve dysphagia symptoms caused by esophageal strictures. Since strictures do not occur as commonly in children, esophageal dilation is not as commonly performed in children with EoE as compared to adults with EoE (Chehade, 2018) (Furuta, 2017). The standard therapies for EoE are limited by variable response rates, relapse after therapy cessation, and adverse effects on quality of life. These limitations lead to a significant unmet need for new treatments targeting key pathways driving EoE inflammation (Spergel, 2012)

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

(Greuter, 2017). Proton pump inhibitors can result in histologic remission in approximately 50% of patients with EoE (Lucendo, 2017) with the remaining patients unresponsive. Swallowed topical corticosteroids have been reported in clinical trials to induce partial clinical responses and histologic remission; however, they are not uniformly effective and may be associated with local fungal infections, as well as a risk of growth suppression and hypothalamic–pituitary–adrenal axis suppression following systemic absorption (Golekoh, 2016), limiting their use to short term.

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 immunoglobulin E (IgE) (Hamilton, 2014). Additionally, preclinical data demonstrate that treatment with dupilumab prevents infiltration of eosinophils into tissues.

Dupilumab was evaluated in adult patients with EoE in a phase 2, multicenter, double-blind, randomized, placebo-controlled study (R668-EE-1324), where substantial improvements in clinical, histologic, and endoscopic aspects of the disease were demonstrated (Hirano, 2019a). Dupilumab was well tolerated by the study patients, with safety data generally consistent with other dupilumab studies and with no new safety signals associated with use in the EoE patient population (Hirano, 2019b). These results support pursuing further development of dupilumab for the treatment of EoE in adult, adolescent, and pediatric patients. As such, a multi-part phase 3 trial evaluating the efficacy and safety of dupilumab in adult and adolescent patients with EoE (R668-EE-1774) was initiated. This study consists of three parts: Part A and Part B are 24-week treatment, randomized, double-blind, placebo-controlled study phases and Part C is a 28-week, extended active treatment phase that enrolls patients from Part A and Part B. The co-primary endpoints for the adult and adolescent study include both a validated symptom measurement utilizing the dysphagia symptom questionnaire (DSQ) and histologic evaluation. Part A of study R668-EE-1774 evaluating the once weekly (QW) regimen revealed a significant effect on both of the co-primary endpoints. In Part B of study R668-EE-1774, the dupilumab [redacted] mg weekly demonstrated a significant effect on both of the co-primary endpoints and clinically meaningful improvements in other secondary histological, endoscopic, molecular and other patient reported outcomes. Although dupilumab [redacted] mg Q2W dosing regimen showed significant improvement in the histologic primary endpoint over a 24-week treatment period, dupilumab [redacted] mg Q2W did not show improvement in EoE disease symptoms compared with placebo even though, the magnitude of improvements in all other secondary histologic, endoscopic, and molecular endpoints of EoE were similar to the ones observed with the dupilumab [redacted] mg QW dosing regimen. Histological and molecular evidence suggest that the disease has the same underlying pathogenesis across age groups and responds similarly to swallowed topical corticosteroid treatment regardless of age (Straumann, 2012). Therefore, for the pediatric trial, where symptoms are heterogeneous, success of the trial will be determined by histologic measures; however, symptom assessments will be evaluated through secondary and exploratory endpoints.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Study R668-EE-1877 is a randomized, 2-part, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in pediatric EoE patients aged ≥ 1 year to <12 years. Children with active EoE, aged ≥1 year to <12 years, who are PPI non-responsive as determined by esophageal histology, will be randomized 2:2:1:1 to receive either a higher exposure dupilumab dose regimen (n=30) or a lower exposure dupilumab dose regimen (n=30) (in a weight-tiered dosing schema) or a higher exposure-matched placebo (n=15) or a lower exposure-matched placebo (n=15) over 16 weeks (Figure 1). Primary efficacy will be assessed by a histological endpoint: proportion of patients with histologic remission (≤6 eos/hpf). A total sample size of 90 patients is based on the number of patients to inform the primary efficacy histological endpoint and to characterize the safety profile of dupilumab in pediatric patients with EoE.

1.2. Study Objectives

1.2.1. Primary Objectives

To demonstrate the efficacy of dupilumab treatment compared with placebo in pediatric patients aged ≥ 1 year to <12 years with active EoE based on histologic improvement meeting validated histologic criteria.

1.2.2. Secondary Objectives

The secondary objectives of the study are:

- To demonstrate the efficacy of dupilumab compared to placebo in pediatric patients with active EoE after 16 weeks of treatment as assessed by endoscopic visual measurements of disease activity using the Eosinophilic Esophagitis-Endoscopic Reference Score (EoE-EREFS) and histologic abnormalities as measured by the EoE Histology Scoring System (EoE-HSS)
- To evaluate the safety, tolerability, and immunogenicity of dupilumab treatment for up to 16 weeks in pediatric patients with active EoE
- To evaluate the effects of dupilumab on transcriptomic signatures associated with EoE and type 2 inflammation
- To study the effects of dupilumab on the type 2 inflammation gene expression signature
- To evaluate the concentration-time profile of functional dupilumab in serum in this population
- To assess efficacy of long-term (52 weeks) dupilumab treatment
- To assess safety, tolerability, and immunogenicity of long-term (52 weeks) dupilumab treatment
- To evaluate the impact of dupilumab treatment on EoE signs and symptoms

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

1.2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To explore impact of dupilumab treatment on health-related quality of life
- To explore impact of dupilumab on global impression of change and severity of disease
- To explore impact of dupilumab treatment on changes in weight and growth during the double-blind and extended active phases
- To conduct exploratory research to study EoE and dupilumab mechanism of action in pediatric patients, including predictive biomarker discovery and/or validation

1.2.4. Modifications from the Statistical Section in the Final Protocol

NA

1.2.5. Revision History for SAP Amendments

The purpose of this SAP amendment is to make the following revisions before the Part A database lock [redacted]:

(1) Clarification of primary analysis for primary efficacy variable

(2) Modification of hierarchical testing order

(3) Specification of supplementary analyses

Description of Change	Section Changed
To clarify the intercurrent events strategy and missing data handling, and to clarify that the CMH test will be performed on binary efficacy variables with the Mantel-Haenszel estimates provided	1. Section 5.6 Analyses of Efficacy Variables, "Table 1 Summary of Primary Estimand for Primary Endpoint and Secondary Endpoints in Part A" 2. Section 5.6.1 Analysis of Primary Efficacy Variable 3. Section 5.6.2 Analysis of Secondary Efficacy Variables
To add a supplementary analysis for the primary endpoint with patients discontinuing treatment considered as non-responders	Section 5.6.1 Analysis of Primary Efficacy Variable
To add a supplementary analysis for the secondary endpoint of change from baseline to week 16 in the proportion of days with 1 or more EoE signs, as measured by the PESQ-C	Section 5.6.2 Analysis of Secondary Efficacy Variables
To update the hierarchical testing order	Section 5.6.3 Adjustment for Multiple Comparison
To add subgroup analyses for the secondary endpoint of change from baseline to week 16 in the proportion of days with 1 or more EoE signs, as measured by the PESQ-C	Section 5.6.4 Subgroup Analysis

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

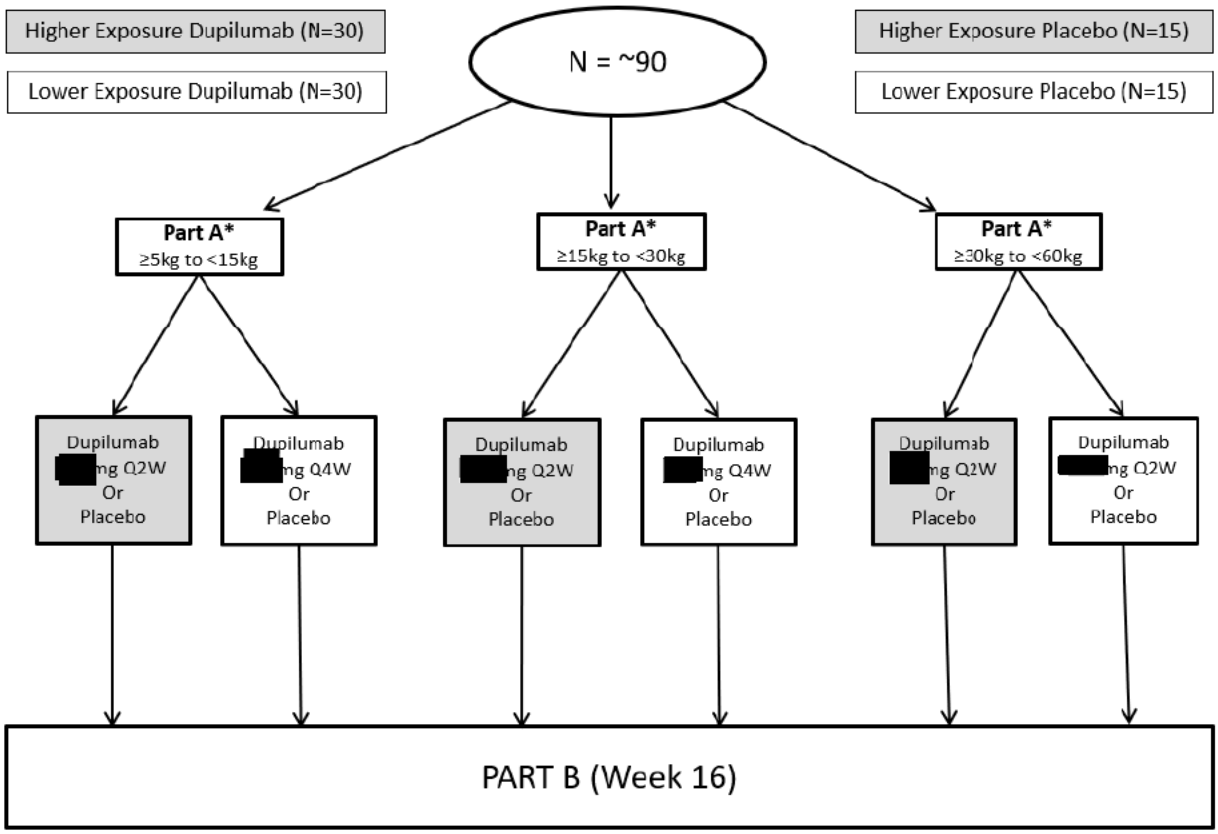
This is a phase 3, multicenter, randomized, 2-part, double-blind, placebo-controlled study investigating the efficacy, safety, tolerability, PK, and immunogenicity of dupilumab in pediatric patients (aged ≥1 to <12 years) with active EoE.

In Part A, approximately 90 patients aged ≥ 1 year to <12 years will be randomized in a 2:2:1:1 ratio to receive a higher exposure dosing regimen, a lower exposure dosing regimen of dupilumab, a higher exposure-matched placebo or a lower exposure-matched placebo for a 16-week treatment period according to a central randomization scheme provided by an IWRS to the designated study pharmacist (or qualified designee). Randomization will be stratified according to weight at baseline (≥5 kg to <15 kg, ≥15 kg to <30 kg, or ≥30 kg to <60 kg). The dosing of the placebo group will be matched with high exposure and low exposure dupilumab regimens in the respective weight tiers. Patients will remain within the originally assigned higher or lower dosing exposure arm throughout the study. At the end of Part A, eligible patients will be provided an option to enter into Part B, which is a 36-week extended active treatment period with dupilumab. All patients (Part A active and placebo) will receive dupilumab based on body weight at visit 8/week 16 per the higher- and lower-exposure dosing group to which they were assigned at randomization. Treatment assignment in Part B is managed by an IWRS to maintain blinding of treatment assignment. Since the objective of using the tiered body weight dose level approach is to maintain a uniform drug exposure, as patients grow over the course of the study if a patient's weight tier has increased at visit 12/week 32, the patient will be re-assigned to the corresponding extended active treatment regimen based on weight tier at visit 12/week 32. All patients will be followed up for an additional 12 weeks after completing Part B. Patients in Part A who are not entering Part B would enter a 12-week follow-up period immediately after Part A.

See Figure 1 and Figure 2 for Part A/Part B weight-tiered dosing regimens of study drug.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

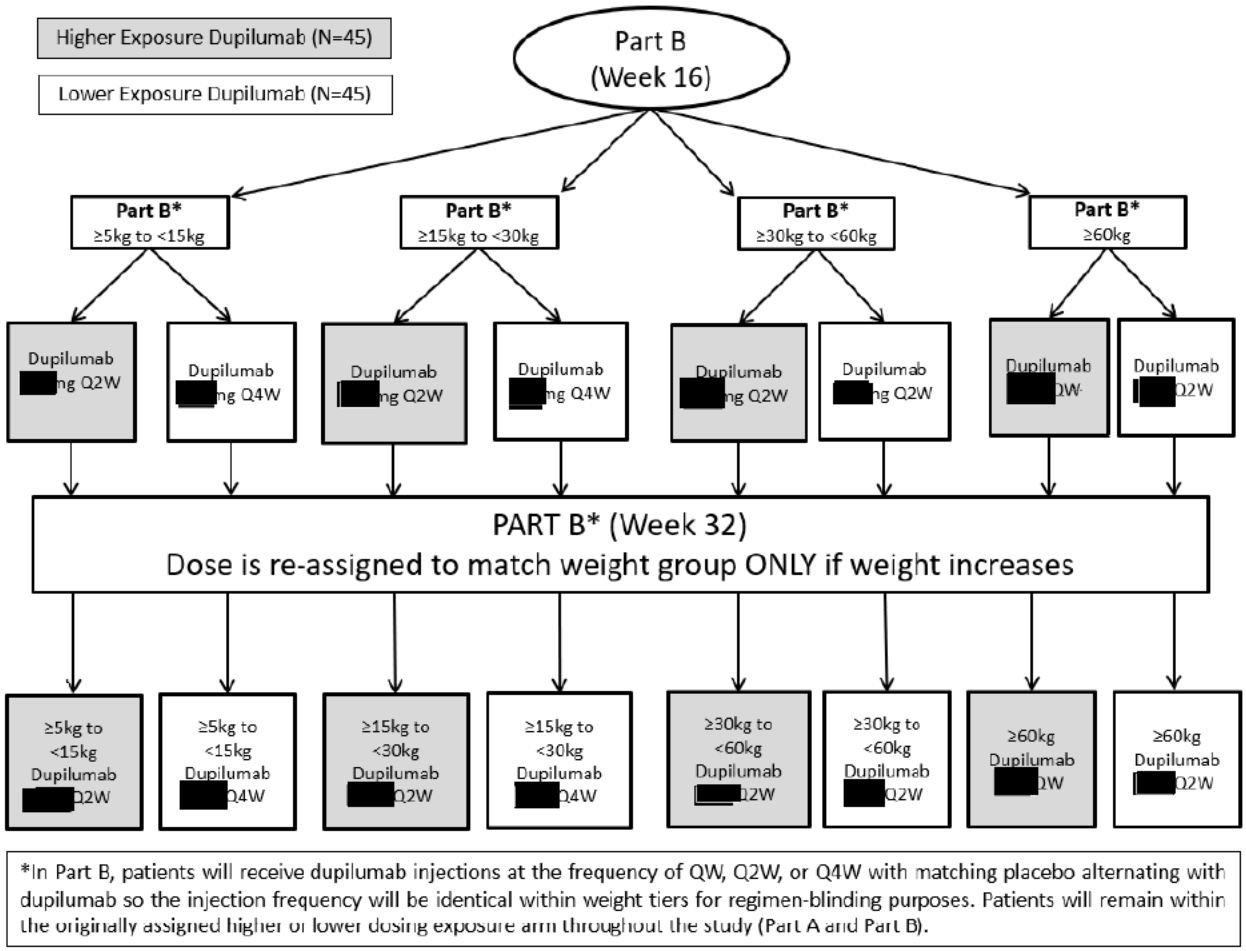
Figure 1: Part A Weight-Tiered Dosing Regimens of Study Drug



*In Part A, patients will receive dupilumab injections at the frequency of Q2W or Q4W with matching placebo alternating with dupilumab so the injection frequency will be identical within weight tiers for regimen-blinding purposes. Patients will remain within the originally assigned higher or lower dosing exposure arm throughout the study (Part A and Part B).

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Figure 2: Part B Weight-Tiered Dosing Regimens of Study Drug



*In Part B, patients will receive dupilumab injections at the frequency of QW, Q2W, or Q4W with matching placebo alternating with dupilumab so the injection frequency will be identical within weight tiers for regimen-blinding purposes. Patients will remain within the originally assigned higher or lower dosing exposure arm throughout the study (Part A and Part B).

2.2. Statistical Hypothesis

The following null hypothesis and alternative of the primary endpoint will be tested for the comparison of each dupilumab treatment group to placebo for Part A:

- Null hypothesis (H_0): The success rate (where success is achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 16) is equal between dupilumab groups (higher exposure group or lower exposure group) and placebo.
- Alternative hypothesis (H_1): The success rate differs at week 16 between dupilumab and placebo.

No formal hypothesis testing will be undertaken for Part B and hence there will be no adjustment for multiplicity for Part B.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

2.3. Sample Size and Power Considerations

The planned sample size is a total of approximately 90 patients (2:2:1:1 ratio, 30 patients in the higher exposure dupilumab group, 30 patients in the lower exposure dupilumab group, 15 patients in the higher exposure-matched placebo group, and 15 patients in the lower exposure-matched placebo group).

The assumptions used in the sample size calculation were based on Part A of the R668-EE-1774 study in adults and adolescents with EoE. Based upon the similarity of pathophysiology and expected similarity of histologic response between adults and pediatric patients, a similar proportion of responders at week 16 was assumed for sample size calculation. The lower exposure dupilumab group was assumed to have a similar treatment effect to the higher exposure dupilumab group. The treatment group difference observed in the R668-EE-1774 Part A adolescents was assumed for the sample size calculation for this study in children aged ≥1 year to <12 years. In Part A of R668-EE-1774, the proportions of patients achieving a peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24 were 59.5% and 5.1% for dupilumab and placebo, respectively. In Part A of R668-EE-1774, the proportions of adolescent patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24 were 36.4% and 0% for dupilumab and placebo, respectively. The treatment group difference observed in adolescents was approximately 36.5%. It is estimated that with a total number of 90 patients (30 patients in the higher exposure dupilumab group, 30 patients in the lower exposure dupilumab group, and 30 patients in the combined placebo group), at the 2-sided 5% significance level using Fisher's exact test, the study can provide 95% power to detect a treatment difference of 35.6% in the proportion of histologic responders (i.e., patients achieving peak esophageal intraepithelial eosinophil count ≤6 eos/hpf) at week 16 between placebo (5.1%) and each dupilumab treatment group (40.7%).

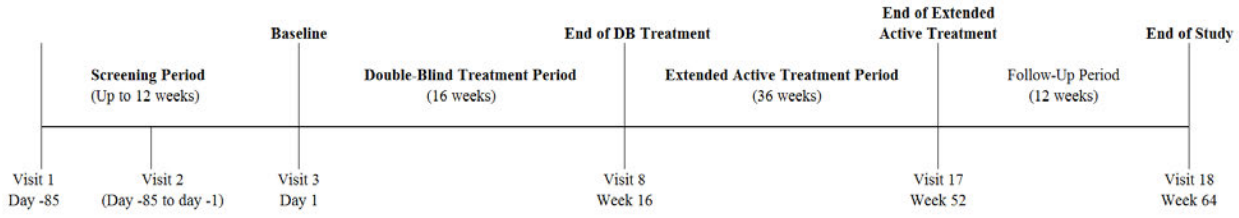
Sample size calculations were performed using nQuery Advisor 7.0.

2.4. Study Plan

Patients will undergo a screening period of up to 85 days, a double-blind 16-week treatment period (Part A), a 36-week extended active treatment period (Part B), and a 12-week follow-up period.

The study flow diagram is provided in Figure 3

Figure 3 Study Flow Diagram



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

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Patients are required to have a documented diagnosis of EoE which may be established *either* by a prior historical biopsy, as demonstrated by intraepithelial eosinophilic infiltration (peak eosinophils/high power field ≥15 eos/hpf) (400×) from at least 1 esophageal region and performed after at least 8 weeks of treatment with an approved PPI regimen, *or* by biopsies performed after approximately 8 weeks of PPI treatment initiated prior to screening or during the screening period, which demonstrates ≥15 eos/hpf) (400×) from at least 2 of the 3 esophageal regions (proximal, mid, and distal); if the PPI regimen is stopped, biopsies must occur within 2 weeks of stopping the PPI. Patients who are on PPIs during the screening period and are eligible to enroll in the study, have the choice either to remain on the PPI regimen during the entire study or stop the PPI regimen prior to baseline and then must remain off PPIs during the entire study.

Biopsies will be obtained during endoscopy at screening visit 2, at the week 16 visit, and at the week 52 visit, or immediately prior to start of rescue medication or procedures. A total of at least 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 histology (needed for study inclusion criteria, as well as endpoint assessment) and the others for RNA extraction. Biopsies will be used for exploratory research to study EoE, dupilumab mechanism of action, and to identify or validate predictive biomarkers (efficacy and/or safety). Exploratory analyses of the biopsies may include but are not limited to immunohistochemistry [IHC] and RNA sequencing (or other methods for assessing RNA expression and RNAscope).

Patients may be re-screened if they fail the screening evaluation, unless the reason for screen failure is related to histologic inclusion criteria. The baseline endoscopy with biopsies 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.

Patients who permanently discontinue from study drug will be encouraged to remain in the study. Those who agree and do not withdraw from the study will be asked to return to the clinic for all remaining study visits per the visit schedule.

At the end of the double-blind treatment period (week 16), eligible patients in Part A may enter Part B, which consists of 36-week extended active treatment. Patients who do not enter Part B will enter a 12-week follow-up period.

NOTE: If there are restrictions to the clinical study as a result of the COVID-19 pandemic, it may be necessary to adjust the visit schedule, convert in-person visits to telephone contacts, and postpone study procedures until the next available in clinic study visit. It is necessary that the randomization visit (visit 3) and the first visit of Part B occur in the clinic. Endoscopies with biopsies are required at approximately week 16 and week 52. If it is not possible to complete the endoscopies with biopsies due to COVID-19 restrictions and provided there are no specific safety concerns for the patient, patients may be allowed to continue their current study medication regimen until the endoscopies with biopsies can be performed. All temporary mechanisms utilized, and deviations from planned study procedures in response to COVID-19 will be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency. Once COVID-19 conditions resolve, all study visits and procedures should follow the schedule of events.

The study event table is presented in Section 11.2.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

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 Part A safety analysis set (SAF) is the basis for Part A safety analyses.

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

3.1. The Full Analysis Set (FAS)

For Part A, the FAS includes all randomized patients in Part A; it is based on the treatment allocated (as randomized). Efficacy endpoints in Part A (double-blind treatment period) will be analyzed using the FAS.

For Part B, the efficacy endpoints in Part B (extended active treatment period) will be summarized for all patients who received any study drug in Part B.

3.2. The Safety Analysis Set (SAF)

Part A:

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

Part B:

For safety analyses of Part B (extended active treatment period), only a subset of SAF (Part B SAF) will be included, which is defined as those patients who received at least 1 dose of Part B study drug.

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

- For a patient randomized to higher exposure dupilumab or lower exposure dupilumab, if the patient received all placebo injections in Part A, the actual treatment will be assigned as placebo.
- For a patient randomized to higher exposure dupilumab or lower exposure dupilumab, if the patient received at least one dupilumab injections in Part A, the actual treatment will be assigned as the planned treatment.
- For a patient randomized to placebo, if the patient received at least one dupilumab injections in Part A, the actual treatment will be assigned as lower exposure dupilumab.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

For safety summaries, the following analysis periods are defined:

- Part A 16-week treatment period is defined as:
  - For patients who entered Part B: Day 1 to the date of first dose of study drug for Part B Extended Active Treatment period (or week 16 visit if patient entered Part B but never received any Part B study drug)
  - For patients who did not enter Part B
    - Day 1 to week 16 visit if patients completed week 16 visit with a known visit date
    - Day 1 to study day 113 (+7 days) if patients had missing week 16 visit date, or to patients' last study participation date if patients did not complete week 16, whichever is earlier. For patients who received extended dosing in the double-blind treatment period due to the COVID-19 pandemic, and week 16 visit date is not available, 16-week treatment period will end on their last study participation date.
- Part B extended treatment period for patients who entered Part B is defined as:
  - The day after the first dose of study drug in Part B to the date of week 52 visit if patients completed week 52 with known visit date
  - The day after the first dose of study drug in Part B to study day 365 (+7 days) if patients had missing week 52 visit date, or to the last study participation date if patients did not complete week 52 visit, whichever is earlier. For patients who received extended dosing in the extended treatment period due to the COVID-19 pandemic, and week 52 visit date is not available, 36-week extended treatment period will end on their last study participation date
- Follow-up period is defined as:
  - For patients who entered Part B: the day after the end of Part B extended treatment period to the patient last study participation date
  - For patients who did not enter Part B: the day after the end of Part A 16-week treatment period to the last study participation date

The Part A and Part B SAFs will be the basis for the safety analyses for the Part A treatment period and Part B treatment period, respectively; however, for the analyses during 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 16 visit (for Part A SAF) or week 52 visit (for Part B SAF).

Due to COVID-19 pandemic, patients are allowed to extend their current assigned dose regimen of study drug (Part A and/or Part B) until endoscopy with biopsy can be performed at week 16 visit and/or week 52 visit. The safety data during the extended dosing period will also be presented in the corresponding analysis period.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

3.3. The Pharmacokinetic Analysis Set (PKAS)

The PK analysis population includes all patients who received any study drug and who had at least 1 non-missing result following the first dose of study drug. The PK analysis set is based on the actual treatment received (as treated) rather than as randomized.

3.4. The Immunogenicity Analysis Set

The ADA analysis set (AAS) includes all patients who received any amount of study drug (active or placebo [safety analysis set]) and had at least one non-missing anti-drug antibody result following the first dose of study drug or placebo. The ADA analysis set is based on the actual treatment received (as treated) rather than as randomized.

The NAb analysis set includes all treated patients who received any study drug (active or placebo), have at least one non-missing anti-drug antibody result following the first dose of study drug (active or placebo), and either tested negative at all ADA sampling times or tested positive for ADA with at least one non-missing NAb result after first dose of the study drug (active or placebo). Patients who are ADA negative are set to negative and included as such in the NAb analysis set.

3.5. 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 primary efficacy and safety analyses:

- Age group (years; ≥1- <6, ≥6 -<12; ≥1- <8, ≥8 -<12)
- Sex (Male, Female)
- Duration of EoE (years from start date of EoE to randomization date; <5, ≥5)
- Baseline weight group (≥5 - <15 kg, ≥15- <30 kg, ≥30- <60 kg)
- Prior use of swallowed topical steroids (STC) for the treatment of EoE (Yes, No)
- Inadequate response, intolerant and/or contraindicated to swallowed topical corticosteroids (STC) (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)

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Subgroups to be considered for primary efficacy endpoint only:

- Baseline BMI group (kg/m^2; overweight: ≥85 percentile of BMI for ≥2 years based on age and gender, ≥95 percentile of weight based on length (height), age and gender for <2 years, not overweight: not meeting the criteria of overweight) [based on CDC (Center for Disease Control and Prevention) chart]
- 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)

Subgroup to be considered for selected secondary efficacy endpoints only (details are in Section 5.6.4):

- Prior use of swallowed topical steroids (STC) for the treatment of EoE (Yes, No)

NOTE: The subgroup analysis may not be performed if the number of patients within the subgroup is <10% of overall sample size. The stratification factor is not included in the subgroup analysis of primary efficacy endpoint.

* The inadequate response, intolerant and/or contraindicated to STC subgroup is defined as

- Contraindicated to STC: patients never used STC for the treatment of EoE, and the reasons for never using STC were concomitant medical concern or contraindication (e.g., diabetes, immunomodulating treatment) or potential side-effect(s) from STC
- Inadequate response: patients had used STC for the treatment of EoE but the treatment with STC was not effective in relieving EoE symptoms
- Intolerant to STC: patients had used STC for the treatment of EoE and the treatment with STC was effective in relieving EoE symptoms, with the reasons for stopping STC for EoE being concomitant medical concern or contraindication or side effect(s)

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

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; 1-<6 years, 6-<12 years; 1-<8 years, ≥8-<12 years), Sex (Male, Female), Ethnicity with grouping (Hispanic or Latino, Not-Hispanic or Latino), Race with grouping (White, Black or African American, Asian, Other), Country, Baseline weight as a continuous variable and with grouping (kg; ≥5-<15 kg, ≥15- <30 kg, ≥30-<60 kg), Height/length (cm), and calculated BMI (kg/m^2; overweight, not overweight) [see the BMI grouping definition in Section 3.5].
- Baseline disease characteristics
  - Pediatric EoE Sign Questionnaire (PESQ-C [caregiver version]) (details of PESQ-C are in Section 4.4.2)
    - Proportion of days with 1 or more EoE signs for PESQ-C
    - Proportion of total segments within a day (night, morning, afternoon, evening) with 1 or more EoE signs for PESQ-C
    - Number of sign-free days during the 14-day period preceding baseline visit for PESQ-C
  - Pediatric EoE Symptom Questionnaire (PESQ-P [patient version]) (details of PESQ-P are in Section 4.4.2)
    - Proportion of days with 1 or more EoE symptoms for PESQ-P
    - Proportion of total segments within a day (night, morning, afternoon, evening) with 1 or more EoE symptoms for PESQ-P
    - Number of symptom-free days during the 14-day period preceding baseline visit for PESQ-P
  - Pediatric Eosinophilic Esophagitis Symptom Score (PEESSv2.0 [caregiver version])
  - Global Impression of Severity (GIS-P [patient version], GIS-C [caregiver version], GIS-Clin [clinician version]) (details of GIS-P, GIS-C and GIS-Clin are in Section 4.4.3)
  - Pediatric EoE Impact Scale (PEIS-C [caregiver version] and PEIS-P [patient version]) (details of PEIS-C and PEIS-P are in Section 4.4.3)
  - Duration of EoE as a continuous variable and with grouping (years; <5, ≥5)
  - Age at EoE onset as a continuous variable and with grouping (years; <5, ≥5)
  - Peak esophageal intraepithelial eosinophil count (eos/hpf) of three regions (proximal, mid, and distal)

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

- Mean stage score from the EoE-HSS summed over three regions (proximal, mid, and distal)
- Mean grade score from the EoE-HSS summed over three regions (proximal, mid, and distal)
- Prior use of STC for EoE (Yes, No)
- Effectiveness of prior use of STC for EoE (Yes, No)
- Inadequate response, intolerant and/or contraindicated to STC (Yes or No)
- Prior esophageal dilations (Yes, No)
- Number of prior esophageal dilations
- Patients treated with PPI at randomization (Yes, No)
- Patient on food elimination diet in past (Yes, No)
- Patient on food elimination diet at screening (Yes, No)
- Historical esophageal biopsy showing ≥15 (eso/hpf [400 ×]) after 8 weeks of high-dose PPI (Yes, No)
- Prior use of STC for EoE and prior esophageal dilation (Yes, No)
- EREFS total score
- Baseline serum total immunoglobulin E (IgE) as a continuous variable and with grouping (IU/mL; <100, ≥100)
- Baseline blood peripheral EOS as a continuous variable and with grouping (Giga/L; <0.15, ≥0.15; <0.30, ≥0.30; <0.50, ≥0.50)

4.2. Medical History

Medical history will be coded using MedDRA. The same MedDRA version will be used for Part A and Part A patients' data in Part B within the scope of DBL. Information related to EoE medical history and comorbid atopic conditions include diagnosis of EoE, atopic dermatitis, asthma, allergic rhinitis, allergic conjunctivitis, chronic rhinosinusitis, nasal polyps, food allergy, hives, contact dermatitis, 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 has ever been on a food elimination diet in the past, type of food elimination, and reason for elimination of specific food.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

4.3. Pre-Treatment/Concomitant Medication/Procedures

Medications/Procedures will be recorded from the day of informed consent until the end-of-study (EOS) visit. Medications will be coded using WHO Drug Dictionary (WHODRUG). Medications of interest include PPIs and swallowed topical/systemic corticosteroids for the treatment of EoE.

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

Concomitant medications/procedures (CM/CP): medications taken or procedures performed following the first dose of study drug through the EOS visit. This includes medications or procedures 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 3.2):

- CMs/CPs taken during the Part A 16-week double-blind treatment period
- CMs/CPs taken during the Part B 36-week extended active treatment period
- CMs/CPs taken during the 12-week follow-up period

Prohibited concomitant medications/procedures during the study:

Treatment with the following concomitant medications is prohibited through week 52 and may result in temporary or permanent discontinuation of study drug:

- Swallowed topical corticosteroids (may be used as rescue treatment of EoE)
- Systemic corticosteroids (may be used as rescue treatment of EoE)
  - NOTE: One-time use of a corticosteroid as a part of the anesthetic preparation used during each endoscopy procedure is allowed
- Systemic immunosuppressive/immunomodulating drugs (including, but not limited to, mepolizumab, omalizumab, cyclosporine, mycophenolate-mofetil, azathioprine, methotrexate, IFN-γ, or other immunomodulatory biologics)
- Treatment with an investigational drug (other than dupilumab)
- Initiation, discontinuation, or change in dosage regimen after baseline of the following medications (stable doses of these medications are allowed):
  - Proton pump inhibitors
  - Systemic leukotriene inhibitors
- Initiation, discontinuation, or change in dosage regimen of nasal and/or inhaled corticosteroids within 8 weeks prior to visit 2, visit 8, or visit 17 endoscopies with biopsies
- Initiation of SCIT, or change in dose for those patients on a stable dose of SCIT, within 1 year prior to screening
- Sublingual immunotherapy (SLIT)
- OIT
- Epicutaneous immunotherapy (EPIT)

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

- Treatment with a live (attenuated) vaccine, e.g.:
  - Chickenpox (varicella)
  - FluMist-influenza
  - Intranasal influenza
  - Measles (rubeola)
  - Measles-mumps-rubella combination
  - Measles-mumps-rubella-varicella combination
  - Mumps
  - Oral polio (Sabin)
  - Oral typhoid
  - Rubella
  - Smallpox (vaccinia)
  - Yellow fever
  - Bacille Calmette-Guerin
  - Rotavirus
  - Varicella zoster (shingles)

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 director (or medical monitor) before database locks with documented procedures.

Rescue treatments (including both medications and procedures): If medically necessary (e.g., for treatment of intolerable EoE symptoms), rescue medications (systemic and/or swallowed topical corticosteroids) or emergency esophageal dilations are allowed for study patients. An endoscopy with biopsy will be performed prior to the initiation of rescue therapy. Patients who undergo an endoscopy with biopsy due to initiation of rescue therapy will not undergo the subsequent scheduled endoscopy/biopsy at week 16 and/or week 52. Patients who receive rescue treatment during the double-blind period of the study will not be eligible for the 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

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

and will be asked to return to the clinic for all remaining study visits for the double-blind treatment period and the follow-up period and participate in all assessments for these visits except for endoscopy/biopsy, as noted above. For the purpose of primary endpoint efficacy analyses, patients who receive rescue treatment during the study will be considered treatment failures.

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 duodenum will be obtained at visit 2 in all patients to rule out alternate etiologies of esophageal eosinophilia. Gastric biopsy samples should include 2 samples from the antrum and 2 samples from the body. Duodenal biopsy samples should include 2 bulb samples and 2 from another portion of the duodenum. All randomized patients found to have stomach and/or duodenal abnormalities at baseline will have follow-up stomach and/or duodenal biopsies at week 16 and week 52.

4.4. Efficacy Variable

4.4.1. Primary Efficacy Variable

The primary endpoint is:

- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf (400×) at week 16

Peak esophageal intraepithelial eosinophil count

Peak esophageal intraepithelial eosinophil count will be measured from esophageal biopsies. Biopsies will be obtained by endoscopy at the second screening visit (visit 2), at week 16, and at week 52 visits, and immediately prior to start of rescue medication or rescue procedure and during the early termination visits. A total of at least 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 histology (needed for study inclusion criteria, as well as endpoint assessment) and the others for RNA extraction. 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. Biopsy samples for histopathological analyses will be sent to a central pathology laboratory for processing and analysis. If required by the investigator institution, biopsy samples will be processed and analyzed by the local laboratory, and the processed specimen will be sent to the central pathology laboratory for central reading. The peak esophageal intraepithelial eosinophil count at each visit is the maximum of the quantities of eosinophils in the most inflamed high power fields (hpfs) across the 3 regions. For example, if 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 will be considered as 4/hpf for week 16. 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.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

4.4.2. Secondary Efficacy Variable(s)

The secondary endpoints are:

- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf at week 16
- Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 16
- Absolute change in mean EoE grade score from the EoE-HSS from baseline to week 16
- Absolute change in mean EoE stage score from the EoE-HSS from baseline to week 16
- Absolute change in EoE-EREFS from baseline to week 16
- Change from baseline to week 16 in the proportion of days with 1 or more EoE signs as measured by the PESQ-C (for patients aged ≥1 to <12 years)
- Number of sign-free days during the 14-day period preceding week 16 as measured by the PESQ-C (for patients aged ≥1 to <12 years)
- Change from baseline to week 16 in the proportion of total segments within a day (night, morning, afternoon, evening) with 1 or more EoE signs as measured by the PESQ-C (for patients aged ≥1 to <12 years)
- Change from baseline to week 16 in the proportion of days with 1 or more EoE symptoms as measured by the PESQ-P (for patients aged ≥8 to <12 years)
- Number of symptom-free days during the 14-day period preceding week 16 as measured by the PESQ-P (for patients aged ≥8 to <12 years)
- Change from baseline to week 16 in the proportion of total segments within a day (night, morning, afternoon, evening) with 1 or more EoE symptoms as measured by the PESQ-P (for patients aged ≥8 to <12 years)
- Change in total score from baseline to week 16 as measured by the PEESSv2.0 (caregiver version) (for patients aged ≥1 to <12 years)
- Normalized Enrichment Scores (NES) for the relative change from baseline to week 16 in the EoE diagnostic panel (EDP) transcriptome signature
- NES for the relative change from baseline to week 16 in the type 2 inflammation transcriptome signature

NOTE: All the above primary and secondary endpoints assessed at week 16 for Part A will be assessed at week 52 for Part B (except for PEESSv2.0 [caregiver version]) as secondary endpoints and summarized with descriptive statistics based on the treatment assignment in the double-blind treatment period as well as the extended active treatment assignment for patients previously in the placebo group.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Eosinophilic Esophagitis Histology Scoring System (EoE-HSS)

The EoE-HSS is a recently validated histologic scoring system that measures other histological abnormalities in addition to the density of eosinophilic infiltration. It has been confirmed in adults to have external reliability and this scoring system is highly responsive to treatment (Collins, 2017) (Warners, 2018). Eosinophilic esophagitis grade and stage scores evaluate 8 features: eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, dilated intercellular spaces, surface epithelial alteration, dyskeratotic epithelial cells, and lamina propria fibrosis (absent/present). Assessment of lamina propria fibrosis may not be possible if the esophageal biopsy specimens do not contain adequate amounts of subepithelium lamina propria; in this case it will not be included in the overall EoE grade and stage scores.

Histology results will be interpreted by a pathologist at a central pathology reading center who will be blinded to the treatment assignment. Severity (grade) and extent (stage) of abnormalities will be scored using a 4-point scale (0 normal; 3 maximum change). The detailed scoring scheme for each feature is provided in Section 11.5. The mean grade or mean stage score from EoE-HSS is the ratio of the sum of the assigned score for each evaluated feature divided by the maximum possible score (maximum value is 24). For example, if each of 8 features has maximum grade of 3 for a biopsy, the mean grade score is 1 (24/24). If one feature is not evaluated, the maximum possible score is reduced by 3. Maximum possible score reduction may occur when lamina propria fibrosis is not present. If all other features are evaluable, the maximum possible score for a biopsy lacking lamina propria fibrosis is reduced from 24 to 21 because of 7 evaluated features. Both mean grade and mean stage scores will be determined for biopsies from 3 esophageal regions (proximal, mid, and distal). The algorithm of the calculation of mean grade and mean stage scores is as follows.

- The mean grade and mean stage scores summed over the 3 regions is the final score used in the primary analysis of the associated endpoints. An example table is provided below to illustrate the calculation of mean grade and mean stage scores. For example, the mean grade 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).
- If a mean score is available from at least 1 of the 3 regions, the sum of available mean scores will be used as final mean score. For example, if the mean grade score is 0.33 and 0.33 from the proximal and mid regions but missing from distal region, the final mean grade score will be 0.66 (0.33+0.33).

Feature	Esophageal region		
	Proximal	Mid	Distal
Eosinophilic inflammation	3	3	3
Basal zone hyperplasia	2	3	3
Eosinophil abscess	2	2	3
Surface layering	0	0	0
Dilated intercellular spaces	0	0	0
Surface epithelial alteration	0	0	0
Dyskeratotic epithelial cells	0	0	0
Lamina propria fibrosis	Missing due to absence	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

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Eosinophilic Esophagitis-Endoscopic Reference Score (EoE-EREFS)

The EoE esophageal characteristics will be analyzed based on the EoE-EREFS, a validated scoring system for inflammatory and remodeling features of disease using both overall scores and scores for each individual characteristic (Hirano, 2013). The EoE-EREFS utilizes a composite score using standardized methodology to assess clinical signs of EoE disease. Imaging should be collected for EoE-EREFS analysis and scoring by a centralized reading center. The proximal and distal esophageal regions will be scored separately; the score for each region ranges from 0 to 9 and the overall score ranges from 0 to 18. 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 score for each region is the sum of assigned scores for each of the above 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 the score is available only from 1 of the 2 regions, that available score is used as total score. For example, if score is 8 from the proximal region and missing from the distal region, the total score is 8.

In addition to the major features above, data for the following minor features will be assessed by the investigator:

- 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 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 screening visit 2, week 16, and week 52 or ET visits by centralized reading center. For patients who receive rescue treatment, endoscopy/imaging for EoE-EREFS/biopsy procedures will be performed prior to initiation of rescue treatment.

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, 2017). 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 (Regeneron unpublished data). The gene lists comprising the EDP and type 2 transcriptomes can be found in Section 11.6.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

A Normalized Enrichment Score (NES) is a way to generate a single numerical value to represent a complex gene expression signature. Changes in the NES score represents the overall changes in the expression of that molecular phenotype. A NES score 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 (Barbie, 2009) (Subramanian, 2005). NES of the relative change from baseline to week 16 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.

Pediatric EoE Sign/Symptom Questionnaire (PESQ)

The PESQ has a patient version (PESQ-P) and a caregiver version (PESQ-C).

PESQ-P is a patient-reported outcome measure intended to be completed independently by EoE patients ≥8 to <12 years of age.

- The PESQ-P measures of the symptoms of EoE and will be collected using an electronic diary (eDiary). Patients are asked to complete the eDiary every day just before they go to bed for the night. The symptoms measured by the PESQ-P include stomach pain, heartburn, acid reflux, regurgitation, vomiting, food refusal, and trouble swallowing food.
  - [redacted]
- Patient-reported information on the occurrence of EoE symptoms during the day or during one or more segments of the day will be used for the derivation of PESQ-P-based endpoints. [redacted]

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Symptoms	PESQ-P	
	Occurrence (Yes/No)	Symptoms occurred during time period of day [1]
Stomach pain	✓	✓
Heartburn (Burning feeling in chest)	✓	✓
Acid reflux (Acid coming up from stomach into throat)	✓	✓
Regurgitation (Food came up from stomach into mouth [but did not throw up])	✓	✓
Vomiting (Threw up)	✓	✓
Food refusal (Refused to eat a meal)	✓	✓ [3]
Trouble swallowing food	✓	✓ [3]
Food got stuck in throat [2]	✓	✓ [3]

[1] Time periods include "Last night", "This morning", "This afternoon", or "This evening" (except refused to eat a meal and trouble swallowing food).
[2] Patients are only asked if 'food got stuck in the throat' if they indicate that they had trouble swallowing food.
[3] [redacted]

PESQ-C is an observer-reported outcome measure intended to be completed independently by caregivers of all pediatric EoE patients in the study.

- The PESQ-C measures the signs of EoE and will be collected via an eDiary. Caregivers of all patients are asked to complete the eDiary every day after the patient has gone to bed for the night. The signs measured by the PESQ-C include stomach pain, heartburn, acid reflux, regurgitation, vomiting, food refusal, and trouble swallowing food.
  - [redacted]

[redacted]

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

- Caregiver-reported information on the occurrence of EoE signs during the day or during one or more segments of the day will be used for the derivation of PESQ-C-based endpoints. [redacted]

Signs [1]	**PESQ-C**	
	Occurrence (Yes/No)	Signs occurred during time period of day [2]
Stomach pain	✓	✓
Heartburn (Burning feeling in chest)	✓	✓
Acid reflux (Acid coming up from stomach into throat)	✓	✓
Regurgitation (Food came up from stomach into mouth [but did not throw up])	✓	✓
Vomiting (Threw up)	✓	✓
Food refusal (Refused to eat a meal)	✓	✓ [4]
Trouble swallowing food	✓	✓ [4]
Food got stuck in throat [3]	✓	✓ [4]

[1] For symptoms that are not directly observable by the caregiver (e.g., heartburn), caregivers may infer their occurrence through patient verbalizations, "Observers should only be asked to rate signs and behaviors that are observable, or verbalizations made by the pediatric patient on how he or she is feeling" (FDA Guidance Document, 2020).

[2] Time periods include "Last night", "This morning", "This afternoon", or "This evening" (except refused to eat a meal and trouble swallowing food).

[3] Caregivers are only asked if 'food got stuck in the throat' if they indicate that the patient had trouble swallowing food.

[4] [redacted]

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

[redacted]

Pediatric Eosinophilic Esophagitis Symptom Score (PEESS)

The Pediatric Eosinophilic Esophagitis Symptom Score (PEESS) version 2.0 (caregiver version) is a caregiver-reported outcomes measure which assesses the frequency and severity of EoE symptoms among pediatric patients (Franciosi, 2011). The PEESSv2.0 (caregiver version) consists of 20 items and has a one-month recall period. Each item has a 0-4 scale, which is transformed to 0-100 as follows: 0 = 0, 1 = 25, 2 = 50, 3 = 75, 4 = 100. The mean total PEESSv2.0 score is computed as the sum of all the item scores over the number of items answered. The total score should not be calculated if more than 50% of the total items are missing. The total PEESSv2.0 (caregiver version) score ranges from 0 to 100; higher scores indicate greater symptom burden of among pediatric EoE patients. This questionnaire will be collected on paper at baseline visit 3, week 16, or ET visit before follow-up or unscheduled visit before rescue treatment.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

4.4.3. Exploratory Variable(s)

The exploratory endpoints are:

- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤1 eos/hpf at week 16
- Percent change in total score of Pediatric EoE Impact Scale (caregiver version) (PEIS-C) from baseline to week 16 (for patients aged ≥1 to <12 years)
- Percent change in total Pediatric EoE Impact Scale (patient version) (PEIS-P) score from baseline to week 16 (for patients aged ≥8 to <12 years)

NOTE: Total score of PEIS-C or PEIS-P refers to averaging the scores of each of the individual questions, not totaling the scores from each of the individual questions.

- Change in GIC-patient, caregiver, and clinician version score

NOTE: Change in GIC for different questionnaires refers to the question itself asking the overall change of patient's/caregiver's EoE condition, not the change from baseline (the GIC is not administered at baseline).

- Change in GIS-patient, caregiver, and clinician version score
- Change from baseline in body weight for age percentile at week 16
- Change in body mass index for age z-score from baseline to week 16 for patients ≥2 years of age
- Change in weight for age z-score from baseline to week 16
- Change in weight for height z-score from baseline to week 16
- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 16 and achieving absolute change from baseline to week 16 in the proportion of days with 1 or more EoE signs as measured by PESQ-C
- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 16 and achieving percent change from baseline to week 16 in the proportion of days with 1 or more EoE signs as measured by PESQ-C
- Absolute change from baseline to week 16 in EREFS (excluding stricture)
- Absolute change from baseline to week 16 in EREFS inflammation sub-score
- Absolute change from baseline to week 16 in EREFS remodeling sub-score

NOTE: All the above exploratory endpoints assessed at week 16 will be assessed at week 52 as exploratory endpoints and summarized with descriptive statistics based on the treatment assignment in the double-blind treatment period as well as the extended active treatment assignment for patients previously in the placebo group.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Pediatric EoE Impact Scale (PEIS)

The Pediatric EoE Impact Scale (PEIS) has a patient version (PEIS-P) and a caregiver version (PEIS-C).

PEIS-P is a patient-reported outcome measure intended to be completed independently by pediatric EoE patients ≥8 to <12 years of age. The PEIS-P will assess the impact of EoE on the patient during the past 1 week. Response to each item below (except item 5) is on a 5-point scale (0 = "Never", 1 = "Almost never", 2 = "Sometimes", 3 = "Almost always", 4 = "Always"). Response to item 5 is on a 6-point scale (0 = "Never", 1 = "Almost never", 2 = "Sometimes", 3 = "Almost always", 4 = "Always", 5 = "Not applicable - I did not go to school during the past 7 days"). The PEIS-P average score is the sum of non-missing responses divided by the number of items with non-missing responses (note: response of "Not Applicable - I did not go to school during the past 7 days" is considered as missing response and not be counted in the average score). The average score could range from 0 to 4.

Item No.	Question
1	During the past 7 days, how often were you worried because of your EoE?
2	During the past 7 days, how often did you feel sad because of your EoE?
3	During the past 7 days, how often were you embarrassed in front of other people because of your EoE?
4	During the past 7 days, how often did you have difficulty sleeping at night because of your EoE?
5	During the past 7 days, how often did you have difficulty concentrating at school because of your EoE?
6	During the past 7 days, how often did you have difficulty playing with your friends because of your EoE?

PEIS-C is intended to be completed independently by caregivers of pediatric EoE patients ≥1 to <12 years of age. The PEIS-C will assess the impact of the pediatric patient's EoE on caregiver anxiety, social and professional activities, activities of daily living, and relationships during the past 1 week. Response to each item (except item 4 and 4a) is on a 5-point scale (0 = "Not at all", 1 = "Very little", 2 = "A little", 3 = "Very much", 4 = "Extremely"). If response to item 4 is "No", items 4a and 4b will be skipped and considered as missing response. The PEIS-C average score is the sum of non-missing responses divided by the number of items with non-missing responses (note: response to item 4a is not included in the score calculation). The average score could range from 0 to 4.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Item No.	Question
1	During the past 7 days, how worried were you because of your child's EoE?
2	During the past 7 days, how sad were you because of your child's EoE?
3	During the past 7 days, how much did your child's EoE limit your social activities?
4	Are you currently employed (working for pay)? (*If "Yes", go to question 4a and then 4b. If "No", go to Question 5*)
4a	During the past 7 days, how many days did you miss work because of your child's EoE
4b	During the past 7 days, how much did your child's EoE limit your productivity while you were working?
5	During the past 7 days, how much did your child's EoE limit your everyday activities (for example: house chores, going shopping)?
6	During the past 7 days, how much did your child's EoE cause problems with your personal relationships?

Global Impression of Change (GIC)

The GIC has a patient version (GIC-P), a caregiver version (GIC-C), and a clinician version (GIC-Clin).

- The GIC-P is a single-item patient-reported outcome measure intended to be completed independently by pediatric EoE patients ≥8 to <12 years of age. The GIC-P will assess the patient's impression about the overall change (improvement or worsening) in his/her EoE condition since study treatment initiation.
- The GIC-C is a single-item observer-reported outcome measure intended to be completed independently by caregivers of pediatric EoE patients ≥1 to <12 years of age. The GIC-C will assess the caregiver's impression about the overall change (improvement or worsening) in the pediatric patient's EoE condition since study treatment initiation.
- The GIC-Clin is a single-item observer-reported outcome measure intended to be completed independently by study investigator-physician of all pediatric EoE patients in the study. The GIC-Clin will assess the study investigator's/clinician's impression about the overall change (improvement or worsening) in the pediatric patient's EoE condition since study treatment initiation.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

The GIC-P, GIC-C, GIC-Clin score could range from 1 to 7.

Questionnaire	Question	Response (score)
GIC-P	Since you started getting the study injection, how would you describe the overall change in your eosinophilic esophagitis (EoE)?	A lot better (1)
		Somewhat better (2)
		A little better (3)
		No change (4)
		A little worse (5)
		Somewhat worse (6)
		A lot worse (7)
GIC-C	Since your child started getting the study injection, how would you describe the overall change in your child's eosinophilic esophagitis (EoE)?	Very much improved (1)
		Much improved (2)
		Minimally improved (3)
		No change (4)
		Minimally worse (5)
		Much worse (6)
		Very much worse (7)
GIC-Clin	Since your patient started getting the study injection, how would you describe the overall change in your patient's eosinophilic esophagitis (EoE)?	Very much improved (1)
		Much improved (2)
		Minimally improved (3)
		No change (4)
		Minimally worse (5)
		Much worse (6)
		Very much worse (7)

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Global Impression of Severity (GIS)

The GIS has a patient version (GIS-P), a caregiver version (GIS-C), and a clinician version (GIS-Clin).

- The GIS-P is a single-item patient-reported outcome measure intended to be completed independently by pediatric EoE patients ≥8 to <12 years of age. The GIS-P will assess the patient's impression about the overall severity of his/her EoE condition during the past 1 week.
- The GIS-C is a single-item observer-reported outcome measure intended to be completed independently by caregivers of pediatric EoE patients ≥1 to <12 years of age. The GIS-C will assess the caregiver's impression about the overall severity of the pediatric patient's EoE condition during the past 1 week.
- The GIS-Clin is a single-item observer-reported outcome measure intended to be completed independently by study investigator-physician of all pediatric EoE patients in the study. The GIS-Clin will assess the study investigator's/clinician's impression about the overall severity of the pediatric patient's EoE condition during the past 1 week.

The GIS-P, GIS-C, and GIS-Clin score could range from 1 to 4.

Questionnaire	Question	Response (score)
GIS-P	During the past 7 days, how bad was your eosinophilic esophagitis (EoE)?	Not bad (1)
		A little bad (2)
		Bad (3)
		Very bad (4)
GIS-C	During the past 7 days, how severe was your child's eosinophilic esophagitis (EoE)?	Mild (1)
		Moderate (2)
		Severe (3)
		Very severe (4)
GIS-Clin	Overall, how severe is your patient's eosinophilic esophagitis (EoE)?	Mild (1)
		Moderate (2)
		Severe (3)
		Very severe (4)

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Body Weight and Body Mass Index (BMI) Z-scores and Percentiles

Body weight for age z-score, body weight for age percentile, body weight for height/length z-score, and BMI for age z-score at each visit will be calculated based on the growth charts from Centers for Disease Control and Prevention (CDC) for ages 0 to 20 years (for ages 2 to <12 years) and World Health Organization (WHO) growth charts for ages 0 to <2 years (for ages 1 to <2 years). These charts included a set of smoothed percentiles along with CDC LMS (Lambda-Mu-Sigma) parameters to allow the calculation of other percentiles or z-scores (Flegal, 2013). To obtain the z-score for body weight or BMI, the following equation will be used $Z = [(X/M)^{L}-1]/(L\times S)$ for $L\neq 0$; $Z = \ln(X/M)/S$ for $L = 0$, where X is the measured body weight or BMI at each visit and L, M, and S values are from CDC table. The corresponding percentile can be obtained from standard normal distribution. The following CDC growth charts will be used. The growth chart is provided in half month intervals for age.

- Weight-for-age chart (weight in kilograms) for birth to 36 months population by sex and age
- Weight-for-age chart for 2 to 20 years population in kilograms by sex and age
- Weight-for-stature chart (weight in kilograms) by sex and stature (stature in centimeters)
- BMI for age charts for 2 to 20 years population by sex and age

For example, to obtain the weight for age z-score of a 24-month-old male who weighs 14.5 kg, the corresponding L, M, and S values in weight-for-age charts for 2 to 20 years population are -0.20615245, 12.6707633, 0.108125811, respectively. By applying the above LMS method equation z-score is 1.23 and the corresponding percentile is 89%.

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

The EREFS (excluding stricture), inflammation sub-score, and remodeling sub-score 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 sub-score	Edema + Exudates + Furrows	0 - 5	0 -10
Remodeling sub-score	Rings + Stricture	0 - 4	0 - 8

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

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 using the Medical Dictionary for Regulatory Activities (MedDRA).

The definition of adverse events and serious adverse events are provided in protocol Section 10.2.1 and Section 10.2.2. Pre-treatment AE and treatment-emergent AE (TEAE) are defined as follows:

- Pre-treatment signs and symptoms (pre-treatment AEs) are AEs that developed or worsened in severity during the pre-treatment period.
- TEAEs are defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the treatment-emergent period.
  - TEAEs for part A treatment period are defined as TEAEs with onset date during the Part A treatment period.
  - TEAEs for part B extended active treatment period are defined as TEAEs with onset during the Part B extended treatment period.
  - TEAEs for follow-up period are defined as TEAEs with onset during the follow-up period.

4.5.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) for this study include the following:

- Anaphylactic reactions
- Systemic hypersensitivity reactions
- Helminthic infections
- Any severe type of conjunctivitis or blepharitis
- Keratitis
- Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)
- Severe injection site reactions
- Herpes simplex infection
- Arthralgia

For detailed definition of these AESIs, please see Section 11.4.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

4.5.3. Laboratory Safety Variables

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory. Samples will be collected predose at time points according to visit schedule (Section 11.2). Tests will include:

Blood Chemistry

Sodium	Creatinine
Potassium	Blood urea nitrogen (BUN)
Chloride	Aspartate aminotransferase (AST)
Carbon dioxide	Alanine aminotransferase (ALT)
Calcium	Alkaline phosphatase
Glucose	Lactate dehydrogenase (LDH)
Albumin	Estimated glomerular filtration rate (eGFR)
Total protein, serum	Total and indirect bilirubin

Hematology

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

Urinalysis

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

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

Other Laboratory Tests

- Pregnancy testing will be performed for all WOCBP. Serum or urine pregnancy testing will be performed at time points listed in visit schedule (Section 11.2).
- Tuberculosis testing will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics boards.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

4.5.4. Vital Signs

Vital signs, including heart rate, blood pressure, respiration rate, and body temperature will be collected predose and 30 minutes post-dose at time points listed in the schedule of events in Section 11.2. 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. Body weight in kg and height in cm (or length for patients <2 years of age) will be measured at the time points listed in the schedule of events table in Section 11.2. Body mass index will be programmatically calculated based on the weight and height data.

4.5.5. Physical Examination Variables

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

A thorough and complete physical examination will be performed at the screening visit 1, baseline visit 3, week 16, week 52, ET visit before follow-up or unscheduled visit before rescue treatment.

4.6. Pharmacokinetic Variables

The PK variable is the concentration of functional dupilumab in serum and time for individual patients. Serum samples for measuring functional dupilumab concentrations will be collected at time points according to Section 11.2.

4.7. Immunogenicity Variables

The immunogenicity variables include ADA status, NAb status, and titer at nominal sampling time/visit. Serum samples for ADA will be collected at the clinic visits specified in Section 11.2. Samples positive in the dupilumab ADA assay will be further characterized for ADA titers and for the presence of NAb against dupilumab.

4.8. Biomarker Variables

Biomarkers to be analyzed in this study are:

- Serum total IgE
- Eotaxin-3

Serum/plasma samples for measurements of biomarkers to study the pharmacodynamic activity of dupilumab in EoE patients will be collected at time points according to Section 11.2.

4.9. Clinical Outcome Assessments for Psychometric Validity Assessment

The measurement properties of the PESQ-C and PESQ-P (as described in Section 4.4.2) will be evaluated using anchor-based methods and qualitative insights from the week 16 exit interviews. The details of the analyses are specified in the R668-EE-1877 psychometric analysis plan.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

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.

All data will be summarized by the following treatment groups in each study period:

- Part A
  - Higher exposure dupilumab dose regimen
  - Lower exposure dupilumab dose regimen
  - Combined dupilumab group (for safety analysis only)
  - Placebo
- Part B
  - Higher exposure dupilumab dose regimen/Higher exposure dupilumab dose regimen
  - Lower exposure dupilumab dose regimen/Lower exposure dupilumab dose regimen
  - Combined dupilumab group (for safety analysis only)
  - Placebo/Higher exposure dupilumab dose regimen
  - Placebo/Lower exposure dupilumab dose regimen
  - Placebo/Combined dupilumab group (for safety analysis only)
  - Total (for safety analysis only)

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 will be provided for Part B SAF patients.

5.2. Medical History

Medical history will be summarized by primary System Organ Class (SOC) and Preferred Term (PT) for each treatment group and for study total based on the FAS. The table will be sorted by decreasing frequency of SOC followed by PT based on the overall incidence across treatment groups.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

5.3. Prior/Concomitant Medications/Procedures

Number and proportion of patients taking prior/concomitant medications, prohibited medications/procedures, and rescue medications/procedures will be summarized for each treatment group and study total, based on study period specific FAS, by ATC Level 2 and ATC Level 4, sorted by decreasing frequency of ATC Level 2 and ATC Level 4 in the combined dupilumab treatment group. Patients will be counted once in each medication class linked to the medication.

Number and proportion of patients taking PPIs for the treatment of EoE will be summarized by PPI therapy name. In addition, number and proportion of patients taking swallowed topical/systemic corticosteroids for the treatment of EoE will be summarized for swallowed topical corticosteroids and systemic corticosteroids by ATC Level 2 and ATC Level 4, respectively.

Number and proportion of patients undergoing prior/concomitant procedures will be summarized for each treatment group and study total, based on the study period specific FAS, by SOC and PT, and sorted by decreasing frequency of SOC and PT in the combined dupilumab treatment group.

Separate summaries will be provided for Part A and Part B concomitant medications/procedures.

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 (including COVID-19 related reasons)
- The total number of patients who discontinued the study in Part A, and the reasons for discontinuation (including COVID-19 related reasons)
- Number of patients who entered into Part B
- The total number of patients who discontinued the study treatment in Part B, and the reasons for discontinuation (including COVID-19 related reasons)
- The total number of patients who discontinued the study in Part B, and the reasons for discontinuation (including COVID-19 related reasons)
- Number of patients who entered 12-week follow-up period from Part A and Part B, respectively

Summary table of important protocol deviations in each study treatment period will be provided.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

5.5. Extent of Study Treatment Exposure

5.5.1. Exposure to Investigational Product

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

> (Date of last study drug injection in the respective study period – date of first study drug injection in the respective study part) + 14

NOTE: exposure will be calculated based on the last study drug injection date and first study drug injection date regardless of temporary dosing interruption or dosing extension due to COVID-19. For patients with extended dosing due to COVID-19, the duration of exposure may exceed 16 weeks for Part A or 36 weeks for Part B as study design.

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 the number of patients, mean, standard deviation, median, Q1, Q3, minimum, and maximum. These summaries will be provided for Part A and Part B separately.

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

- Part A: ≥ 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, with an increment of 1 week for each subsequent category.
- Part B: ≥ 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, ≥175 days, ≥182 days, ≥189 days, ≥196 days, ≥203 days, ≥210 days, ≥217 days, ≥224 days, ≥231 days, ≥238 days, ≥245 days, ≥252 days, with an increment of 1 week for each subsequent category.

For patients who received at least 1 dose of study drug, the total duration of exposure to study drug during the study (throughout Part A and Part B) is calculated as:

> (Date of last study drug injection in the study – date of first study drug injection) + 14

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

> (Date of last study visit – date of first study injection) + 1

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

The duration of observation period will be summarized descriptively using number of patients, mean, standard deviation, median, Q1, Q3, minimum, and maximum. In addition, the number (n) and proportion (%) of patients with observation periods will be presented by specific time periods. The time periods of interest are specified as follows:

- Part A: ≥ 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, with an increment of 1 week for each subsequent category.
- Part B: ≥ 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, ≥176 days, ≥183 days, ≥190 days, ≥197 days, ≥204 days, ≥211 days, ≥218 days, ≥225 days, ≥232 days, ≥239 days, ≥246 days, ≥253 days, with an increment of 1 week for each subsequent category.

5.6. Analyses of Efficacy Variables

The analyses of efficacy variables are described in the subsections below and summarized in Section 11.1. The intercurrent events, strategies, and the corresponding missing data handling approaches for the primary estimand of interest for the primary endpoint are provided in Table 1 .

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Table 1: Summary of Primary Estimand for Primary Endpoint and Secondary Endpoints in Part A

Endpoint Category	Estimands			
	Endpoint(s)	**Population**	**Intercurrent event(s) strategy and missing data handling**	**Population-level summary/Analysis**
Primary Endpoint	Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf (400×) at week 16	FAS	The intercurrent events will be handled as follows: • Treatment discontinuation: data collected after the patient discontinued treatment will be included in the analysis (treatment policy strategy) • Initiation of treatment with systemic and/or swallowed topical corticosteroids drugs and dilation: patients will be considered as non-responders after such event (composite variable strategy) Note: the composite strategy will be considered if a patient receives rescue treatment [a] any time during the study. Missing data handling: patients with a missing value for the primary endpoint at week 16 due to study discontinuation or other reasons will be considered non-responders. Missing data due to COVID-19 will be imputed by multiple imputation (MI).	Cochran-Mantel-Haenszel (CMH) test adjusting for the randomization stratification factor (baseline weight group) will be utilized. The Mantel-Haenszel estimate of odds ratios between each of dupilumab groups and placebo, and its 2-sided 95% confidence intervals will be provided.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Endpoint Category	Estimands			
	Endpoint(s)	**Population**	**Intercurrent event(s) strategy and missing data handling**	**Population-level summary/Analysis**
Secondary Endpoints	Binary endpoints (e.g., proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf at week 16)	FAS	The intercurrent events strategy and missing data handling methods will be the same with the primary endpoint.	The primary analysis method will be the same as for the primary endpoint.
	Continuous endpoints that are scheduled to be measured repeatedly post-baseline up to week 16 (e.g., change in the proportion of days with 1 or more EoE signs from baseline to week 16 as measured by the PESQ-C)	FAS	The intercurrent events will be handled as follows: • Treatment discontinuation: data collected after the patient discontinued treatment will be included in the analysis (treatment policy strategy) • Initiation of treatment with systemic and/or swallowed topical corticosteroids drugs and dilation: data after such events will be assigned by the worst observed value (composite variable strategy) Missing data handling: after discontinuation of the study due to AE/lack of efficacy [b] prior to week 16, patients with a missing value at week 16 will be imputed using WOCF method, and MI approach will be used for the missing data due to other reasons.	Continuous secondary efficacy endpoints at week 16 will be analyzed using an analysis of covariance (ANCOVA) model with treatment groups, randomization stratification factor, and relevant baseline measurement as a covariate included in the model. The least square (LS) means and difference in LS means between dupilumab groups and placebo will be presented.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Endpoint Category	Estimands			
	Endpoint(s)	**Population**	**Intercurrent event(s) strategy and missing data handling**	**Population-level summary/Analysis**
	Continuous endpoints that are scheduled to be measured only once post-baseline up to week 16 (e.g., absolute change in EoE-EREFS from baseline to week 16)	FAS	The intercurrent events will be handled as follows: • Treatment discontinuation: data collected after the patient discontinued treatment will be included in the analysis (treatment policy strategy) • Initiation of treatment with systemic and/or swallowed topical corticosteroids drugs and dilation: data after such events will be assigned by the worst observed value (composite variable strategy) Missing data handling: patients with a missing value due to COVID-19 will be imputed using MI approach, and WOCF method will be used for missing not due to COVID-19. WOCF method refers to missing values at week 16 will be imputed with patient's baseline value or the available post-baseline value, whichever is worse.	

[a]: The rescue treatment(s) include systemic and/or swallowed topical corticosteroid drugs and esophageal dilation. Blinded adjudication (blinded to the treatment assignment) of rescue treatment(s) will be performed by medical director (or medical monitor) prior to the Part A database lock.

[b]: Patients who are discontinued from the study due to AE or lack of efficacy are captured in the case report form "Study Completion".

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

5.6.1. Analysis of Primary Efficacy Variable

The primary analysis of proportion of patients achieving a histologic response of peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 16 will be analyzed using the Cochran-Mantel-Haenszel (CMH) test (chi-squared test based on the odds ratio), adjusting for the randomization stratification factor (baseline weight group [≥5 - <15 kg, ≥15- <30 kg, ≥30- <60 kg]). The randomization stratification of baseline weight group may be pooled to ensure the sufficient sample size of each stratum. The pooling algorithm of the baseline weight group will be applied if the number of patients in one of the treatment arms in a baseline weight group is ≤ 4. In this case the weight group will be pooled with an adjacent tiered weight group that has the least number of patients in that weight group (e.g. if the number of patients in >=15-<30kg weight group is ≤ 4 in one of the treatment arms, the weight group will be pooled with the smaller of either the >=5-<15kg weight group or the <=30 kg weight group). Estimates of odd ratios and its 95% confidence intervals (CI) will be presented along with the p-values between each dupilumab group and placebo. In addition, the estimates of treatment difference and its 95% CI will be provided based on the Mantel-Haenszel (MH) method.

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

To account for the use of rescue treatment, patients will be considered as non-responder for all time points subsequent to the use of rescue treatment in the primary analysis.

If week 16 biopsy is performed after the date when the first dose of Part B study drug is administered, patients will be considered as non-responder in the analysis.

Due to COVID-19 restrictions, patients may postpone the week 16 visit until an in-clinic visit can be done for biopsy. Before the biopsy procedure could be performed, study drug would be shipped to patients directly to enable them to extend their current assigned dose regimen of study drug. The data from those delayed week 16 visits will be used in the primary analysis as long as the patients keep the extended dosing before biopsy. If patients whose extended dosing due to COVID-19 is interrupted (ie. investigational product not administered for 4 consecutive weeks or missing >=3 total injections for non-safety reasons), their week 16 biopsy data will be set to missing and imputed using multiple imputation (MI).

Missing data at week 16 will be handled according to the reasons for missingness as follows:

- If the peak esophageal intraepithelial eosinophil count at week 16 is missing due to COVID-19 pandemic, the data will be imputed by multiple imputation (MI) using a seed number of 6681877 for 10 times based on patients who have non-missing eosinophil counts at week 16. The MI will utilize the regression method with treatment group, randomization stratification factor, baseline eosinophil count as covariates and week 16 eosinophil count as response variable in the regression model. The imputed week 16 eosinophil counts 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 16 due to reasons not related to the COVID-19 pandemic (e.g., discontinuation from study), the patient will be classified as a non-responder at week 16.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Each of the imputed complete datasets will be analyzed by the CMH test. The estimates of odds ratios will be log-transformed to normalize these estimates before applying Rubin's formula. The Wilson-Hilferty (WH) (Wilson & Hilferty, 1931) transformation will be used to normalize test statistics before combining result of the CMH test. Statistical inference obtained from the Wilson-Hilferty transformed statistics of all imputed data will be combined using Rubin's formula (Ratitch, 2013). See Appendix 11.7 for the Statistical Analysis Software (SAS) syntax code for the multiple imputation and the analysis.

Sensitivity analyses

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

1. **Tipping point analysis approach**: To assess the robustness of analysis results under MNAR (missing not at random) assumption, a delta-adjusting pattern-mixture approach for tipping point analysis (Ratitch, 2013) will be conducted for the primary endpoint. The impact from missing data due to study discontinuation or other reasons on the comparisons in proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 16 between each dupilumab group and placebo control group will be examined, by adjusting for stratification factor:
    - A series of analyses will be performed by applying a specified sequence of different values of shift parameter to the 3 treatment groups for the data imputation: in the placebo group, different values (>0) of shift parameter will be subtracted from the imputed peak eosinophil count; in each of dupilumab group, different values (<0) of shift parameter will be added to the imputed peak eosinophil count. The imputed peak eosinophil count which is negative will be replaced by 0. Patients who achieve peak eosinophil count of ≤6 eos/hpf will be derived based on the imputed peak eosinophil count after shifting.
    - For each combination of different values of shift parameter applied to the 3 treatment groups, 10 multiple imputed datasets will be generated using a seed number of 6681877. Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf will be analyzed using CMH test. The results obtained from 10 multiple imputed datasets will be combined using Rubin's formula (Ratitch, 2013) for statistical inference, i.e., p-value and treatment difference between active treatment groups and placebo group.
    - A "tipping point" will be identified when the result is no longer statistically significant (i.e., p-value >0.05).
2. **Worst observation carried forward - multiple imputation (WOCF-MI) approach**: Data after rescue treatment or the missing peak esophageal intraepithelial eosinophil count at week 16 due to AE/lack of efficacy will be imputed with patient's baseline value or the available post-baseline value up to week 16, whichever is worse, i.e., WOCF. The missing data due to other reasons will be imputed by MI using a seed number of 6681877 for 10 times based on patients who have non-missing eosinophil counts at week 16. The imputed week 16 eosinophil counts will determine whether that patient will be classified as a responder or non-responder. The 10 complete datasets after the imputations will be

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

analyzed using CMH test. The results from the 10 analyses will be combined using the SAS MIANALYZE procedure (Ratitch, 2013).

Supplementary analysis

A supplementary analysis will be performed to consider the composite strategy for treatment discontinuation, in which the patient will be considered as a non-responder after treatment discontinuation regardless of the reason for discontinuation.

5.6.2. Analysis of Secondary Efficacy Variables

Binary endpoints at week 16

Secondary efficacy endpoints that measure binary responses at week 16 will be analyzed in the same fashion as the primary endpoint, including the method to handle missing data.

Continuous endpoints at week 16

Continuous secondary efficacy endpoints at week 16 will be analyzed using an analysis of covariance (ANCOVA) model for the FAS with treatment groups, randomization stratification factor, and relevant baseline measurement as a covariate included in the model. For endoscopy/biopsy-based endpoints (i.e., esophageal intraepithelial eos count, EoE-EREFS, EoE-HSS), if week 16 endoscopy/biopsy is performed after the date when the first dose of Part B study drug is administered, data from that endoscopy/biopsy will be set to missing in the analysis.

To account for the use of rescue treatment, data will be set to missing for all time points subsequent to the use of rescue treatment.

For continuous efficacy data that are scheduled to be measured repeatedly post-baseline up to week 16 (e.g., change in the proportion of days with 1 or more EoE signs from baseline to week 16 as measured by the PESQ-C), missing data will be imputed by the pattern-mixture approach. Specifically, the WOCF-MI approach, where the WOCF approach will be used for imputing the missing data if data are missing subsequent to rescue treatment or discontinuation of study due to AE/lack of efficacy as captured in CRF "Study Completion"; the MI approach will be used for the missing data due to other reasons (e.g., missing PESQ-C data due to less than 8 diary entries for the 14-day period). The rescue treatment(s) include systemic and/or swallowed topical corticosteroids drugs and esophageal dilation. Blinded adjudication (blinded to the treatment assignment) of rescue treatment(s) will be performed by medical director (or medical monitor) prior to the Part A database lock.

MI will follow the steps below using a seed number of 6681877 in both steps:

- Step 1: Use the Markov Chain Monte Carlo (MCMC) method to fill in the intermittent missing values so that a monotone missing pattern will be formed.
- Step 2: For each of the imputed datasets with monotone missing pattern in Step 1, the remaining missing data will be imputed using regression method with treatment group, randomization stratification factor, relevant baseline measurement as a covariate, and the post-baseline measurements up to week 16 as response variable.
- Step 3: Each of the 40 imputed datasets will be combined with the dataset imputed by WOCF approach, and then analyzed using the ANCOVA.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

- Step 4: The results from the 40 analyses on the complete datasets will be combined to generate a valid overall statistical inference using Rubin's formula (Ratitch, 2013). The least square (LS) means and difference in LS means between dupilumab groups and placebo will be presented.

The cumulative distribution function (CDF) of the absolute change from baseline in the proportion of days (or total segments within a day) with 1 or more EoE signs as measured by the PESQ-C at week 16 and from baseline in the proportion of days (or total segments within a day) with 1 or more EoE symptoms as measured by the PESQ-P at week 16 will be graphed to present the between-treatment-group differences at each level of the change.

For continuous efficacy data that are scheduled to be measured only once post-baseline up to week 16 (e.g., absolute change in EoE-EREFS from baseline to week 16), a hybrid approach WOCF-MI will be used to handle missing data. That is, missing values at week 16 due to reasons not related to COVID-19 pandemic will be imputed with patient's baseline value or the available post-baseline value, whichever is worse, i.e., a WOCF approach, and missing values at week 16 due to COVID-19 pandemic will be imputed using MI as described in the primary analysis of the primary endpoint of histologic response in Section 5.6.1. 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.

The primary analysis of EoE-EREFS will be based on centralized readings.

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 16 between the dupilumab and placebo groups is statistically significant. Missing NES data will be imputed by Last Observation Carried Forward (LOCF) approach. P-values will be reported.

For the change from baseline to week 16 in the proportion of days with 1 or more EoE signs as measured by the PESQ-C, a supplementary analysis will be performed to require a minimum of 4 eDiary entries (including days when caregivers did not observe any EoE signs) per week to derive the proportion during a 14-day period.

Secondary endpoints in Part B

Secondary endpoints at week 52 (Part B) will be analyzed descriptively at given visits for treatment received in Part B as well as by treatment group as in Part A (double-blind treatment period). No missing values will be imputed.

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 patients 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 B 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 3). Part B baseline is the last available valid measurement taken prior to or on the

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

date of the first dose of extended active treatment period (scheduled to be administered at week 16 visit).

5.6.3. Adjustment for Multiple Comparison

The following multiplicity adjustment approach, a hierarchical procedure, will be used to control the overall Type-1 error rate at 0.05 for the primary endpoint and the secondary endpoints across the 2 dupilumab dose regimens versus placebo in Part A only. Each hypothesis will be formally tested only if the preceding one is significant at the 2-sided 0.05 significance level. The hierarchical testing order is shown in the below table (all comparisons are with the placebo).

	Endpoints	Dupilumab	
		Higher Exposure Dupilumab	**Lower Exposure Dupilumab**
Primary endpoint	Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 16	1	2
Secondary endpoints	Proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf at week 16	3	11
	Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 16	4	12
	Absolute change in mean EoEHSS grade score from the EoE-HSS from baseline to week 16	5	13
	Absolute change in mean EoEHSS stage score from the EoE-HSS from baseline to week 16	6	14
	NES for the relative change from baseline to week 16 in the type 2 inflammation transcriptome signature	7	15
	NES for the relative change from baseline to week 16 in the EoE diagnostic panel (EDP) transcriptome signature	8	16
	Absolute change in EoE EREFS from baseline to week 16	9	17
	Change from baseline to week 16 in the proportion of days with 1 or more EoE signs as measured by the PESQ-C (for patients aged ≥1 to <12 years)	10	18

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

5.6.4. Subgroup Analysis

Subgroups described in Section 3.5 will be summarized for the primary efficacy endpoint (as listed in Section 4.4.1) and the below selected secondary endpoints. Treatment difference and its 95% confidence interval in subgroups of patients will be presented in forest plots. The stratification factor (baseline weight group) will not be included in the subgroup analysis when applying the CMH test and ANCOVA.

- Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 16
- Absolute change in mean EoEHSS grade score from the EoE-HSS from baseline to week 16
- Absolute change in mean EoEHSS stage score from the EoE-HSS from baseline to week 16
- Absolute change in EoE EREFS from baseline to week 16
- Change from baseline to week 16 in the proportion of days with 1 or more EoE signs as measured by the PESQ-C (for patients aged ≥1 to <12 years)

5.6.5. Analysis of Exploratory Efficacy Variables

The exploratory efficacy endpoints at week 16 or week 52 will be analyzed descriptively.

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.

The CDF of the proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 16 and achieving absolute/percent change from baseline to week 16 in the proportion of days with 1 or more EoE signs as measured by PESQ-C will be graphed to present the between-treatment-group differences at each level of the change.

5.7. Analysis of Safety Data

The analysis of safety and tolerance will be performed on the SAF, as defined in Section 3.2.

The safety analysis will be based on the reported AEs and other safety information (clinical laboratory evaluations and vital signs).

Thresholds for Potential Clinically Significant Values (PCSV) in laboratory variables and vital signs are defined in Section 11.3. 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 B, baseline for Part B PCSVs is the last available valid measurement taken prior to the first dose of extended active treatment in Part B (scheduled to be administered at week 16 visit).

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 treatment group for each study period. For safety variables/summaries involving baseline values, e.g., absolute change from baseline or shift table, study period specific baseline will be utilized. Summaries for Part A will use the study

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

baseline (i.e., the latest available valid measurement prior to the first dose of study drug in the study). Summaries for Part B and follow-up period will use Part B baseline (i.e., the last available valid measurement prior to the first dose of extended active treatment in Part B).

5.7.1. Adverse Events

The number and proportion of patients reporting TEAEs will be summarized for Part A 16-week double-blind treatment period, Part B 36-week extended active treatment period, and 12-week follow-up period, as described in Section 3.2.

AE incidence tables will be presented by treatment group for the SAF as well as subgroups defined for safety analysis (Section 3.5). TEAE summaries will present the number (n) and percentage (%) of patients experiencing an TEAE by SOC and PT, sorted by decreasing frequency of SOC and PT for the combined dupilumab treatment group. Multiple occurrences of AEs of the same PT (or SOC) in the same patient will be counted only once for that PT (or SOC). For tables presenting severity of events, the worst severity will be chosen for patients 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 3.2.

An overall summary of TEAEs will be provided with number (n) and percentages (%) of patients with any:

- TEAE
- Serious TEAE
- TEAE of special interest (AESI)
- TEAE with fatal outcome
- TEAE leading to permanent treatment discontinuation

Detailed summaries of all TEAEs in each treatment group will include:

- TEAEs
  - TEAEs by primary SOC/PT
  - TEAEs by primary SOC/PT with incidence of PT ≥5% in any treatment group
  - TEAEs by severity and by primary SOC/PT
  - TEAEs related to study medication as assessed by the investigator by primary SOC/PT
  - TEAEs of special interest by AESI category (see Section 11.4) and primary SOC/PT
- Serious TEAEs by SOC/PT
- TEAEs leading to permanent discontinuation of study treatment by primary SOC/PT
- TEAEs with fatal outcome by primary SOC/PT

The number and proportion of patients with injection site reaction by PT will be summarized.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

5.7.2. Clinical Laboratory Measurements

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

- Descriptive statistics of laboratory result and change from baseline by visit
- The number (n) and percentage (%) of patients with treatment-emergent PCSVs. This summary will be provided on the subgroup of SAF patients who did not meet the PCSV criterion at the 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

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. This summary will be provided on the subgroup of SAF patients who did not meet the PCSV criterion at the 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

5.7.4. Physical Exams

Abnormal status will be tabulated 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 profiles. Plots of concentration vs time will be provided as both non-log and semi-log. When plotted as non-log, concentrations less than LLOQ will be set to zero (0). When plotted as semi-log, for concentrations less than LLOQ, LLOQ/2 will be imputed.
- Graphical presentations of individual functional dupilumab concentration in serum vs actual sampling time profiles. When plotted as non-log, concentrations less than LLOQ will be set to zero (0). When plotted as semi-log, for concentrations less than LLOQ, LLOQ/2 will be imputed.
- Assessment of the impact of anti-drug antibodies on functional dupilumab concentrations in serum

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

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 status, ADA category, and maximum titer observed in patients in the ADA analysis set.

The ADA status of each patient may be classified as one of the following:

- Positive
- Pre-existing - If the baseline sample is positive and all post baseline ADA titers are reported as less than 4-fold the baseline titer value
- Negative - If all samples are found to be negative in the ADA assay

The ADA category of each positive patient is classified as:

- Treatment-boosted - A positive result at baseline in the ADA assay with at least one post baseline titer result ≥ 4-fold the baseline titer value
- Treatment-emergent - A negative result or missing result at baseline with at least one positive post baseline result in the ADA assay. Patients that are treatment-emergent will be further categorized as follows:
  - Persistent - A positive result in the ADA assay detected in at least 2 consecutive post baseline samples separated by at least a 12-week post baseline period (based on nominal sampling time), with no ADA-negative results in-between, regardless of any missing samples
  - Indeterminate - A positive result in the ADA assay at the last collection time point only, regardless of any missing samples
  - Transient - Not persistent or indeterminate, regardless of any missing samples

The maximum titer category of each patient is classified as:

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

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

The following listings will be provided by treatment group and ADA titer level:

- Number (n) and percent (%) of ADA-negative patients
- Number (n) and percent (%) of patients with pre-existing immunoreactivity
- Number (n) and percent (%) of treatment-emergent ADA positive patients
  - 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

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

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.

- Negative: Samples tested negative in the ADA assay, or samples positive in the ADA assay but tested negative in the NAb assay.
- Positive: Samples tested positive in the NAb assay.

5.10. Association of Immunogenicity with Exposure, Safety and Efficacy

The analyses in this section will only be performed if the incidence of treatment emergent ADA positive is sufficient to make meaningful conclusions (i.e., more than 5% in any treatment group).

5.10.1. Association of immunogenicity with exposure

Potential association between immunogenicity 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 category, maximum titer category, and NAb status on individual patient drug concentration profile.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

5.10.2. Immunogenicity and Safety/Efficacy

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

- TEAE
- Serious TEAE
- TEAE leading to permanent treatment discontinuation
- Injection site reaction (HLT= "Injection site reaction")
- Hypersensitivity (AESI category "Hypersensitivity")
- Anaphylaxis (SMQ: Anaphylactic Reaction [Narrow])

Potential association between immunogenicity variables and 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 Positive
  - Treatment-emergent
  - Treatment-boosted
- Maximum post-baseline titer category
- NAb positive

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. Biomarker values after the first rescue treatment used are set to missing (censoring), then LOCF approach will be used to impute the missing data at each visit for Part A analysis, and all observed values will be used for Part B analysis.

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.

Correlation of baseline Eotaxin-3 and total IgE (measured value) with the histologic responder (histologic response of peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 16) will be explored using the logistic model. The model will include the histologic responder/non-responder as the dependent variable, with randomization stratification factor, 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. Patients are considered non-responders after the rescue treatment is used. In addition, patients with missing peak eosinophil count at week 16 are considered as non-responders.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

5.12. Analysis of Psychometric Validity of Clinical Outcome Assessment Measures

Results of psychometric analysis of the PESQ-C and PESQ-P will be summarized in a clinical outcome assessment (COA) dossier. Evidence of content validity and measurement properties of relevant COAs will be submitted to the Agency.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

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 Baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of investigational product. If any randomized patients are not treated, the baseline will be the last value on or prior to the randomization. Part B baseline is defined as the last available valid measurement taken prior to the first dose of extended treatment in Part B.

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

1. The date and time of first injection will be used to determine the baseline for the AE, vital sign, lab (including biomarker), PK, and ADA data.
2. Only the date of first injection will be used to determine the baseline for other data except AE, vital sign, lab (including biomarker), PK, or ADA.

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 patient ID or enrolled patient ID.

6.2. General Data Handling Convention

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 TEAEs. 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’.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

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 01January. 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.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

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 data management and study medical director.

PCSV

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

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

6.4. Visit Windows

Data analyzed by-visit-analysis (efficacy [excluding daily diary data], laboratory data, vital sign, ADA) will be summarized by the study scheduled visits described in study protocol and SAP Section 11.2, "Schedule of Time and Events".

The analysis visit windows will be created per study Schedule of Events table for each parameter and will be applied if the data from the study scheduled visits are unavailable. The following general rules will be applied to unscheduled visit and/or early termination (ET) visit mapping for each parameter:

1. If ET visit falls in an analysis window which has no missing value of this parameter, ET visit will be mapped to the next scheduled visit.
2. If both ET visit and unscheduled visit of the same parameter are available in the same analysis visit window, only ET visit will be mapped.
3. If multiple unscheduled visits of the same parameter are available in the same analysis visit window, the unscheduled visits will be mapped using the following rules:
   a. The closest unscheduled visit from the target day will be selected.
   b. If multiple unscheduled visits occur on the same day, the first unscheduled visit will be utilized.
4. If unscheduled visit is greater than 4 weeks apart from the target day of the scheduled visit, the unscheduled visit will not be mapped.

Unscheduled visit and early termination (ET) visit will be mapped per the analysis visit windows for Part A and Part B (Table 2-6) based on the study day and visit of each parameter, respectively. The analysis visit windows may be applied to the scheduled assessments for PEIS, GIC and GIS.

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

Table 2 Analysis Visit Window for Efficacy Endpoints in Part A

Visit from SOE	Target Study Day in Part A	Analysis Visit Window based on Study Day[a] in Part A		
		Histology endpoints, Transcriptome endpoints, EOE-EREFS, PEIS-P, PEIS-C, PEESS	GIC-P, GIC-C, GIC-Clin	GIS-P, GIS-C
Baseline	1	≤1		≤1
Week 12	85		[2, 99]	[2, 99]
Week 16 (Part A end of treatment)	113	≥2 [b]	≥100 [b]	≥100 [b]

a. Study days are calculated from the day of 1st injection of Part A. Study day = (date of assessment – 1st injection date + 1) when date of assessment is on or after the 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 visit or ET visit occurs in this window, and it is after the first dose of Part B, it will be considered as part of Part B visits.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Table 3 Analysis Visit Window for Safety and Biomarkers in Part A

Visit from SOE	Target Study Day in Part A	Analysis Visit Window based on Study Day[a] in Part A				
		Vital Signs	Physical Examination	Laboratory, PK, Eotaxin-3	ADA	Serum total IgE
Baseline	1	≤1	≤1	≤1	≤1	≤1
Week 2	15	[2, 22]				
Week 4	29	[23, 43]		[2, 71]		≥2[b]
Week 8	57	[44, 71]				
Week 12	85	[72, 99]				
Week 16 (Part A end of treatment)	113	≥100[b]	≥2[b]	≥72[b]	≥2[b]	

a. Study days are calculated from the day of 1st injection of Part A. Study day = (date of assessment – 1st injection date + 1) when date of assessment is on or after the 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 visit or ET visit occurs in this window, and it is after the first dose of Part B, it will be considered as part of Part B visits.

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

Table 4 Analysis Visit Window for Efficacy Endpoints in Part B

Visit from SOE	Target Study Day in Part B	Analysis Visit Window based on Study Day[a] in Part B	
		Histology endpoints, Transcriptome endpoints, EOE-EREFS	PEIS-P, PEIS-C, GIC-P, GIC-C, GIC-Clin, GIS-P, GIS-C, GIS-Clin
Baseline of Part B	1	≤1	≤1
Week 32	113		[2, 183]
Week 52 (Part B end of treatment)	253	≥2	≥184

a. Study days are calculated from the day of 1st injection of Part B. Study day = (date of assessment – 1st injection date + 1) when date of assessment is on or after the 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.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Table 5 Analysis Visit Window for Safety and Biomarker Endpoints in Part B

Visit from SOE	Target Study Day in Part B	Analysis Visit Window based on Study Day[a] in Part B		
		Vital Signs	Physical Examination, Urinalysis, Serum total IgE, Eotaxin-3	Hematology, Chemistry, PK, ADA
Baseline of Part B	1	≤1	≤1	≤1
Week 20	29	[2, 43]		
Week 24	57	[44, 71]		
Week 28	85	[72, 99]		
Week 32	113	[100, 127]		[2, 183]
Week 36	141	[128, 155]		
Week 40	169	[156, 183]		
Week 44	197	[184, 211]		
Week 48	225	[212, 239]		
Week 52 (Part B end of treatment)	253	≥240	≥2	≥184

a. Study days are calculated from the day of 1st injection of Part B. Study day = (date of assessment – 1st injection date + 1) when date of assessment is on or after the 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.

12-week follow-up period after Part A/Part B end of treatment

Table 6 Analysis Visit Window for 12-week Follow-up Period after Part A/Part B End of Treatment

Visit from SOE	Target Study Day after EOT Visit[a]	Analysis Window based on Study Day[a] after EOT
Week 64 EOS Visit (Patient not entering Part B)	85 (relative to week 16 visit)	≥2[b]
Week 64 EOS Visit (Patient entering Part B)	85 (relative to week 52 visit)	≥2[b]

a. Study days are calculated from the day of week 16 visit for patients not entering Part B or the day of week 52 visit for patients entering Part B. Study day = (date of assessment – week 16/week 52 visit +1) when date of assessment is on or after week 16/week 52 visit. If patient does not complete week 16/week 52 visit, week 64 visit will be not applicable for this patient.

b. If unscheduled visit occurs after Part A/Part B EOT visit, and patient enters follow-up period, 1) the study day is ≤42 (6 weeks after Part A/Part B EOT visit), it will be considered for week 16/week 52 visit; 2) the study day is >42, it will be considered for EOS visit.

For PESQ-P and PESQ-C 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 B will not be used for Part A analysis)

Step 1: Diary study day derivation

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

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Step 2: Analysis visit windows are defined as Day -14 to Day -1 = BL, Day 1 to Day 14 = week 2, Day 15 to Day 28 = week 4, etc., with 14-day intervals between visit windows, through Day 99 to Day 112 = week 16. For patients who never entered Part B, analysis windows in the 12-week follow-up period will continue with 14-day intervals as Day 113 to Day 126 = week 18, Day 127 to Day 140 = week 20, etc.

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

Step 1: Diary study day derivation

- For diary date ≥ 1st injection date of study Part B, Part B diary study day = diary date – 1st injection date ***in Part B*** + 1;
- For diary date < 1st injection date of study Part B, Part B diary study day = diary date – 1st injection date in Part B.

Step 2: Analysis visit windows are defined as Day -14 to Day -1 = Part B BL, Day 1 to Day 14 = week 18, Day 15 to Day 28 = week 20, etc., with 14-day intervals between visit windows, through Day 239 to Day 253 = week 52. For patients who entered 12-week follow-up period after Part B, analysis windows will continue with 14-day intervals as Day 254 to Day 267 = week 54, Day 268 to Day 281 = week 56, etc.

6.5. Statistical Technical Issues

None.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

7. INTERIM ANALYSIS

No interim analysis is planned.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

8. TIMING OF STATISTICAL ANALYSIS

The primary analysis will be performed when the last patient has completed the last 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. Available Part B data will also be analyzed and evaluated, including assessment of secondary endpoints at week 52. The final analysis will occur when all patients who enter the 12-week follow-up period immediately from Part A or Part B completed the follow-up period.

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 Part A unblinded 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 Part A unblinded 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.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

9. SOFTWARE

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

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

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VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

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VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

11. APPENDIX

11.1. Summary of Statistical Analyses

11.1.1. Summary of Efficacy Analyses

Endpoint	Analysis Populations	Primary Statistical Method	Supportive/Sensitive Statistical Method	Subgroup Analysis	Other Analyses
Primary Endpoint					
Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf (400×) at week 16	FAS	Cochran-Mantel-Haenszel test/Missing as non-responder	Cochran-Mantel-Haenszel test with tipping point analysis approach and WOCF-MI approach, respectively	Yes [1]	Histogram
Secondary Endpoints					
Secondary continuous variable	FAS	ANCOVA with WOCF-MI approach for endpoints measured repeatedly (e.g., change from baseline in the proportion of days with 1 or more EoE signs as measured by the PESQ-C); ANCOVA with WOCF-MI approach for endpoints measured only once post-baseline up to week 16 (e.g., percent change in peak eosinophil count from baseline to week 16)	NA	Yes [2]	Line plot except EoE-EREFS endpoint; Bar chart for EoE-EREFS endpoint
Secondary binary variable	FAS	Cochran-Mantel-Haenszel test/Missing as non-responder	NA	No	Histogram

[1] Note: The subgroup analysis may not be performed if the number of patients within the subgroup is <10% of overall sample size. The stratification factor is not included in the subgroup analysis of primary efficacy endpoint.
[2] Note: The subgroup analysis will be performed on selected secondary endpoints only, see Section 5.6.4.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

11.1.2. Summary of Safety Analyses

Endpoint	Analysis Populations	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Descriptive statistics	No	TEAEs by Primary SOC/PT only [1]	No
Laboratory Measures	SAF	Descriptive statistics	No	No	No
Vital sign	SAF	Descriptive statistics	No	No	No

[1] Note: The subgroup analysis may not be performed if the number of patients within the subgroup is <10% of overall sample size.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

11.2. Schedule of Time and Events

Table 7: Schedule of Events – Screening and Double-Blind Treatment Period

Study Procedure	Screening Period		Part A: 16-Week Double-Blind Treatment Period					
	Screening[1, 3] V1	Screening[2] V2	Baseline V3	V4	V5	V6	V7	DB EOT[4] V8
Week (W)				W2	W4	W8	W12	W16
Day (D)	D-85 to D-1		D1	D15	D29	D57	D85	D113
Visit Window (Days [d])				±7 d	±3 d	±3 d	±3 d	+7 d
Screening/Baseline:								
Inclusion/Exclusion	X		X					
Informed Consent/Assent	X							
Informed consent/assent for optional genomic sub-study	X							
Informed consent/assent for optional future biomedical research sub-study	X							
Med History/Demographics	X							
Age in months	X	X	X	X	X	X	X	X
Randomization			X					
Treatment:								
Training for SC Injection[5]			X	X				
Administer Study Drug[6]			X	X	X	X	X	
Con Medications/Procedures	X	X	X	X	X	X	X	X
Efficacy:								
Weight, Height (or length for patients <2 years of age)	X		X	X	X	X	X	X
Pediatric EoE Sign/Symptom Questionnaire:[7] Patient version (PESQ-P) Caregiver version (PESQ-C)	◄ (Daily Diary) ►							
Pediatric EoE Impact Scale:[7] Patient version (PEIS-P) Caregiver version (PEIS-C)			X					X
Global Impression of Change:[8] Patient version (GIC-P) Caregiver version (GIC-C) Clinician version (GIC-Clin)							X	X
Global Impression of Severity:[8] Patient version (GIS-P) Caregiver version (GIS-C) Clinician version (GIS-Clin)			X				X	X

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Study Procedure	Screening Period		Part A: 16-Week Double-Blind Treatment Period					
	Screening[1, 3] V1	Screening[2] V2	Baseline V3	V4	V5	V6	V7	DB EOT[4] V8
Week (W)				**W2**	**W4**	**W8**	**W12**	**W16**
Day (D)	**D-85 to D-1**		**D1**	**D15**	**D29**	**D57**	**D85**	**D113**
Visit Window (Days [d])				**±7 d**	**±3 d**	**±3 d**	**±3 d**	**+7 d**
Pediatric Eosinophilic Esophagitis Symptom Score: [15] Caregiver version (PEESSv2.0)			X					X
Endoscopy with Biopsies and EoE-EREFS[2, 9]		X[2a]						X[2,2b]
Exit Interview [16]								X
Safety[10]:								
Vital Signs[11]	X		X[11]	X[11]	X	X	X	X
Physical Examination	X		X					X
Adverse Events	X	X	X	X	X	X	X	X
Laboratory Testing[10, 12]:								
Hematology	X		X		X			X
Chemistry	X		X		X			X
Pregnancy test (WOCBP)[13]	Serum		Urine	Urine	Urine	Urine	Urine	Urine
Urinalysis[14]	X							
PK and ADA Samples[10]:								
Functional dupilumab PK sample			X		X			X
Anti-dupilumab antibody sample			X					X
Biomarkers and Genomics:								
Serum Total IgE			X		X			
Eotaxin-3			X		X			X
Optional pharmacogenetics DNA samples (cheek swab)			X					

ADA = anti-drug antibody; EoE-EREFS = Eosinophilic Esophagitis-Endoscopic Reference Score; EOS = end of study; EOT = end of treatment; PRO = patient-reported outcome; ET = early termination; PEESS = Pediatric Eosinophilic Esophagitis Symptom Score; PESQ-P = Pediatric EoE Sign/Symptom Questionnaire (patient version); PESQ-C = Pediatric EoE Sign/Symptom Questionnaire (caregiver version); PEIS-P = Pediatric EoE Impact Scale (patient version); PEIS-C = Pediatric EoE Impact Scale (caregiver version); GIC-P = Global Impression of Change (patient version); GIC-C = Global Impression of Change (caregiver version); GIC-Clin = Global Impression of Change (clinician version); GIS-P = Global Impression of Severity (patient version); GIS-C = Global Impression of Severity (caregiver version); GIS-Clin = Global Impression of Severity (clinician version)

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Table 8: Schedule of Events – Extended Active Treatment Period and 12-Week Follow-Up Period

Study Procedure	Part B: 36-Week Extended Active Treatment Period										Follow-Up Period
	V8[1]	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18 End of Study
Week (W)	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W64
Day (D)	D113	D141	D169	D197	D225	D253	D281	D309	D337	D365	D449
Visit Window (Days [d])	+7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	+7 d	±7 d
Screening for Part B:											
Inclusion/Exclusion	X										
Treatment:											
Administer Study Drug[4a, 4b]	X	X	X	X	X	X	X	X	X		
Con Meds/Procedures	X	X	X	X	X	X	X	X	X	X	X
Efficacy:											
Age in months	X	X	X	X	X	X	X	X	X	X	X
Weight, Height (or length for patients <2 years of age)[2]	X[4b]	X	X	X	X[4b]	X	X	X	X	X	X
Pediatric EoE Sign/Symptom Questionnaire:[5] Patient version (PESQ-P) Caregiver version (PESQ-C)	← (Daily Diary)										X
Pediatric EoE Impact Scale:[5] Patient version (PEIS-P) Caregiver version (PEIS-C)	X				X					X	X
Global Impression of Change:[6] Patient version (GIC-P) Caregiver version (GIC-C) Clinician version (GIC-Clin)	X				X					X	X
Global Impression of Severity:[6] Patient version (GIS-P) Caregiver version (GIS-C) Clinician version (GIS-Clin)	X				X					X	X
Pediatric Eosinophilic Esophagitis Symptom Score:[11] Caregiver version (PEESSv2.0)	X										
Endoscopy with Biopsies and EoE-EREFS[7,7a]	X[7,7a]									X[7,7a]	

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Study Procedure	Part B: 36-Week Extended Active Treatment Period										Follow-Up Period
	V8[1]	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18 End of Study
Week (W)	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W64
Day (D)	D113	D141	D169	D197	D225	D253	D281	D309	D337	D365	D449
Visit Window (Days [d])	+7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	+7 d	±7 d
Safety:											
Vital Signs[2,3,8]	X[8]	X	X	X	X	X	X	X	X	X	X
Physical Examination[2]	X									X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Hematology[2]	X				X					X	X
Chemistry[2]	X				X					X	X
Pregnancy test (WOCBP)[2,9]	urine	urine	urine	urine	urine	urine	urine	urine	urine	urine	urine
Urinalysis[2,10]	X									X	X
PK and ADA Samples:											
Functional dupilumab PK sample[2]	X				X					X	X
Anti-dupilumab antibody sample[2]	X				X					X	X
Biomarkers:											
Serum total IgE[2]	X									X	
Eotaxin-3[2]	X									X	

ADA = anti-drug antibody; EoE-EREFS = Eosinophilic Esophagitis-Endoscopic Reference Score; EOS = end of study; EOT = end of treatment; PEESS = Pediatric Eosinophilic Esophagitis Symptom Score; PRO = patient-reported outcome; PESQ-P = Pediatric EoE Sign/Symptom Questionnaire (patient version); PESQ-C = Pediatric EoE Sign/Symptom Questionnaire (caregiver version); PEIS-P = Pediatric EoE Impact Scale (patient version); PEIS-C = Pediatric EoE Impact Scale (caregiver version); GIC-P = Global Impression of Change (patient version); GIC-C = Global Impression of Change (caregiver version); GIC-Clin = Global Impression of Change (clinician version); GIS-P = Global Impression of Severity (patient version); GIS-C = Global Impression of Severity (caregiver version); GIS-Clin = Global Impression of Severity (clinician version)

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Table 9: Schedule of Events - Early Termination Visits and Unscheduled Visits

Study Procedure	ET[1] (Before Follow-up)	ET[1] (During Follow-up)	Unscheduled Visit (before Rescue Treatment)	Unscheduled Visit (For Other Reasons)
Treatment:				
Con Meds/Procedures	X	X	X	X
Efficacy:				
Age in months	X	X	X	X
Weight, Height (or length for patients <2 years of age)	X	X	X	
Pediatric EoE Sign/Symptom Questionnaire:[2] Patient version (PESQ-P) Caregiver version (PESQ-C)	← (Daily Diary)	→ X	X	
Pediatric EoE Impact Scale:[2] Patient version (PEIS-P) Caregiver version (PEIS-C)	X	X	X	
Global Impression of Change:[3] Patient version (GIC-P) Caregiver version (GIC-C) Clinician version (GIC-Clin)	X	X	X	
Global Impression of Severity:[3] Patient version (GIS-P) Caregiver version (GIS-C) Clinician version (GIS-Clin)	X	X	X	
Pediatric Eosinophilic Esophagitis Symptom Score:[6] Caregiver version (PEESSv2.0)	X		X	
Endoscopy with Biopsies with EoE-EREFS[4]	X[4, 4a]		X[4b]	
Safety:				
Vital Signs	X	X	X	
Physical Examination	X		X	
Adverse Events	X	X	X	X

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Study Procedure	ET[1] (Before Follow-up)	ET[1] (During Follow-up)	Unscheduled Visit (before Rescue Treatment)	Unscheduled Visit (For Other Reasons)
Laboratory Testing:				
Hematology	X	X		
Chemistry	X	X		
Pregnancy test (WOCBP)	urine	urine		
Urinalysis[5]	X	X		
PK and ADA Samples:				
Functional dupilumab PK sample	X	X		
Anti-dupilumab antibody sample	X	X		
Biomarkers:				
Serum total IgE			X	
Eotaxin-3			X	

ADA = anti-drug antibody; EoE-EREFS = Eosinophilic Esophagitis-Endoscopic Reference Score; EOS = end of study; EOT = end of treatment; PEESS = Pediatric Eosinophilic Esophagitis Symptom Score; PRO = patient reported outcome; PESQ-P = Pediatric EoE Sign/Symptom Questionnaire (patient version); PESQ-C = Pediatric EoE Sign/Symptom Questionnaire (caregiver version); PEIS-P = Pediatric EoE Impact Scale (patient version); PEIS-C = Pediatric EoE Impact Scale (caregiver version); GIC-P = Global Impression of Change (patient version); GIC-C = Global Impression of Change (caregiver version); GIC-Clin = Global Impression of Change (clinician version); GIS-P = Global Impression of Severity (patient version); GIS-C = Global Impression of Severity (caregiver version); GIS-Clin = Global Impression of Severity (clinician version); WOCBP = Women of childbearing potential

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Footnotes for the Schedule of Events Tables

Footnotes for Table 7

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 PPI treatment), the screening period will be extended for up to 12 weeks (day -85) to allow for at least 8 weeks of 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/imaging for EoE-EREFS/biopsy procedures should be performed after all other efficacy and safety assessments.

   2a. The baseline esophageal endoscopy with biopsies and the stomach and/or duodenum endoscopies with biopsies should be performed with sufficient time 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 PPI. Patients may be randomized as soon as their endoscopy/biopsy results are confirmed, and all other eligibility criteria are met.

   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 subsequent scheduled endoscopy/biopsy at week 16 and/or week 52.
3. Patients may be re-screened 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.
4. Assessments indicated for this week 16 (end of treatment) visit should be performed for all patients. For patients who will enter extended treatment, there are additional events listed for the week 16 visit in Table 8.
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) after all assessments are completed. Study drug administered at the study sites by site staff will be performed only by injection personnel who will not perform any clinical assessment/procedures. Study drug will be provided/dispensed for those doses scheduled to be administered at home before the next in-clinic visit. Study drug administration that occurs in clinic should occur per the Schedule of Events in Table 7 and Table 8. Parents (or caregivers) will return the study kit box (for prefilled syringes) at each subsequent in-clinic visit. Parents (or caregivers) who prefer to have the clinic staff administer study drug may choose to have injections administered in the clinic.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

7. The PESQ-P will be completed daily by patients ≥8 to <12 years of age (determined at the time of screening visit 1) just before going to bed for the night. The PESQ-C will be completed daily by caregivers of patients ≥1 to <12 years of age (determined at the time of screening visit 1) after the patients go to bed for the night. The PESQ-P and PESQ-C will be completed via an electronic diary (diary) and site personnel should conduct regular checks of patient and caregiver diary compliance. The PEIS-P and PEIS-C will be completed during site visits as indicated in the Schedule of Events table by the patients and caregivers, respectively.
8. The GIS-P, GIS-C, GIS-Clin and the GIC-P, GIC-C, and GIC-Clin will be completed by patients during site visits (≥8 to <12 years of age determined at the time of screening visit 1), caregivers (of patients ≥1 to <12 years of age determined at the time of screening visit 1), and study investigator/clinician, respectively.
9. EoE-EREFS imaging will be analyzed and scored by a central reading center. Minor esophageal features will be assessed by the investigator.
10. Assessments will be performed, and blood samples will be collected before the administration of study drug. In the event of suspected SAEs, such as anaphylaxis or hypersensitivity, functional dupilumab PK sample and anti-dupilumab antibody sample may be collected at or near the event.
11. Patients will be closely monitored at the study site at visits 3 and 4 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. Vital signs should be taken predose at all other indicated visits.
12. Tuberculosis testing will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ECs.
13. A negative result must be obtained prior to the randomization visit for all females post-menarche. 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.
14. Urinalysis is only required for patients aged ≥6 to <12 years.
15. The Pediatric Eosinophilic Esophagitis Symptom Score (PEESS) version 2.0 will be completed by caregivers of patients ≥1 to <12 years of age (determined at the time of screening visit 1).
16. Exit interviews will be conducted by a trained interviewer via telephone within 14 days of completing Week 16/Visit 8. These interviews will be completed with caregivers. Patients aged ≥8 to <12 years old (determined at the time of screening visit 1] may also join a portion of the exit interview).

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Footnotes for Table 8

1. This visit is the same as the week 16 visit for the double-blind study portion (Table 7), and all other assessments indicated for week 16 (Table 7) should be performed. Endoscopy with biopsies at visit 8/week 16 must be completed prior to administration of study drug for Part B Extended Active Treatment.
2. Study assessments will be performed, and blood samples will be collected prior to administration of study drug. In the event of suspected SAEs, such as anaphylaxis or hypersensitivity, functional dupilumab PK sample and anti-dupilumab antibody sample may be collected at or near the event.
3. 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. 4a. Study drug administration will continue through week 50.

   4b. Weight assessed at visit 8 / week 16 and visit 12 / week 32 will be used to determine weight-tiered dose for the 36-week extended active treatment period. If weight has increased at visit 12 such that the patient meets a larger weight tier, weight-tiered dosing will be re-assigned according to the patient's weight at this visit. If weight is the same or decreased at visit 12, then weight-tiered dosing will remain as originally assigned at visit 8 / week 16. The patient will remain within the original exposure dosing assignment (higher exposure group or lower exposure group). On scheduled in-clinic study visit days, study drug will be administered in the clinic (by the patient, site staff, or caregiver). Study drug administered at the study sites by site staff will be performed only by injection personnel who will not perform any clinical assessment/procedures. Study drug will be provided for those scheduled doses to be administered at home before the next in-clinic visit. Parents (or caregivers) will return the study kit box (for prefilled syringes) at each subsequent in-clinic visit. Study drug administration that occurs in clinic should occur per the Schedule of Events table. Parents (or caregivers) who prefer to have the clinic staff administer study drug may choose to have injections administered in the clinic.
5. The PESQ-P will be completed daily by patients ≥8 to <12 years of age (determined at the time of screening visit 1) just before going to bed for the night. The PESQ-C will be completed daily by caregivers of patients ≥1 to <12 years of age (determined at the time of screening visit 1) after the patients go to bed for the night. The PESQ-P and PESQ-C will be completed via an electronic diary (diary) and site personnel should conduct regular checks of patient and caregiver diary compliance. The PEIS-P and PEIS-C will be completed during site visits as indicated in the Schedule of Events table by the patients and caregivers, respectively.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

6. The GIS-P, GIS-C, GIS-Clin and the GIC-P, GIC-C, and GIC-Clin will be completed during site visits by patients (≥8 to <12 years of age determined at the time of screening visit 1), caregivers (of patients ≥1 to <12 years of age determined at the time of screening visit 1), and study investigator/clinician, respectively.
7. Endoscopy/imaging for EoE-EREFS/biopsy procedures should be performed after all other efficacy and safety assessments. Minor esophageal features will be assessed by the investigator.

   7a. 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 16 and 52.
8. 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 at visit 8.
9. 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.
10. Urinalysis is only required for patients aged ≥6 to <12 years.

11. The Pediatric Eosinophilic Esophagitis Symptom Score (PEESS) version 2.0 will be completed by caregivers of patients ≥1 to <12 years of age (determined at the time of screening visit 1).

Footnotes for Table 9

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. The PESQ-P will be completed daily by patients ≥8 to <12 years of age (determined at the time of screening visit 1) just before going to bed for the night. The PESQ-C will be completed daily by caregivers of patients ≥1 to <12 years of age (determined at the time of screening visit 1) after the patients go to bed for the night. The PESQ-P and PESQ-C will be completed via an electronic diary (diary) and site personnel should conduct regular checks of patient and caregiver diary compliance. The PEIS-P and PEIS-C will be completed during site visits as indicated in the Schedule of Events table by the patients and caregivers, respectively.
3. The GIS-P, GIS-C, GIS-Clin and the GIC-P, GIC-C, and GIC-Clin will be completed during site visits as indicated by patients (≥8 to <12 years of age determined at the time of screening visit 1), caregivers (of patients ≥1 to <12 years of age determined at the time of screening visit 1), and study investigator/clinician, respectively.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

4. EoE-EREFS imaging will be analyzed and scored by a central reading center. Minor esophageal features will be assessed by the investigator.

   4a. For patients who receive rescue treatment, endoscopy/imaging for 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 16 and 52.

   4b. Endoscopy/imaging for EoE-EREFS/biopsy will be performed only if the unscheduled visit is for the purpose of administering rescue therapy.

5. Urinalysis is only required for patients aged ≥6 to <12 years

The Pediatric Eosinophilic Esophagitis Symptom Score (PEESS) version 2.0 will only be completed by caregivers of patients >1 to <12 years of age (determined at the time of screening visit 1) an early termination and/or unscheduled visit before rescue visit(s) performed prior to visit 8 / week 16. There is no requirement to perform PEESS after visit 8 / week 16.

11.3. Criteria for Potentially Clinically Significant Values (PCSV)

Where criteria for ≥6 to <12 years are different from criteria for ≥1 to <6 years, the children criteria are provided in the [brackets] in the combined column. The criteria inside the "Combined" column will be used for display purpose in the reporting outputs. Applicable criteria will be applied to parameters collected in the study to identify treatment-emergent PCSV cases.

Parameter	≥6 to <12 years	≥1 to <6 years	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

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Parameter	≥6 to <12 years	≥1 to <6 years	Combined
Alkaline Phosphatase (ALP)	≥1.5 ULN and baseline < 1.5 ULN	≥1.5 ULN and baseline < 1.5 ULN	≥1.5 ULN and baseline < 1.5 ULN
Total Bilirubin	≥1.3 ULN and baseline < 1.3 ULN	≥1.3 ULN and baseline < 1.3 ULN	≥1.3 ULN and baseline < 1.3 ULN
Conjugated Bilirubin	(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 ≥1.3 ULN) and (Direct Bilirubin ≤35% Total Bilirubin or Total Bilirubin <1.3 ULN) at baseline	(Direct Bilirubin >35% Total Bilirubin and Total Bilirubin ≥1.3 ULN) and (Direct Bilirubin ≤35% Total Bilirubin or Total Bilirubin <1.3 ULN) at baseline
(ALT or AST) and Total Bilirubin (TBILI)	((ALT >3 ULN or AST>3 ULN) and TBILI>2 ULN) and ((ALT ≤3 ULN and AST ≤3 ULN) or TBILI ≤2 ULN) at baseline	((ALT >3 ULN or AST>3 ULN) and TBILI>2 ULN) and ((ALT ≤3 ULN and AST ≤3 ULN) or TBILI ≤2 ULN) at baseline	((ALT >3 ULN or AST>3 ULN) and TBILI>2 ULN) and ((ALT ≤3 ULN and AST ≤3 ULN) or TBILI ≤2 ULN) at baseline
Creatinine	≥90 µmol/L and baseline < 90 µmol/L ≥30% change from baseline	≥1 to <4 years: >62 µmol/L and ≤ 62 µmol/L at baseline ≥4 to <6 years: >71 µmol/L and ≤ 71 µmol/L at baseline	≥90 [≥1 to <4 years: >62; ≥4 to <6 years: >71] µmol/L and baseline < 90 [≥1 to <4 years: ≤ 62; ≥4 to <6 years: ≤ 71] µmol/L ≥30% change from baseline (≥6 to <12 years only)
Albumin	≤25 g/L and >25 g/L at baseline	NA	≤25 g/L and >25 g/L at baseline (≥6 to <12 years only)
Blood Urea Nitrogen (BUN)	≥7.14 mmol/L and <7.14 mmol/L at baseline	≥6.4 mmol/L and <6.4 mmol/L at baseline	≥7.14 [≥6.4] mmol/L and <7.14 [<6.4] mmol/L at baseline
Chloride	<80 mmol/L and ≥ 80 mmol/L at baseline ≥115 mmol/L and <115 mmol/L at baseline	≤80 mmol/L and >80 mmol/L at baseline ≥115 mmol/L and <115 mmol/L at baseline	<80 [≤80] mmol/L and baseline ≥ 80 [>80] mmol/L ≥115 mmol/L and baseline <115 mmol/L
Sodium	<129 mmol/L and ≥ 129 mmol/L at baseline ≥150 mmol/L and < 150 mmol/L at baseline	≤129 mmol/L and >129 mmol/L at baseline ≥150 mmol/L and <150 mmol/L at baseline	<129 [≤129] mmol/L and baseline ≥ 129 [>129] mmol/L ≥150 mmol/L and baseline < 150 mmol/L

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Parameter	≥6 to <12 years	≥1 to <6 years	Combined
Potassium	≤3.5 mmol/L and > 3.5 mmol/L at baseline ≥5.5 mmol/L and < 5.5 mmol/L at baseline	≤3.5 mmol/L and >3.5 mmol/L at baseline ≥5.5 mmol/L and <5.5 mmol/L at baseline	≤3.5 mmol/L and baseline > 3.5 mmol/L ≥5.5 mmol/L and baseline < 5.5 mmol/L
Calcium total	<2.0 mmol/L and ≥2.0 mmol/L at baseline ≥2.9 mmol/L and <2.9 mmol/L at baseline	≤2.0 mmol/L and >2.0 mmol/L at baseline ≥2.9 mmol/L and <2.9 mmol/L at baseline	<2.0 [≤2.0] mmol/L and ≥2.0 [>2.0] mmol/L at baseline ≥2.9 mmol/L and <2.9 mmol/L at baseline
Glucose	Hypoglycaemia: <2.7 mmol/L and ≥2.7 mmol/L at baseline Hyperglycaemia: ≥10.0 mmol/L (unfasted) and < 10.0 mmol/L (unfasted) at baseline; ≥7.0 mmol/L (fasted) and <7.0 mmol/L (fasted) at baseline	Hypoglycaemia: <2.7 mmol/L and ≥2.7 mmol/L at baseline Hyperglycaemia: ≥10.0 mmol/L (unfasted) and < 10.0 mmol/L (unfasted) at baseline; ≥7.0 mmol/L (fasted) and <7.0 mmol/L (fasted) at baseline	Hypoglycaemia: <2.7 mmol/L and ≥2.7 mmol/L at baseline Hyperglycaemia: ≥10.0 mmol/L (unfasted) and < 10.0 mmol/L (unfasted) at baseline; ≥7.0 mmol/L (fasted) and <7.0 mmol/L (fasted) at baseline
Hematology			
WBC	<5.0 Giga/L and ≥5.0 Giga/L at baseline >17.0 Giga/L and ≤17.0 Giga/L at baseline	**≥1 to <2 years**: <4.0 Giga/L and ≥ 4.0 Giga/L at baseline >20.0 Giga/L and ≤20.0 Giga/L at baseline **≥2 to <6 years:** <3.0 Giga/L and ≥ 3.0 Giga/L at baseline >16.0 Giga/L and ≤ 16.0 Giga/L at baseline	<5.0 [≥1 to <2 years: <4.0; ≥2 to <6 years: <3.0] Giga/L and ≥5.0 [≥1 to <2 years: ≥ 4.0; ≥2 to <6 years: ≥ 3.0] Giga/L at baseline >17.0 [≥1 to <2 years: >20.0; ≥2 to <6 years: >16.0] Giga/L and ≤17.0 [≥1 to <2 years: ≤20.0; ≥2 to <6 years: ≤ 16.0] Giga/L at baseline
Lymphocytes (ALC)	<1.0 Giga/L and ≥1.0 Giga/L at baseline >8.0 Giga/L and ≤8.0 Giga/L at baseline	<1.0 Giga/L and ≥ 1.0 Giga/L at baseline >10.5 Giga/L and ≤10.5 Giga/L at baseline	<1.0 Giga/L and ≥1.0 Giga/L at baseline >8.0 [>10.5] Giga/L and ≤8.0 [≤10.5] Giga/L at baseline
Neutrophils	<1.2 Giga/L and ≥1.2 Giga/L at baseline >ULN and baseline ≤ ULN	<1.2 Giga/L and ≥ 1.2 Giga/L at baseline	<1.2 Giga/L and ≥1.2 Giga/L at baseline >ULN and baseline ≤ ULN (≥6 to <12 years 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)

Parameter	≥6 to <12 years	≥1 to <6 years	Combined
Monocytes	>0.7 Giga/L and ≤ 0.7 Giga/L at baseline	NA	>0.7 Giga/L and ≤ 0.7 Giga/L at baseline (≥6 to <12 years only)
Hemoglobin	<100 g/L and ≥100 g/L at baseline or any decrease ≥ 20 g/L ≥200 g/L and <200 g/L at baseline	**≥1 to <2 years:** <90 g/L and ≥ 90 g/L at baseline or any decrease ≥ 20 g/L **≥2 to <6 years:** <100 g/L and ≥ 100 g/L at baseline or any decrease ≥ 20 g/L	<100 [≥1 to <2 years: < 90] g/L and ≥100 [≥1 to <2 years: ≥ 90] g/L at baseline or any decrease ≥ 20 g/L ≥200 g/L and <200 g/L at baseline (≥6 to <12 years only)
Hematocrit	< 32% and ≥ 32% at baseline >47% and ≤ 47% at baseline	**≥1 to <2 years:** < 29% and ≥ 29% at baseline > 42% and ≤ 42% at baseline **≥2 to <6 years:** < 32% and ≥ 32% at baseline > 47% and ≤ 47% at baseline	< 32% [≥1 to <2 years: < 29%] and ≥ 32% [≥1 to <2 years: ≥ 29%] at baseline >47% [≥1 to <2 years: > 42%] and ≤ 47% [≥1 to <2 years: ≤ 42%] at baseline
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
Urinalysis			
Ketonuria	Presence and absence at baseline	NA	Presence and absence at baseline (≥6 to <12 years only)
Glycosuria	Presence and absence at baseline	NA	Presence and absence at baseline (≥6 to <12 years only)
Microscopic Hematuria	>5 RBCs/hpf and ≤5 RBCs/hpf at baseline	NA	>5 RBCs/ hpf and ≤5 RBCs/ hpf at baseline (≥6 to <12 years only)
Proteinuria	≥ 1+ and <1+ at baseline	NA	≥ 1+ and <1+ at baseline (≥6 to <12 years only)
Vital Signs			
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	**≥1 to <3 years**: ≤63 bpm and decrease from baseline ≥20 bpm ≥140 bpm and increase from baseline ≥20 bpm **≥3 to <6 years**: ≤59 bpm and decrease from baseline ≥20 bpm ≥140 bpm and increase from baseline ≥20 bpm	≤50 [≥1 to 3 years: ≤63; ≥3 to <6 years: ≤59] bpm and decrease from baseline ≥20 bpm ≥120 [≥140] bpm and increase from baseline ≥20 bpm

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Parameter	≥6 to <12 years	≥1 to <6 years	Combined
SBP	≤80 mmHg and decrease from baseline ≥20 mmHg ≥120 mmHg and increase from baseline ≥ 20 mmHg	**≥1 to <3 years**: ≤70 mmHg and decrease from baseline ≥20 mmHg ≥116 mmHg and increase from baseline ≥20 mmHg **≥3 to <6 years**: ≤70 mmHg and decrease from baseline ≥20 mmHg ≥121 mmHg and increase from baseline ≥20 mmHg	≤80 [≤70] mmHg and decrease from baseline ≥20 mmHg ≥120 [≥1 to 3 years: ≥116; ≥3 to <6 years: ≥121] mmHg and increase from baseline ≥ 20 mmHg
DBP	≤48 mmHg and decrease from baseline ≥10 mmHg ≥72 mmHg and increase from baseline ≥ 20mmHg	**≥1 to <3 years**: ≤34 mmHg and decrease from baseline ≥10 mmHg ≥77 mmHg and increase from baseline ≥10 mmHg **≥3 to <6 years**: ≤34 mmHg and decrease from baseline ≥10 mmHg ≥83 mmHg and increase from baseline ≥10 mmHg	≤48 [≤34] mmHg and decrease from baseline ≥10 mmHg ≥72 [≥1 to 3 years: ≥77; ≥3 to <6 years: ≥83] mmHg and increase from baseline ≥ 20 mmHg [≥ 10 mmHg]
Temperature	Rectal, ear (Tympanic): >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 (Tympanic): >102.2 °F/39.0 °C Oral or pacifier: >102.2°F/39.0°C Axillary or skin infrared (temporal): >102.2°F/39.0°C	Rectal, ear (Tympanic): >100.4 °F/38.0 °C [>102.2 °F/39.0 °C] Oral: >99.5 °F/37.5 °C [>102.2°F/39.0°C] Axillary or skin infrared (temporal): >99 °F/37.2 °C [>102.2°F/39.0°C]
Respiratory rate	<16 per minutes and ≥16 per minute at baseline >30 per minute and ≤30 per minute at baseline	<20 per minute and ≥20 per minute at baseline >34 per minute and ≤34 per minute at baseline	<16 [<20] per minute and ≥16 [≥ 20] per minute at baseline >30 [> 34] per minute and ≤30 [≤ 34] per minute at baseline
Weight	≥5 % weight loss from baseline	≥5 % weight loss from baseline	≥5 % weight loss from baseline

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

11.4. Search Criteria for TEAEs of Special Interest

AESI Category	Search Criteria
Anaphylactic reactions	Narrow SMQ for anaphylactic reaction
Systemic hypersensitivity reactions	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
Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)	HLT = Eosinophilic disorders PT = Eosinophil count increased Note: manual adjudication of relevant PTs will be required by the study medical monitor, before database lock.
Any severe type of conjunctivitis or blepharitis	Broad CMQ conjunctivitis PTs 1. Conjunctivitis 2. Conjunctivitis allergic 3. Conjunctivitis bacterial 4. Conjunctivitis viral 5. Atopic keratoconjunctivitis 6. Blepharitis 7. Dry eye 8. Eye irritation 9. Eye pruritus 10. Lacrimation increased 11. Eye discharge 12. Foreign body sensation in eyes 13. Photophobia 14. Ocular hyperaemia 15. Conjunctival hyperaemia 16. Xerophthalmia Blepharitis PTs 1. Blepharitis allergic 2. Bacterial blepharitis AND Serious AE= “Yes” OR Severity= “severe”
Keratitis	Narrow SMQ for corneal disorders
Severe injection site reactions	HLT=Injection Site Reactions AND Serious AE= “Yes” OR Severity= “severe”
Herpes simplex infection	HLT=Herpes viral infections
Arthralgia	PT=Arthralgia

Note: The search criteria are meant to assist the process of identification of TEAE of Special Interest/TEAE Syndrome. However, since these criteria might not be exhaustive in some cases or may not be specific in other cases, an additional blinded review of all PTs in the database may be performed by the medical monitor, based on medical judgement, to identify any TEAE of Special Interest/TEAE Syndrome that might have been missed by the criteria or to identify any TEAE may been inaccurately assigned as AESI by the algorithmic search.

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

11.5. EoE Histology Scoring System (EoE-HSS) Feature Evaluation Per Collins 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

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

Feature	Grade Score	Stage Score
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
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)

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

11.6. Gene Lists Comprising Each Transcriptome Endpoint

EoE diagnostic panel	Type 2 inflammation signature
CDH26	IL4
CDH20	IL13
CLDN10	IL13RA1
CTNNAL1	IL4R
DSG1	IL5
CHL1	IL33
CXCL6	TSLP
CCL26	IL25
CXCL1	CCL11
IL8	CCL13
IL5	CCL17
IL13	CCL18
CCR3	CCL24
CLC	CCL26
IL5RA	IL1RL1
CRISP2	FCER1A
FLG	FCER2
UPK1A	CCR3
SPINK7	CCR4
CRISP3	SIGLEC8
ACPP	HDC
UPK1B	PTGDS
CA2	PTGDR2
PHLDB2	CLC
MUC4	ALOX15
GCNT3	MUC5B
EPPK1	MUC5AC
ZNF365	POSTN
CITED2	DPP4
ARG1	CMA1
ALOX12	TPSAB1
IGJ	HRH1
TNFAIP6	GATA1
CFB	GATA3
HRH1	ARG1
CFI	STAT6
APOBEC3A	
MMP12	
CD200R1	
HPGDS	
FCGR3A	
FCGR3B	
RUNX2	
ALOX15	
GRK5	
SAMSN1	
PMCH	
SLC16A6	

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

EoE diagnostic panel	Type 2 inflammation signature
KCNJ2	
ANO1	
SLC26A4	
TPSAB1	
TPSB2	
CPA3	
CMA1	
NEFM	
NEFL	
PNLIPRP3	
ENDOU	
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	

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

11.7. SAS Syntax Code for Multiple Imputation with CMH Test

The multiple imputation with CMH test for the primary analysis of proportion of patients achieving a histologic response of peak esophageal intraepithelial eosinophil count ≤6 eos/hpf at week 16 will be taken the following 5 steps:

Step 1: Use the MCMC method to fill in intermittent missing values so that a monotone missing pattern will be formed.

Step 2: Using the datasets from step 1, missing data through week 16 will be imputed using the regression method with treatment group, randomization stratification, relevant baseline measurement, and post-baseline measurement up to week 16 included in the regression model.

SAS syntax code for MI:

Note: From Steps 1 and 2, missing data at week 16 will be imputed 10 times to generate 10 complete datasets using the MI procedure in SAS with seed number of 6681877.

Step 3: Analyze each of the 10 complete datasets using SAS FREQ procedure with CMH test.

SAS syntax code for CMH

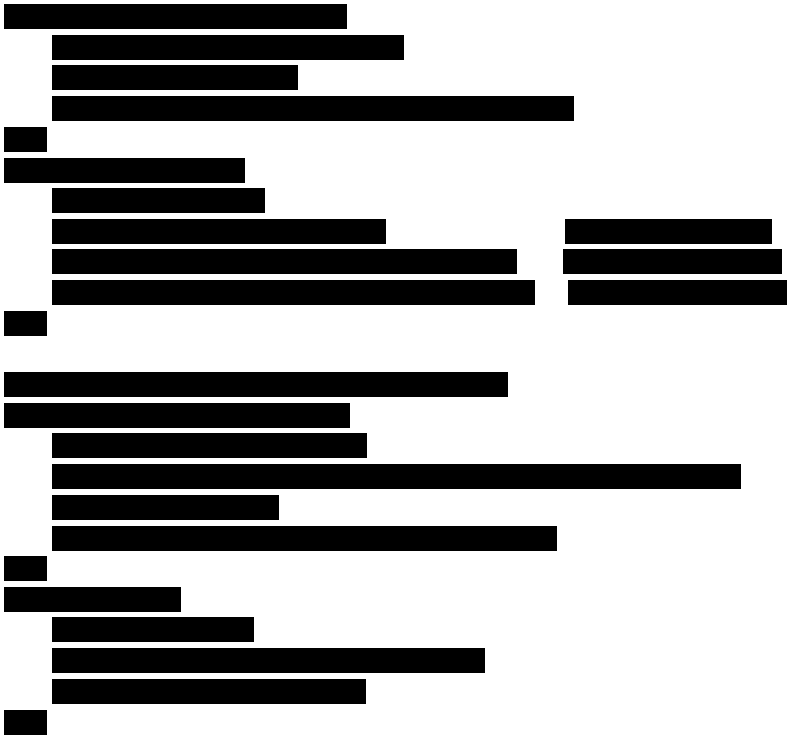
Step 4: Apply Wilson-Hilferty (WH) transformation to normalize the test statistic

SAS syntax code for WH transformation

Step 5: Use Rubin's rule to combine the odds ratio and WH transformation for p-value using SAS MIANALYZE procedure

SAS syntax code for Rubin's rule

VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00



VV-RIM-00199013-1.0 Approved - 03 Jun 2022 GMT-5:00

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