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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF DUPILUMAB IN PEDIATRIC PATIENTS WITH ACTIVE EOSINOPHILIC ESOPHAGITIS

Compound:	Dupilumab
Study Name:	EoE KIDS
Clinical Phase:	3
Protocol Number:	R668-EE-1877
Protocol Version:	R668-EE-1877 Amendment 4
Amendment 4 Date of Issue	*See appended electronic signature page*
Amendment 3 Date of Issue	13 June 2021
Amendment 2 Date of Issue	18 Nov 2020
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[redacted]

LIST OF ABBREVIATIONS AND DEFINITIONS 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
C_{max}	Maximal concentration
CMH	Cochran-Mantel-Haenszel (test)
COA	Clinical outcome assessment
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
CRSwNP	Chronic rhinosinusitis with nasal polyps
C_{trough}	Trough concentration
DMC	Data monitoring committee
DSQ	Dysphagia symptom questionnaire
EC	Ethics committee
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
EU	European Union
FAS	Full analysis set
FeNO	Fractional exhaled nitric oxide
FLG	Filaggrin
GCP	Good Clinical Practice
GIC	Global Impression of Change
GIS	Global Impression of Severity
HIV	Human immunodeficiency virus
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
IRB	Institutional Review Board
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
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
SPRR3	Small proline-rich protein 3
SUSAR	Suspected unexpected serious adverse reaction
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

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AMENDMENT HISTORY

Amendment 4

The primary purpose of this protocol amendment is [redacted] for the addition of a long-term extension period to evaluate the long-term safety of dupilumab in pediatric patients 1 to less than 12 years of age with active eosinophilic esophagitis. This long-term extension period will add up to 108 weeks of open-label treatment or until dupilumab becomes commercially available in the country of the participating patients (whichever comes first).

Description of Change	Rationale	Section Changed
Added an open-label extension (OLE) period (Part C) for patients completing Part B of this study. Patients who have completed their end of study (EOS) visit prior to amendment 4 will be re-evaluated for eligibility at a Re-Entry visit for participation in the open-label extension period (Part C) and Safety Follow-up period.	To assess the long-term safety of repeat doses of dupilumab in pediatric patients with eosinophilic esophagitis.	Clinical Study Protocol Synopsis: Objectives, Study Design, Study Duration, Treatments, Endpoints, Statistical Plan Section 2.2 Secondary Objectives Section 3.2.1 Rationale for Study Design Section 3.2.2 Rationale for Dose Selection Section 4.1.2 Secondary Endpoints Section 4.1.3 Exploratory Endpoints Section 6.1 Study Description and Duration Figure 1 Study Flow Diagram Section 7.2.2.2 Exclusion Criteria for Part B – Extended Active Treatment (and also for Entry into Part C for Patients with Uninterrupted Participation in the Study) Section 8.1 Investigational and Reference Treatments Figure 5 Part C (OLE) Weight-Tiered Dosing Regimens of Study Drug Section 8.7 Blinding Table 2 Schedule of Events - Extended Active Treatment Period and Re-Entry Visit Table 4 Schedule of Events Open-Label Extension Part C (OLE) and EOS Schedule of Events

Description of Change	Rationale	Section Changed
		Section 9.1.1.2 Footnotes for Table 2; Footnotes 12 and 13 Section 9.1.1.4 Footnotes for Table 4 Section 9.1.4 Re-Entry Visit Section 9.2.2.3 Endoscopy with EoE-EREFS, Biopsies, and Imaging Section 11.4.3.2 Secondary Efficacy Analysis Section 11.4.5 Safety Analysis Section 11.4.5.1 Adverse Events Section 11.4.9 Timing of Statistical Analysis
Updated the Risk section	The language has been updated with recently identified risks of dupilumab treatment	Section 3.3.1.2 Risk
Changed study drug dosing for OLE Part C • Changed the weight threshold from ≥60 kg to ≥40 kg to receive [redacted] mg QW in Part C of the study • Changed the dosing regimen for the ≥5kg to <15kg weight tier from [redacted]mg Q2W to [redacted]mg Q3W	The pharmacokinetics of dupilumab are independent of age in children at least 6 years of age. The weight tier is being modified to align with the US-approved dose ([redacted] mg QW) for adult and adolescent patients with EOE weighing at least 40 kg to ensure patients <12 years of age and ≥40 kg achieve exposures that were associated with clinically meaningful and significant symptomatic improvement in adults and adolescents. Similarly, the dose for patients ≥5 to <15 kg in Part C has been adjusted from [redacted] mg Q2W to [redacted] mg Q3W in order to provide exposures closer to that was observed in adult and adolescents with EOE receiving [redacted] mg QW.	Clinical Study Protocol Synopsis: Treatment Section 3.2.2 Rationale for Dose Selection Section 8.1 Investigational and Reference Treatments Figure 5 Part C (OLE) Weight-Tiered Dosing Regimens of Study Drug
Updated the exploratory objective and endpoints assessing the impact of dupilumab treatment on changes in weight and growth to secondary objective and endpoints during the extended active period	Growth rate and weight changes are important efficacy indicators of dupilumab treatment in pediatric EOE patients.	Clinical Study Protocol Synopsis: Objectives and Endpoints Section 2.2 Secondary Objectives Section 4.1.2 Secondary Endpoints Section 4.1.3 Exploratory Endpoints Section 11.4.3.2 Secondary Efficacy Analysis
Updated language in the confidentialy statement	To align with Regeneron's recent Clinical Study Protocol template	Title Page
Minor editorial corrections	For clarification	Throughout the protocol

Amendment 3

The primary purpose of this protocol amendment is [redacted] for including an exit interview, to add symptom/sign-free days based on the PESQ-P or PESQ-C as a secondary endpoint, and to update the definition of primary estimand for patients treated with corticosteroids.

Description of Change	Rationale	Section Changed
Added a new procedure for an exit interview at Week 16/Visit 8 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.	[redacted]	Clinical Study Protocol Synopsis: Procedures and Assessments Table 1 Schedule of Events - Screening and Double-Blind Treatment Period Section 9.1.1.1 Footnotes for Table 1, footnote number 16 Section 9.2.2.1.6 Exit Interview
Added secondary endpoints for assessing sign-free days as reported in the PESQ-C for all patients and symptom-free days as reported in the PESQ-P for patients aged ≥8 to <12 years.	[redacted]	Clinical Study Protocol Synopsis: Secondary Endpoints Section 4.1.2 Secondary Endpoints Section 9.2.2.1.1 Pediatric EoE Sign/Symptom Questionnaire (PESQ)
Updated the primary estimand intercurrent event for initiation of treatment with systemic corticosteroids to include use of systemic and/or swallowed topical corticosteroids.	[redacted]	Section 11.4.3.1 Primary Efficacy Analysis
Added a physical examination at the baseline visit	[redacted]	Table 1 Schedule of Events - Screening and Double-Blind Treatment Period
Added tipping point analysis approach and WOCF-MI approach as sensitivity analyses for primary endpoint and removed the single imputation method for sensitivity analyses.	[redacted]	Clinical Study Protocol Synopsis: Analysis Methods Section 11.4.3.1 Primary Efficacy Analysis Section 11.4.3.2 Secondary Efficacy Analysis
Added that the randomization stratification of baseline weight group may be pooled for CMH test adjusting for the randomization stratification factor (baseline weight group)	The randomization stratification of baseline weight group may be pooled to ensure sufficient sample size of each stratum.	Clinical Study Protocol Synopsis: Statistical Plan Section 11.4.3.1 Primary Efficacy Analysis
Editorial changes to statistical analysis sections	To improve clarity.	Clinical Study Protocol Synopsis: Statistical Plan Section 11 Statistical Plan Section 11.1 Statistical Hypothesis Section 11.2 Justification of Sample Size Section 11.4.1 Patient Disposition

Description of Change	Rationale	Section Changed
		Section 11.4.5.1 Adverse Events Section 11.4.5.3 Treatment Exposure Section 11.4.7 Analysis of Immunogenicity Data

Amendment 2

The purpose of this protocol amendment is to add an additional treatment arm to evaluate a lower exposure of dupilumab, [redacted]. Additional updates were made for clarification of study conduct. The following table outlines the changes made to the protocol and the rationale.

Description of Change	Rationale	Section Changed
Added an additional treatment arm to evaluate lower exposure of investigational product. Accordingly, the number of study sites was increased, and the sample size was updated to reflect the new study design. There will be 90 patients randomized in a 1:1:1 ratio to receive either dupilumab in a higher (N=30) or lower (N=30) exposure dose arm, or matching placebo (N=30). There will be high exposure and low exposure placebo groups to match dupilumab regimens in the respective weight tiers and the details of randomization will be specified in the interactive voice/web response system (IVRS/IWRS) requirement document. High exposure and low exposure placebo groups will be pooled for analysis. Part A: Higher exposure regimens: • [redacted] mg once every 2 weeks (Q2W) in patients who weigh ≥5 kg to <15 kg • [redacted] mg Q2W in patients who weigh ≥15 kg to <30 kg • [redacted] mg Q2W in patients who weigh ≥30 kg to <60 kg Lower exposure regimens: • [redacted] mg once every 4 weeks (Q4W) in patients who weigh ≥5 kg to <15 kg • [redacted] mg Q4W in patients who weigh ≥15 kg to <30 kg • [redacted] mg Q2W in patients who weigh ≥30 kg to <60 kg Part B Higher exposure regimens:	[redacted]	Clinical Study Protocol Synopsis: Site Locations, Study Design, Population, Treatments, Statistical Plan Section 3.2.1 Rationale for Study Design Section 3.2.2 Rationale for Dose Selection Section 6.1 Study Description and Duration Section 7.1 Number of Patients Planned Section 8 Study Treatments Section 8.1 Investigational and Reference Treatments Figure 3 Part A Weight-Tiered Dosing Regimens of Study Drug Figure 4 Part B Weight-Tiered Dosing Regimens of Study Drug Section 8.6 Method of Treatment Assignment Section 8.7 Blinding Section 9.1.1.1 Footnotes for Table 1, footnote #6 Section 9.1.1.2 Footnotes for Table 2, footnote #4b Section 11.1 Statistical Hypothesis Section 11.2 Justification of Sample Size Section 11.4.4 Control of Multiplicity Section 11.4.5 Safety Analysis

Description of Change	Rationale	Section Changed
• [redacted] mg Q2W in patients who weigh ≥5 kg to <15 kg • [redacted] mg Q2W in patients who weigh ≥15 kg to <30 kg • [redacted] mg Q2W in patients who weigh ≥30 kg to <60 kg • [redacted] mg QW in patients who weigh ≥60 kg Lower exposure regimens: • [redacted] mg Q4W in patients who weigh ≥5 kg to <15 kg • [redacted] mg Q4W in patients who weigh ≥15 kg to <30 kg • [redacted] mg Q2W in patients who weigh ≥30 kg to <60 kg • [redacted] mg Q2W in patients who weigh ≥60 kg		
Added re-assignment of weight tiered extended active treatment during Part B if weight has increased to a larger weight tier at visit 12 / week 32.	To maintain appropriate study drug exposure throughout the extended active treatment period.	Clinical Study Protocol Synopsis: Treatments Section 3.2.2 Rationale for Dose Selection Section 8.1 Investigational and Reference Treatments Figure 4 Weight-Tiered Dosing Regimens of Study Drug – Part B Section 9.1.1.2 Footnotes for Table 2, footnote #4b
Updated language referring to a "36-week open-label treatment period" to be "36-week extended active treatment period".	For clarification that treatment will remain blinded for the extended active treatment period.	Clinical Study Protocol Synopsis: Study Design, Statistical Plan Section 2.3 Exploratory Objectives Section 6.1 Study Description and Duration Section 11.3.1 Efficacy Analysis Sets Section 11.4.5.1 Adverse Events Section 11.4.9 Timing of Statistical Analysis

Description of Change	Rationale	Section Changed
Updated text referring to an ongoing phase 3 trial evaluating the efficacy and safety of dupilumab in adult and adolescent patients with EoE (R668-EE-1774) to clarify that Part A has now been completed.	To align with the most recent data from R668-EE-1774.	Clinical Study Protocol Synopsis: Statistical Plan Section 1 Introduction Section 3.2.1 Rationale for Study Design Section 3.2.2 Rationale for Dose Selection Section 3.3.1.1 Benefit Section 3.3.1.3 Benefit-Risk Conclusion Section 11.2 Justification of Sample Size
Added language to clarify general changes in study conduct in the context of the COVID-19 pandemic.	To address guidance from the US and EU regarding the conduct of clinical trials during the COVID-19 pandemic.	Section 3.3.1 Risk-Benefit for Participating in the Study Section 6.1 Study Description and Duration Section 9.1 Section 9.1 Schedule of Events Section 11 Statistical Plan
Revised the adverse events of special interest (AESIs) definitions and adverse drug reactions (ADRs) for the dupilumab clinical development program.	For program consistency [redacted] and to align with the most recent Investigator's Brochure.	Section 3.3.1.2 Risk Section 10.1.3 Events that Require Expedited Reporting to Sponsor
Added a primary estimand for the primary endpoint.	To implement a concept estimand in our primary analysis approaches for the primary endpoints based on ICH E9 (R1).	Section 11.4.3.1 Primary Efficacy Analysis
Minor editorial corrections.	For clarification.	Throughout the protocol.

Amendment 1

The purpose of this amendment is to add the Pediatric Eosinophilic Esophagitis Symptom Score (PEESSv2.0- caregiver version) questionnaire as a secondary endpoint and to change the Pediatric EoE Sign/Symptom Questionnaire (PESQ-Caregiver and PESQ-Patient) questionnaires from exploratory to secondary endpoints. Additionally, the Eosinophilic Esophagitis-Endoscopic Reference Score (EoE-EREFS) procedure was revised to allow for centralized reading and scoring. Minor changes were made to clarify inclusion and exclusion criteria. Other minor changes were made [redacted] for general clarification. The following table outlines the changes made to the protocol and the rationale.

Description of Change	Brief Rationale	Section # and Name
Added the PEESS questionnaire at baseline and week 16 and added corresponding secondary objectives and endpoints.	[redacted]	Clinical Study Protocol Synopsis: Objectives, Endpoints, Procedures and Assessments, Statistical Plan Section 2.2 Secondary Objectives Section 3.2.1 Rationale for Study Design Section 4.1.2 Secondary Endpoints Section 5.2 Efficacy Variables Table 1 Schedule of Events - Screening and Double-Blind Treatment Period Table 2: Schedule of Events - Extended Active Treatment Period and 12-Week Follow-Up Period Table 3: Schedule of Events - Early Termination Visits and Unscheduled Visits Section 9.1.1.1 Footnotes for Table 1, footnote #15 Section 9.1.1.2 Footnotes for Table 2, footnote #11 Section 11 Footnotes for Table 3, footnote #6 Section 9.2.2.1.5 Pediatric Eosinophilic Esophagitis Symptom Score (PEESS) Section 19 References
Updated the PESQ-Caregiver and PESQ-Patient questionnaires from exploratory objectives and endpoints to secondary objectives and endpoints.	[redacted]	Clinical Study Protocol Synopsis: Objectives, Endpoints, Statistical Plan Section 2.2 Secondary Objectives Section 2.3 Exploratory objectives Section 3.2.1 Rationale for Study Design Section 4.1.2 Secondary Endpoints Section 4.1.3 Exploratory Endpoints Section 11.4.3.2 Secondary Efficacy Analysis
Revised the EoE-EREFS procedure to allow for centralized reading and scoring	To minimize inter-rater variability for this endpoint.	Clinical Study Protocol Synopsis: Procedures and Assessments

Description of Change	Brief Rationale	Section # and Name
and specified that video is the preferred method of imaging.		Section 9.1.1.1 Footnotes for Table 1, footnotes #2 and #9 Section 9.1.1.2 Footnotes for Table 2, footnote #7 Section 11 Footnotes for Table 3, footnote #4 Section 9.2.2.3 Endoscopy with EoE-EREFS and Biopsies, and Imaging Section 11.4.3.2 Secondary Efficacy Analysis
Clarified the endpoints and variables for transcriptome sequencing for analyzing RNA expression of EoE and type 2 inflammation.	For clarification.	Clinical Study Protocol Synopsis: Objectives, Endpoints, Procedures and Assessments Section 2.2 Secondary Objectives Section 4.1.2 Secondary Endpoints Section 9.2.6.2 EoE Diagnostic Panel and Type 2 Inflammation Transcriptomics Section 11.4.3.2 Secondary Efficacy Analysis Section 19 References
Added endpoints at week 52 (corresponding to assessments already included in this study) for all secondary and exploratory endpoints (except for the PEESSv2.0 caregiver version).	For clarification	Clinical Study Protocol Synopsis: Endpoint(s) Section 4.1.2 Secondary Endpoints Section 4.1.3 Exploratory Endpoints
Added laboratory collection and analysis of blood samples at visit 5/week 4 and visit 12/week 32 for chemistry and hematology.	[redacted]	Table 1 Schedule of Events - Screening and Double-Blind Treatment Period Table 2: Schedule of Events - Extended Active Treatment Period and 12-Week Follow-Up Period
Updated the permanent discontinuation of study drug for severe abnormal laboratory value requirements for neutrophil count, platelet count, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) values to include all events of these severe laboratory values, regardless of assessment of relatedness to study drug.	[redacted]	Section 8.4.2.1 Reasons for Permanent Discontinuation of Study Drug
Updated inclusion criteria to add the requirement for completion of at least 8 out of 14 days of eDiary for the PESQ-C prior to baseline/visit 3.	For clarification.	Section 7.2.1 Inclusion Criteria, criterion #5 Section 9.2.2.1 Patient-, Caregiver-, or Clinician-Reported Outcome Measures
Clarified exclusion criterion #13 for the double-blind period and prohibited medications to allow for one-time steroid use with the anesthetic preparation (not	For clarification.	Section 7.2.2.1 Part A – Double-Blind Treatment, criterion #13 Section 8.10.1 Prohibited Medications and Procedures

Description of Change	Brief Rationale	Section # and Name
for EoE) used during the endoscopy procedures.		
Clarified the requirement that all pre-dosing procedures (including endoscopy with biopsy) at the scheduled visit 8/week 16 must occur prior to dosing with Part B/Extended Active Treatment study drug.	For clarification.	Section 9.1.1.2 Footnotes for Table 2, footnote #1
Minor changes in language.	For clarification and consistency throughout the protocol.	Section 9.1.1.1 Footnotes for Table 1, footnote #14 Section 11 Footnotes for Table 3, footnote #5 Section 9.2.2.1.3 Global Impression of Change (GIC) Section 9.2.3.3 Laboratory Testing Section 9.2.8 Future Biomedical Research (Optional) Section 9.2.8.1 Pharmacogenomic Analysis (Optional)

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Dupilumab in Pediatric Patients with Active Eosinophilic Esophagitis
Site Locations	Approximately 30 global study sites
Principal Investigator	To be determined
Objectives	**Primary:** To demonstrate the efficacy of dupilumab treatment compared with placebo in pediatric patients with active eosinophilic esophagitis (EoE) based on histologic improvement meeting validated histologic criteria. **Secondary:** • 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 (up to 160 weeks) dupilumab treatment • To assess the impact of dupilumab treatment on changes in weight and growth during the extended active period and open-label extension period of the study • To assess safety, tolerability, and immunogenicity of long-term (up to 160 weeks) dupilumab treatment • To evaluate the impact of dupilumab treatment on EoE signs and symptoms • To assess the impact of dupilumab treatment on changes in weight and growth during the extended active and open-label extension period of the study
Study Design	This is a phase 3, multicenter, randomized, 3-part, double-blind, placebo-controlled study investigating the efficacy, safety, tolerability, pharmacokinetics (PK), and immunogenicity of dupilumab in pediatric patients (ages ≥1 year to <12 years) with active EoE. This study consists of 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), a 108-week open-label extension period (Part C) and a 12-week follow-up period. After patients and their legal parents/legal guardians provide informed assent (as appropriate) and informed consent, patients will be assessed for study eligibility.

	Patients are required to have a documented diagnosis of EoE that 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 proton pump inhibitor (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). Patients who are on PPIs during the screening period to rule out EoE disease management with this treatment, 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 (visit 3); they then must remain off of PPIs during the entire study. Biopsies will be obtained by endoscopy at screening visit 2, the week 16 visit, the week 52 visit, the week 100 visit, the week 160 visit, or immediately prior to start of rescue medication or procedures (only applies to rescue medication and/or procedures that occur before the week 52 visit). 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 other for RNA extraction. Patients may receive concomitant medications (except for prohibited medications specified in the protocol body) as needed, at the discretion of the investigator, while continuing study treatment. Frequency of use and type of product will be documented. Efficacy, safety, laboratory assessments, and samples for assay of concentration of functional dupilumab in serum and potential anti-drug antibody (ADA) response to dupilumab, as well as research samples, will be performed or collected at specified time points throughout the study according to Schedule of Events specified in the protocol body.
Study Duration	The duration of the study for a patient is up to 172 weeks, excluding the screening period.
End of Study Definition	The end of study is defined as the date the last patient completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).
Population	
Sample Size:	Approximately 90 patients
Target Population:	Eligible patients for this study consist of patients with active EoE. Key inclusion criteria include the following: • Males and females aged ≥1 year to <12 years. • A documented diagnosis of EoE by endoscopic biopsy prior to screening, as demonstrated by intraepithelial eosinophilic infiltration (peak eosinophil count ≥15 eos/hpf) (400×) from at least 1 esophageal region and performed after at least 8 weeks of treatment with a PPI regimen. If the patient discontinued PPI therapy, the biopsy must have been performed within 2 weeks of the date of discontinuation.

If a prior (documented) endoscopic biopsy meeting these criteria is not available (or no prior biopsy is available), patients who meet other clinical and laboratory eligibility criteria will undergo treatment with a PPI regimen for at least 8 weeks during the screening period before their baseline endoscopy/biopsies.

- Baseline endoscopic biopsies with a demonstration on central reading of intraepithelial eosinophilic infiltration (peak eosinophil count ≥15 eos/hpf) in at least 2 of the 3 biopsied esophageal regions (proximal, mid, or distal).
- History (by patient or caregiver report) of symptom(s) determined by the investigator to be the result of EoE (eg, abdominal pain, chest pain, acid reflux, food regurgitation, dysphagia, vomiting, or refusal to eat) in the month prior to screening.

Treatments

Study Drug Dupilumab

Dose/Route/Schedule:

Part A: Part A is the double-blind, placebo-controlled portion of the study. Subcutaneous (SC) administration at tiered dosing regimens based on body weight at baseline.

Higher exposure dupilumab regimens (Part A):

- [redacted] mg once every 2 weeks (Q2W) in patients who weigh ≥5 kg to <15 kg
- [redacted] mg Q2W in patients who weigh ≥15 kg to <30 kg
- [redacted] mg Q2W in patients who weigh ≥30 kg to <60 kg

Lower exposure dupilumab regimens (Part A):

- [redacted] mg once every 4 weeks (Q4W) in patients who weigh ≥5 kg to <15 kg
- [redacted] mg Q4W in patients who weigh ≥15 kg to <30 kg
- [redacted] mg Q2W in patients who weigh ≥30 kg to <60 kg

NOTE: In Part A, patients will receive dupilumab injections at the frequency of Q2W or Q4W with matching placebo alternating with dupilumab doses so the injection frequency will be Q2W for both groups for regimen-blinding purposes per treatment assignment.

Part B: Part B is the extended active treatment portion of the study. All patients (Part A active and placebo) will receive dupilumab based on body weight at visit 8 (week 16, end of double-blinded treatment period or start of extended treatment period) per the higher and lower exposure group to which they were assigned at randomization. If weight tier has increased at visit 12 / week 32, patients will be re-assigned to an extended active treatment regimen based on weight tiered dosing regimens below.

Higher exposure dupilumab regimens (Part B):

- [redacted] mg Q2W in patients who weigh ≥5 kg to <15 kg
- [redacted] mg Q2W in patients who weigh ≥15 kg to <30 kg
- [redacted] mg Q2W in patients who weigh ≥30 kg to <60 kg
- [redacted] mg QW in patients who weigh ≥60 kg

Lower exposure dupilumab regimens (Part B):

- [redacted] mg Q4W in patients who weigh ≥5 kg to <15 kg
- [redacted] mg Q4W in patients who weigh ≥15 kg to <30 kg
- [redacted] mg Q2W in patients who weigh ≥30 kg to <60 kg
- [redacted] mg Q2W in patients who weigh ≥60 kg

NOTE: In Part B, study drug or matching placebo will be administered Q2W for all patients in <60 kg weight-groups and QW for all patients in ≥60 kg weight-groups. Patients will receive alternating doses of dupilumab or placebo Q2W for patients <60 kg assigned to Q4W regimens or QW for patients ≥60 kg assigned to Q2W regimens for regimen-blinding purposes.

Part C: Part C is the open-label extension portion of the study. All patients (Part C) will receive higher exposure dupilumab regimens based on body weight at visit 17 (week 52, end of extended active treatment period) or start of open-label period (for re-entry patients). All patients who received lower exposure dupilumab during Part B will be re-assigned to higher exposure dupilumab regimens at the start of the open-label (Part C) period. If weight increases place a patient into a higher weight tier at visit 17 / week 52 (or start of open-label period for re-entry patients) or at specified in-clinic visits in Part C, the patient will be re-assigned to an open-label treatment regimen based on the weight tiered dosing regimen specified below.

Higher exposure dupilumab regimens (Part C):

- [redacted] mg Q3W in patients who weigh ≥5 kg to <15 kg
- [redacted] mg Q2W in patients who weigh ≥15 kg to <30 kg
- [redacted] mg Q2W in patients who weigh ≥30 kg to <40 kg
- [redacted] mg QW in patients who weigh ≥40 kg

NOTE: In Part C, only active study drug (dupilumab) will be administered. No matching placebo will be administered in Part C. The weight-based dosing regimens will be as listed above.

For Part C only: Patients located in a country where dupilumab is commercially available for treatment of EoE in patients ≥12 years old will be provided treatment with study drug until they are both (1) at least 12 years of age and (2) weigh at least 40 kg or the lowest weight for which the indication is approved for EoE. These patients will have an end of treatment visit at the next scheduled study visit upon meeting both criteria, followed by an end of study follow-up visit after 12 weeks.

Placebo

Route/Schedule:

Matching dupilumab for the respective body-weight tier and exposure regimen (Part A and B only).

Placebo for Part A: Dose matching placebo Q2W or alternating with dupilumab Q4W so the frequency will be Q2W for both groups for regimen-blinding purposes in Part A.

Placebo for Part B: Dose matching placebo alternating with dupilumab Q2W or Q4W so the frequency will be Q2W for the weight-based groups <60kg and QW for the weight-based group of ≥60 kg for regimen-blinding purposes in Part B.

No matching placebo will be administered in Part C.

Background Treatment

Patients who are on PPIs during the screening period to rule out EoE disease management with this treatment, and are eligible to enroll in the study, have

Dose/Route/Schedule:	the choice either to remain on the PPI regimen during the entire study or stop the PPI regimen prior to baseline; they then must remain off of PPIs during the entire study.

Endpoints

Primary:	Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf (400×) at week 16
Secondary:	**Secondary Efficacy Endpoints for Part A and B:** • 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 in the type 2 inflammation transcriptional signature score at week 16 • Change from baseline to week 16 in the proportion of days with 1 or more EoE signs as measured by the Pediatric EoE Sign/Symptom Questionnaire-caregiver version (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 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 PESQ-P (patient version) (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 (patient version) (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 PESQ-P (for patients aged ≥8 to <12 years) • Change in total score from baseline to week 16 as measured by the Pediatric Eosinophilic Esophagitis Symptom Score (PEESS) v2.0-caregiver version questionnaire (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 (except for PEESSv2.0- caregiver version questionnaire) assessed at week 16 will be assessed at week 52 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.
- Change from baseline in body weight for age percentile at week 52
- Change in body mass index for age z-score from baseline to week 52 for patients ≥2 years of age
- Change in weight for age z-score from baseline to week 52
- Change in weight for height z-score from baseline to week 52

Secondary Efficacy Endpoints for Part C (open-label extension period) only:

- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf (400×) at week 100 and week 160
- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf at week 100 and week 160
- Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 100 and week 160
- Absolute change in mean EoE grade score from the EoE-HSS from baseline to week 100 and week 160
- Absolute change in mean EoE stage score from the EoE-HSS from baseline to week 100 and week 160
- Absolute change in EoE-EREFS from baseline to week 100 and week 160
- Normalized Enrichment Scores (NES) for the relative change from baseline to week 100 and 160 in the EoE diagnostic panel (EDP) transcriptome signature
- NES for the relative change from baseline to week 100 and week 160 in the type 2 inflammation transcriptome signature
- Change in total score from baseline to week 160 as measured by the PEESSv2.0- caregiver version questionnaire
- Proportion of patients (with food elimination diet regimens at baseline) that have a re-introduction of a previously eliminated food group by week 100 and by week 160
- Change from baseline in body weight for age percentile up to week 160
- Change in body mass index for age z-score for patients ≥2 years of age from baseline to up to week 160
- Change in weight for age z-score from baseline to up to week 160
- Change in weight for height z-score from baseline to up to week 160

Safety Endpoints (Parts A, B, and C):

- Incidence of treatment-emergent adverse events (TEAEs) during the 16-week double-blind treatment period
- Incidence of TEAEs during the 36-week extended treatment period

- Incidence of TEAEs during the 108-week open-label extension period
- Incidence of treatment-emergent serious adverse events (SAEs) during the 16-week double-blind treatment period
- Incidence of treatment-emergent SAEs during the 36-week extended treatment period
- Incidence of treatment-emergent SAEs during the 108-week open-label extension period
- Incidence of treatment-emergent adverse events of special interest (AESIs) during the 16-week double-blind treatment period
- Incidence of treatment-emergent AESIs during the 36-week extended treatment period
- Incidence of treatment-emergent AESIs during the 108-week open-label extension period
- Incidence of TEAEs leading to permanent discontinuation of study treatment during the 16-week double-blind treatment period
- Incidence of TEAEs leading to permanent discontinuation of study treatment during the 36-week extended treatment period
- Incidence of TEAEs leading to permanent discontinuation of study treatment during the 108-week open-label extension period
- Incidence of treatment-emergent ADA responses and titer during the 16-week double-blind, 36-week extended treatment periods, and 108-week open-label extension period

Clinical Pharmacology Endpoint:

- Concentrations of functional dupilumab in serum by treatment regimen at each assessment time point from baseline to end of study

Procedures and Assessments	**Efficacy procedures and assessments** include the following:
	• Endoscopy with EoE-EREFS and biopsies
	  o EoE-EREFS imaging will be performed to assess the presence of exudates, edema, furrows, esophageal rings, and strictures. EoE-EREFS imaging will be read and scored by a qualified centralized reading center. For all endoscopies, the investigators will assess minor esophageal features including mucosal inflammatory and remodeling features.
	  o Esophageal endoscopy with biopsies: After EoE-EREFS imaging has been completed, biopsies will be obtained for histologic assessments including intraepithelial eosinophil count and EoE-HSS (EoE grade score and EoE stage score). Biopsies will be evaluated by pathologists at a central pathology laboratory who will be blinded to treatment assignment.
	• Patient-, caregiver-, or clinician-reported outcome measures
	  o Pediatric EoE Sign/Symptom Questionnaire (PESQ), including a patient version (PESQ-P) and caregiver version (PESQ-C)
	  o Pediatric EoE Impact Scale (PEIS), including a patient version (PEIS-P) and a caregiver version (PEIS-C)
	  o Global Impression of Change (GIC), including a patient version (GIC-P), a caregiver version (GIC-C), and a clinician version (GIC-Clin)
	  o Global Impression of Severity (GIS), including a patient version (GIS-P), a caregiver version (GIS-C), and a clinician version (GIS-Clin)
	  o The Pediatric Eosinophilic Esophagitis Symptom Score (PEESS) v2.0- caregiver version questionnaire
	  o Telephone exit interview
	• Body weight and height (or length for patients <2 years of age); body mass index will be programmatically calculated based on the weight and height/length data
	
	Safety and tolerability procedures and assessments include vital signs, physical examination, clinical laboratory tests, ADA assessment, and clinical evaluations. Patients will be asked to report all adverse events (AEs) experienced from the time of informed assent/consent until their last study visit.
	
	Pharmacokinetics: Serum samples will be collected at specified time points for assay of functional dupilumab concentration.

Statistical Plan

Sample Size:

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

The assumptions used in sample size calculation were based on Part A of the R668-EE-1774 study (a phase 3 study for adults and adolescents with EoE) and R668-EE-1324 (a phase 2 study for adults with EoE). In Part A of the R668-EE-1774, the proportions of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24 were 59.5% and 5.1% for dupilumab and placebo, respectively. 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%. In the R668-EE-1324 study, the proportions of patients achieving histologic response at week 12 were 65% and 0% for dupilumab and placebo, respectively. The efficacy of dupilumab can be established as early as week 12. Based upon the similarity of pathophysiology and expected similarity of 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 is assumed to have a similar treatment effect as 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. 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 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 (ie, patients achieving peak esophageal intraepithelial eosinophil count ≤6 eos/hpf) at week 16 between placebo (5.1%) and each dupilumab treatment group (40.7%).

Efficacy Analysis Set for Part A:

The full analysis set (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.

Safety Analysis Set for Part A:

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

Analysis Set for Part B and Part C

For efficacy and safety analyses of Parts B and C, only a subset of SAF for Part A will be included, which is defined as those patients who received at least 1 dose of corresponding Part B or/and C study drug.

Analysis Methods:

Primary Efficacy Analysis in Part A

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 full analysis set (FAS), adjusting for the randomization stratification factor (baseline weight group). The randomization stratification of baseline weight group may be pooled to ensure the sufficient sample size of each stratum.

To account for use of rescue treatment, patients will be considered as non-responder after rescue treatment.

If a patient has missing value for the histological response (peak esophageal intraepithelial eosinophil count ≤6 eos/hpf) at week 16, the patient will be classified as a non-responder at week 16.

Sensitivity analyses will assess alternative methods to impute missing data. The sensitivity analyses will include a tipping point analysis approach and a worst observation carried forward -Multiple Imputation (WOCF-MI) approach.

Subgroup analyses (eg, by weight) may be performed. Details will be specified in the SAP.

Secondary Efficacy Analysis

Analysis of secondary endpoints in Part A

Secondary efficacy endpoints that measure binary responses (eg, peak esophageal intraepithelial eosinophil count <15 eos/hpf) will be analyzed in the same fashion as the primary endpoint.

Continuous secondary efficacy endpoints will be analyzed using an analysis of covariance (ANCOVA) model for the FAS with treatment group, randomization stratification factor, and relevant baseline measurement as a covariate included in the model.

For continuous efficacy data that are scheduled to be measured repeatedly post-baseline up to week 16, missing data will be imputed by the pattern-mixture approach. Specifically, the WOCF-Multiple Imputation (WOCF-MI) approach.

Analysis of secondary endpoints in Part B

Efficacy data in Part B will be summarized with descriptive statistics 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.

Analysis of secondary endpoints in Part C

Efficacy data in Part C will be summarized with descriptive statistics for treatment received in Part C as well as by treatment group in Part A (double-blind treatment period) and Part B (extended active treatment period). No missing values will be imputed.

Multiplicity Consideration

For multiplicity adjustment, a hierarchical procedure will be used to control the overall Type-1 error rate at 0.05 for the primary endpoint and the selected secondary efficacy endpoints for each dupilumab dose regimen 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 primary endpoint will be tested for the higher exposure dupilumab group

	first and then for the lower exposure dupilumab group. The hierarchical order of the selected secondary endpoints will be specified in the SAP. Part B and Part C data will be summarized using descriptive statistics, there is no multiplicity issue. Safety Analysis Safety analysis will be based on the safety analysis set (SAF) in the respective study part. This includes reported TEAEs and other safety data (ie, clinical laboratory evaluations and vital signs). A descriptive summary of safety results will be presented by treatment group for each study part.

1. INTRODUCTION

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). There is a low rate of spontaneous remission. 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). In the United Sates, based on data from insurance claims within the Truven MarketScan database, the estimated number of patients between newborn and 11 years of age with EoE is approximately 35,000. Gender differences in EoE have been consistently reported, with males affected 3 to 4 times more often than females (Dellon, 2014), but there are no gender-related differences in the clinical symptoms (Kapel, 2008) (Prasad, 2009) (Veerappan, 2009) (Hruz, 2011) (Ally, 2015). 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 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 in 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) (Greuter, 2017). Dietary modification is a standard treatment for patients with EoE. Diets eliminating specific foods can be effective in a significant percentage of patients; however, 30%

to 40% of patients do not have resolution of disease with dietary modification (Nhu, 2019). 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. Emergency endoscopy for prolonged and/or painful food impaction, and esophageal dilation to provide relief from strictures, are associated with a risk of severe esophageal injury and do not alter the underlying pathogenesis or progression of the disease. To date, the United States (US) Food and Drug Administration (FDA) has not approved pharmacologic therapies for EoE for children less than 12 years; the European Commission has approved budesonide oral dispersible tablets for the treatment of EoE in adults, but no approved medicinal product is available for the treatment of EoE in children in the European Union (EU).

Growing evidence suggests that a type 2 immune response plays an important pathogenic role in the development of EoE in genetically susceptible individuals. Food allergens permeate an impaired esophageal epithelial barrier and initiate an inflammatory reaction where activated type 2 helper T cells (Th2) increase tissue levels of type 2 cytokines, such as interleukin (IL)-5, IL-13, and IL-4. These cytokines are responsible for driving eosinophil recruitment and activation. Several genes in the epidermal differentiation complex such as filaggrin (*FLG*), desmogelin 1 (*DSG1*), and the esophagus-specific esophagin (small proline-rich protein 3 [*SPRR3*]), are down-regulated by type 2 cytokines with resultant epithelial barrier dysfunction (Blanchard, 2007) (Blanchard, 2010) (Wen, 2013). Eotaxin-3 (chemokine [C-C motif] ligand 26 gene [CCL26]) is a potent eosinophil chemoattractant which is highly regulated by IL-13 and IL-4, and variants in the gene are associated with increased EoE risk; it is 1 of the top upregulated genes in esophageal pinch biopsies in EoE patients compared to controls (Blanchard, 2006) (Sherrill, 2014). Upon activation, eosinophils can secrete a variety of pro-inflammatory cytokines and chemokines or degranulate, releasing preformed granules containing cationic and cytotoxic proteins that are injurious to the tissues. While EoE involves an eosinophil-predominant inflammation, there is evidence to suggest that other immune cells, such as mast cells, basophils, and invariant natural killer T cells also mediate the inflammation (Straumann, 2012) (O'Shea, 2018).

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 (brand name DUPIXENT®) is approved in the US and EU for the treatment of adult and adolescent patients aged 12 years and older with atopic dermatitis (AD). Dupilumab has also been approved in the US as an add-on maintenance treatment for adults and adolescents (age 12 and older) with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid-dependent asthma; it is approved in the EU for severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised fractional exhaled nitric oxide (FeNO) in patients who are inadequately controlled with a high-dose inhaled corticosteroid

plus another medicinal product for maintenance treatment. Dupilumab has also been approved in the US and EU for chronic rhinosinusitis with nasal polyps (CRSwNP). Dupilumab is currently approved in the United States for the treatment of adult and pediatric patients aged 12 years and older, weighing at least 40 kg, with eosinophilic esophagitis (EoE).

Dupilumab was evaluated in adult patients with EoE in a phase 2, multicenter, double-blind, randomized, placebo-controlled study (R668-EE-1324), where it demonstrated substantial improvements in clinical, histologic, and endoscopic aspects of the disease (Hirano, 2019a). In the dupilumab group, Straumann Dysphagia Index Patient-Reported Outcome scores were reduced by a mean value of 3.0 at week 10, compared with a mean reduction of 1.3 in the placebo group (P=.0304). At week 12, dupilumab reduced peak esophageal intraepithelial eosinophil count by a mean 86.8 eos/high power field (hpf) (reduction of 107.1 %, P <.0001 vs placebo), and the endoscopic reference score was reduced by 1.6 (P=.0006 vs placebo). 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 phase 3 trial evaluating the efficacy and safety of dupilumab in adult and adolescent patients with EoE (R668-EE-1774) was initiated. The co-primary endpoint for the adult and adolescent trial includes both a validated symptom measurement utilizing the dysphagia symptom questionnaire (DSQ) and histologic evaluation.

R668-EE-1774 Part A met both of its co-primary endpoints in symptomatic (dysphagia) and histological response, as well as all key secondary endpoints in histologic, endoscopic, and molecular (transcriptomic) domains for patients treated with dupilumab [redacted] mg QW. R668-EE-1774 Part B of the study was considered positive for treatment with dupilumab [redacted] mg QW, as this dose regimen showed statistically significant improvement in both co-primary endpoints. In contrast, treatment with dupilumab [redacted] mg Q2W did not meet the co-primary endpoint of symptomatic improvement but demonstrated statistically significant improvement in the co-primary endpoint for histological response. Further, dupilumab [redacted] mg Q2W demonstrated a similar magnitude in response as [redacted] mg QW for other secondary histologic, endoscopic, and molecular (transcriptomic) endpoints.

Histological and molecular evidence suggest that the disease has the same underlying pathogenesis in different age groups and responds similarly to swallowed topical corticosteroid treatment regardless of age (Straumann, 2012). Therefore, for the pediatric trial, where symptoms are more heterogeneous, success of the trial will be determined by histologic measures; however, symptom assessments will be evaluated through exploratory endpoints.

The R668-EE-1877 phase 3 Part A study met its primary endpoint (proportion of patients with peak eosinophil count ≤6/high power field [hpf] in esophageal biopsy tissue) for both higher and lower exposure dupilumab regimens at week 16 (p-values < 0.0001). Additionally, as part of a prespecified exploratory analysis, the dupilumab treatment groups experienced increases in body weight for age percentile from baseline as compared to placebo at week 16. Safety results from R668-EE-1877 Part A were generally consistent with the known safety profile of dupilumab in its approved EoE indication for children and adults aged 12 years and older who weigh at least 40 kg.

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

2. STUDY OBJECTIVES

2.1. Primary Objective

To demonstrate the efficacy of dupilumab treatment compared with placebo in pediatric patients with active EoE based on histologic improvement meeting validated histologic criteria.

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 (up to 160 weeks) dupilumab treatment
- To assess the impact of dupilumab treatment on changes in weight and growth during the extended active period and open-label extension period of the study
- To assess safety, tolerability, and immunogenicity of long-term (up to 160 weeks) dupilumab treatment
- To evaluate the impact of dupilumab treatment on EoE signs and symptoms
- To assess the impact of dupilumab treatment on changes in weight and growth during the extended active and open-label extension period of the study

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 phase.
- To conduct exploratory research to study EoE and dupilumab mechanism of action in pediatric patients, including predictive biomarker discovery and/or validation

3. HYPOTHESIS AND RATIONALE

3.1. Hypotheses

In pediatric patients (ages ≥1 year to <12 years) with active EoE, dupilumab will significantly reduce eosinophilic inflammation compared to placebo, as measured by reduction in eosinophilic esophageal infiltration (assessed by change in esophageal peak intraepithelial eosinophil count and EoE-HSS score).

3.2. Rationale

3.2.1. Rationale for Study Design

This is a randomized, 3-part, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in pediatric EoE. Children with active EoE, ages ≥1 year to <12 years, who are PPI histologically non-responsive, will be randomized 1:1:1 to receive either higher exposure dupilumab (N=30) or lower exposure dupilumab (N=30) (in a tiered, weight-based dosing schema) or placebo (N=30) over 16 weeks. In the absence of valid and reliable clinical outcomes assessment (COA) tools for symptom assessment, 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 clinical efficacy histological endpoint and to characterize the safety profile of dupilumab in pediatric patients with EoE.

Rationale for Endpoints

In 2017, guidelines on EoE were published to optimize diagnosis and treatment of the condition. An extensive literature search was completed with systematic evidence-based reviews. A task force of 21 physicians and researchers addressed questions related to EoE. There was agreement among members of the task force that clinical symptoms and signs are variable across age groups; however, objectively, the histologic criterion of EoE is at least 15 eos/hpf in esophageal mucosa (Lucendo, 2017).

Given the key disease feature of EoE is esophageal dysfunction, and esophageal health is the only consistent way to observe treatment difference in children, the proposed primary endpoint in this study is the proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf (400×). It is also a responder endpoint that was significantly improved by dupilumab in the adult phase 2 study R668-EE-1324 (65.2% responders at week 12) and is a co-primary endpoint in the adult/adolescent phase 3 study R668-EE-1774. In Part A of this phase 3 study, the proportions of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24 were 59.5% and 5.1% for dupilumab and placebo, respectively. The consensus recommendation for diagnosis of EoE is peak esophageal intraepithelial eosinophil cell count ≥15 eos/hpf. Reduction to ≤6 eos/hpf may be an optimal response threshold for clinical trials, as it identified most patients who had a combined symptomatic and endoscopic response (Dellon, 2007).

The EoE-HSS is a recently validated histologic scoring system that measures other histological abnormalities in addition to the density of eosinophilic infiltration, including eosinophil surface layering, eosinophil abscesses, basal zone hyperplasia, dilated intercellular spaces, surface epithelial alteration, and dyskeratotic epithelial cells. It has been confirmed in adults to have external reliability and this scoring system is highly responsive to treatment (Collins, 2017) (Warners, 2018).

The visual EoE esophageal anatomical 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. 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, present); Rings (absent, mild, moderate, severe); Exudates (absent, mild, severe); Furrows (absent, mild, severe); and Stricture (absent, present). Endoscopic findings in EoE have been well described and are observed in the vast majority of EoE patients, though the type and frequency vary by age. The EoE-EREFS scoring system has been externally validated to identify disease in EoE children and adults, to reflect changes in disease severity after treatment, and it has been used in multiple clinical trials (Hirano, 2017) (Wechsler, 2018).

Other efficacy endpoints, endoscopic analysis of severity by EoE-EREFS, and EoE-HSS histologic response will be collected as secondary efficacy endpoints. In a phase 2 study of RPC4046, a monoclonal antibody against IL-13, the EoE-HSS instrument was used and assessed by a centralized, blinded pathologist with expertise in eosinophilic disorders. This study showed that reductions in mean adjusted EoE-HSS grade scores of 31 points and stage scores of 27 points between RPC4046 and placebo were statistically significant after 16 weeks of anti-IL-13 treatment in adults with active EoE (Hirano, 2019a). In R668-EE-1877 Part A, as part of a prespecified exploratory analysis, the dupilumab treatment groups experienced increases in body weight for age percentile from baseline as compared to placebo at week 16. Given that growth rate and weight changes are important efficacy indicators of dupilumab treatment in pediatric EOE patients, weight and growth changes will be assessed as secondary endpoints for the extended active and open label extension treatment periods.

In terms of clinical outcomes, the caregiver-reported versions of the Pediatric EoE Sign/Symptom Questionnaire (PESQ-C) and the Pediatric Eosinophilic Esophagitis Symptom Score (PEESSv2.0) questionnaire will be used as secondary endpoints. Since patient-reported symptoms are expected to be reliable for pediatric patients ≥8 years of age (Matza, 2013), the patient-reported version of the PESQ (PESQ-P) will also be used as a secondary endpoint. Finally, health-related quality of life (HRQoL) and EoE disease status will be measured as exploratory endpoints using the Pediatric EoE Impact Scale (PEIS) and the Global Impression of Severity (GIS) and Global Impression of Change (GIC) questionnaires.

Safety of dupilumab in this pediatric patient population is a key question, and therefore safety endpoints will also be included as secondary endpoints in this study. In addition, pharmacokinetics (PK) will also be analyzed as a secondary endpoint.

3.2.2. Rationale for Dose Selection

Based on the known safety, efficacy, and PK of dupilumab, which has been studied in adults, adolescents, and children as young as 6 months of age, the dose regimen to be investigated in this study in children with EoE aged ≥1 year to <12 years is weight-based dosing as follows:

Higher exposure dupilumab regimens for Parts A, B, and C (approximates C_{trough} of [redacted] mg QW regimen in adults):

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Lower exposure dupilumab regimens for Part A and B (approximates Ctrough of [redacted] mg Q2W regimen in adults):

- [redacted] mg once every 4 weeks (Q4W) in patients who weigh ≥5 kg to <15 kg
- [redacted] mg Q4W in patients who weigh ≥15 kg to <30 kg
- [redacted] mg Q2W in patients who weigh ≥30 kg to <60 kg
- [redacted] mg Q2W in patients who weigh ≥60 kg (Part B Only)

NOTE: Patients ≥ 60 kg are excluded from enrollment into Part A, but patients may reach this weight tier during the extended active period (Part B) or open label extension period (Part C). All patients will be reassigned a weight-tiered dose for the higher exposure dupilumab regimen in Part C at visit 17 / week 52 (or start of open label period for re-entry patients). At specified in-clinic visits in Part C, patients that have increased in body weight to a higher weight tier will be re-assigned to an appropriate open-label treatment regimen for their corresponding weight.

During Part A and Part B, patients will receive dupilumab injections at the frequency of QW, Q2W, or Q4W with matching placebo alternating with dupilumab doses 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 Part A and Part B.

For Part C, patients will receive the higher exposure dupilumab weight tiered dosing regimen. No matching placebo will be administered in Part C. The doses and regimens of dupilumab are intended to approximate the steady-state trough concentrations (C_{trough}) observed in adult patients receiving [redacted] mg QW for the higher exposure regimen. In order to achieve similar exposures across this broad age range, the doses will be assigned by weight tiers.

In adults, dupilumab regimens of [redacted] mg Q2W were shown to be well tolerated and efficacious in patients with asthma, AD and CRSwNP. The [redacted] mg QW dose in adult patients has shown significant clinical and histological efficacy in a previous proof-of-concept study (R668-EE-1324) as well as in an on-going study in adolescent and adult patients with EoE (R668-EE-1774). The

[redacted] mg QW dose has been shown to be well tolerated in patients with EoE, consistent with its evaluation in other type 2 inflammatory diseases. No clinically significant differences in the pharmacokinetics of dupilumab have been observed between healthy subjects or patients with asthma, AD, CRSwNP, or EoE.

The dupilumab [redacted] mg Q2W dose is an approved dosing regimen in adult patients with atopic dermatitis, chronic rhinosinusitis with nasal polyposis, or asthma (in the US), as well as in adolescent patients 12 years of age or older with asthma (in the US) and adolescents and children (≥6 years of age) with atopic dermatitis who weigh ≥60 kg. The weight-tiered pediatric regimen of dupilumab [redacted] mg Q4W in ≥15 to <30 kg or [redacted] mg Q2W in ≥30 to <60 kg was also approved in the US in patients ≥6 to <12 years of age with AD and was selected to produce exposures in pediatric patients similar to those in adults receiving [redacted] mg Q2W. The safety profile also has been comparable between adult and pediatric (≥6 to <18 years) patients in AD as well as in asthma populations receiving dupilumab [redacted] mg Q2W regimen.

In adults and adolescents with EoE receiving dupilumab [redacted] mg QW or Q2W (R668-EE-1774 Part B), both regimens significantly improved histologic endpoints relative to placebo, but only [redacted] mg QW also improved dysphagia symptoms. Dupilumab [redacted] mg QW is approved in the US for use in adults and adolescents with EoE weighing at least 40 kg. Given the higher exposure and lower exposure dupilumab regimen approximate the steady-state (C_{trough}) observed in adult patients receiving [redacted] mg QW and Q2W, respectively, the higher exposure regimen will be administered in Part C of this study to provide the maximum potential benefit to pediatric patients with EoE. Within the higher exposure dupilumab regimen, the body weight threshold at which patients switch from [redacted] mg Q2W to [redacted] mg QW will be changed from 60 kg in Part B to 40 kg in Part C to align with the approved regimen for adults and adolescents with EoE. The pharmacokinetics of dupilumab are independent of age in children at least 6 years of age and by modifying this weight tier, pediatric patients ≥40 kg will receive the same dupilumab dose in Part C as approved in the US for adult and adolescent patients with EoE of similar body weight. It is expected that pediatric patients who weigh ≥40 kg will be at least 6 years of age (CDC Growth Charts: United States, 2000). The dose for patients ≥5 to <15 kg in Part C will also be adjusted from [redacted] mg Q2W to [redacted] mg Q3W for the higher exposure dupilumab regimen to provide a closer approximation of the trough concentrations in adults and adolescents with EOE receiving [redacted] mg QW.

From trials in the dupilumab program across indications evaluating both the [redacted] mg QW and the [redacted] mg Q2W doses in adult patients with AD or in adult and adolescent patients with EoE, the [redacted] mg Q2W regimen has a similar safety profile to that of [redacted] mg QW regimen, with the exception of a higher incidence of injection site reactions in the [redacted] mg QW regimen, which is likely associated with more frequent injections with drug substance. No loading dose is proposed in this study, consistent with the dosing regimens being evaluated in the phase 3 study of adult and adolescent patients (≥12 years of age) with EoE (R668-EE-1774).

Due to the rarity of EoE in children ≥1 year to <12 years, larger studies evaluating multiple dose regimens are not feasible. Dupilumab exposures in pediatric patients were simulated using a population PK model developed including data collected across multiple studies in pediatric patients with AD ≥6 months to <18 years of age. Both the higher and lower exposure regimens were selected to provide steady-state exposures that did not exceed the 95th percentile of maximal concentrations (C_{max}) for the [redacted] mg QW adult dose, and did not fall below the 5th percentile of

C_{trough} for the [redacted] mg Q2W adult dose. The subset of patients ≥5 to <15 kg receiving [redacted] mg Q3W or ≥40 to <60 kg receiving [redacted] mg QW in Part C may exhibit C_{max} values higher than the overall adult [redacted] mg QW population, but are expected to be within the range of exposures observed for adolescents ≥40 receiving [redacted] mg QW. Dupilumab has a wide safety margin and no exposure-related adverse events have been identified, hence the higher C_{max} in these groups is not considered to be clinically relevant.

Enrollment in Part A is limited to patients weighing <60 kg, but it is possible that patient weight may increase above this threshold during the study. Patients weighing ≥60 kg at the time of dose assignment at visit 8 / week 16 and/or visit 12 / week 32 or ≥40 kg at visit 17 / week 52 of Part B (or at start of open label period for re-entry patients) and/or during specified in-clinic visits for Part C of the study will receive regimens equivalent to the reference adult dose(s). Patients located in a country where dupilumab is commercially available for treatment of EoE in patients ≥12 years old will be provided treatment with study drug until they are both (1) at least 12 years of age and (2) weigh at least 40 kg or the lowest weight for which the indication is approved. These patients will have an end of treatment visit at the next scheduled study visit upon meeting both criteria, followed by an end of study follow-up visit after 12 weeks.

The proposed regimens provide similar exposures that have been effective and well tolerated in multiple indications in adults and adolescents. For the higher exposure regimens, these predicted C_{trough} values are similar to what has been demonstrated to be effective in adult patients with EoE. For the lower exposure regimens, the predicted C_{trough} values are similar to what has been demonstrated to be effective in other type 2 inflammatory indications.

3.3. Benefit-Risk

3.3.1. Benefit-Risk for Participating in the Study

Recognizing that the "Coronavirus Disease 2019" (COVID-19) pandemic will have an impact on the conduct of clinical trials, the sponsor does not intend to screen any patients in this study until the impact of the COVID-19 pandemic is deemed manageable and no longer interfering with the conduct of trials at individual sites, and patients can safely participate in this study. For further information regarding COVID-19 pandemic study impact, see Section 9.

3.3.1.1. Benefit

The efficacy and safety of dupilumab in adults with EoE were evaluated in a phase 2, randomized, double-blind, placebo-controlled study (R668-EE-1324). In the initial phase 2 study, treatment with weekly dupilumab [redacted] mg subcutaneously (SC) for 12 weeks in patients with EoE reduced the frequency and intensity of dysphagia. Improvement in clinical symptoms was accompanied by endoscopic and biopsy histologic evidence of reduced esophageal intraepithelial eosinophil infiltration, esophageal mucosal inflammation, and improved esophageal distensibility.

Additionally, data from the ongoing phase 3 randomized, double-blind, placebo-controlled study (R668-EE-1774-Part A) showed a substantial and statistically significant improvements in clinical, endoscopic, and histologic measures of the disease in adult and adolescent patients treated with dupilumab [redacted]mg SC (N=42) versus placebo (N=39) at week 24. R668-EE-1774 Part B of the study was considered positive for treatment with dupilumab [redacted] mg QW, as this dose regimen showed statistically significant improvement in both co-primary endpoints. In contrast, treatment with dupilumab [redacted] mg Q2W did not meet the co-primary endpoint of symptomatic improvement but demonstrated statistically significant improvement in the co-primary endpoint for histological response. Further, dupilumab [redacted] mg Q2W demonstrated a similar magnitude in response as [redacted] mg QW for other secondary histologic, endoscopic, and molecular (transcriptomic) endpoints. Dupilumab is currently approved in the United States for the treatment of adult and pediatric patients aged 12 years and older, weighing at least 40 kg, with eosinophilic esophagitis (EoE). This is the first time a phase 3 trial with a biologic treatment has reported improvement in patients' ability to swallow food, as reported by a daily questionnaire.

The R668-EE-1877 phase 3 Part A study met its primary endpoint (proportion of patients with peak eosinophil count ≤6/high power field [hpf] in esophageal biopsy tissue) for both higher and lower exposure dupilumab regimens at week 16 (p-values < 0.0001). Additionally, as part of a prespecified exploratory analysis, the dupilumab treatment groups experienced increases in body weight for age percentile from baseline as compared to placebo at week 16.

Although presenting symptoms of EoE may vary when comparing children to adolescents and adults, the underlying disease is thought to be the same. Therefore, the efficacy demonstrated in adults and adolescents with EoE who were treated with dupilumab is expected to be replicated in the pediatric population. Study patients could potentially benefit from dupilumab treatment, including patients randomized to receive placebo in Part A, as all patients have the opportunity to receive dupilumab in the extended active treatment Part B and open-label extension Part C of the study.

3.3.1.2. Risk

Dupilumab has demonstrated a favorable safety profile in clinical studies across all approved indications. Dupilumab was well tolerated by the study patients in trial R668-EE-1774 and safety results from R668-EE-1877 Part A were generally consistent with the known safety profile of dupilumab in its approved EoE indication for children and adults aged 12 years and older who weigh at least 40 kg.

The identified adverse drug reactions (ADR) across all indications are Injection Site Reactions (ISRs), Sickness-like Reaction/Serum Sickness and Anaphylactic Reaction. Though serious serum sickness and serum sickness-like reactions were observed rarely and only in atopic dermatitis (AD) clinical trials; and dupilumab-related anaphylactic reaction was observed rarely and only in an asthma clinical trial, they are considered ADRs across all indications as hypersensitivity is not expected to be indication specific. As protein therapeutics, all mAbs are potentially immunogenic. Systemic hypersensitivity is considered an important identified risk for dupilumab.

Eosinophilia associated with clinical symptoms in asthma patients is an important potential risk, based on cases of eosinophilic granulomatosis with polyangiitis and eosinophilic pneumonia reported in asthma clinical trials (as well as in adult patients with co-morbid asthma in the

CRSwNP development program). These events usually, but not always, may be associated with the reduction of oral corticosteroid therapy. A causal association between dupilumab and these conditions has not been established. The DUPIXENT® US Prescribing Information lists upper respiratory tract infections (composed of several terms including, but not limited to, COVID-19, sinusitis, and upper respiratory tract infection) in the 'Adverse Reactions' section for the adult and adolescent EoE indication. In the AD clinical studies, Conjunctivitis, Conjunctivitis Allergic, Conjunctivitis Bacterial, Blepharitis, Dry Eye, Eye Pruritus, Herpes Simplex (primarily mucocutaneous in nature), Eosinophilia and Oral Herpes were identified ADRs. The eye and herpes related ADRs appear to be predominantly AD indication specific. Conjunctivitis is also considered an ADR for the CRSwNP indication, although it occurred at a lower incidence in these studies than in AD studies. Most events were mild in intensity, transient in nature, and did not necessitate treatment discontinuation. In the completed AD studies in children aged 6 to 17 years, the safety profile was consistent with that reported in adults and there was no new safety concerns identified. In a study in patients aged 6 to 11 years with asthma, Enterobiasis and Eosinophilia were identified as additional ADRs. Angioedema, arthralgia, keratitis, ulcerative keratitis and facial rash have been identified as ADRs in the post-marketing setting.

3.3.1.3. Benefit-Risk Conclusion

The safety data available to date across multiple indications, in conjunction with the clinical benefit of dupilumab demonstrated in the phase 2 EoE study and Part A and B of the phase 3 EoE study, support a favorable benefit-risk profile for dupilumab.

A risk-benefit statement with respect to the overall clinical development program is provided in the Investigator's Brochure.

3.3.2. Benefit-Risk for Background Treatment

Proton pump inhibitors are FDA-approved for the short-term treatment in children for healing of EoE (CMS, 2013). A trial of PPIs prior to endoscopy with biopsy will ensure that pediatric patients with EoE who show improvement/resolution in their signs and symptoms of EoE with this treatment are appropriately excluded from this trial. Proton pump inhibitors are generally well tolerated, and risks associated with short-term use are minimal. The most common adverse reactions seen in pediatric patients are headache, diarrhea, constipation, and nausea. Chronic acid suppression can minimize the effectiveness of any medication requiring an acidic environment for absorption. Commonly prescribed medications affected by acid suppression are ampicillin esters, digoxin, atazanavir, ketoconazole, and iron salts.

4. ENDPOINTS

4.1. Primary and Secondary Endpoints

4.1.1. Primary Endpoint

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

4.1.2. Secondary Endpoints

Secondary Efficacy Endpoints for Part A and B:

- 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 in the type 2 inflammation transcriptional signature score at week 16
- Change from baseline to week 16 in the proportion of days with 1 or more EoE signs as measured by the Pediatric EoE Sign/Symptom Questionnaire-caregiver version (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 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 PESQ-P (patient version) (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 (patient version) (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 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 questionnaire (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 (except for PEESSv2.0- caregiver version questionnaire) assessed at week 16 will be assessed at week 52 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.

- Change from baseline in body weight for age percentile at week 52
- Change in body mass index for age z-score from baseline to week 52 for patients ≥2 years of age
- Change in weight for age z-score from baseline to week 52
- Change in weight for height z-score from baseline to week 52

Secondary Efficacy Endpoints for Part C (open-label extension period) only:

- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf (400×) at week 100 and week 160
- Proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf at week 100 and week 160
- Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to week 100 and week 160
- Absolute change in mean EoE grade score from the EoE-HSS from baseline to week 100 and week 160
- Absolute change in mean EoE stage score from the EoE-HSS from baseline to week 100 and week 160
- Absolute change in EoE-EREFS from baseline to week 100 and week 160
- Normalized Enrichment Scores (NES) for the relative change from baseline to week 100 and 160 in the EoE diagnostic panel (EDP) transcriptome signature
- NES for the relative change from baseline to week 100 and week 160 in the type 2 inflammation transcriptome signature
- Change in total score from baseline to week 160 as measured by the PEESSv2.0-caregiver version questionnaire
- Proportion of patients (with food elimination diet regimens at baseline) that have a re-introduction of a previously eliminated food group by week 100 and by week 160
- Change from baseline in body weight for age percentile up to week 160
- Change in body mass index for age z-score for patients ≥2 years of age from baseline to up to week 160
- Change in weight for age z-score from baseline to up to week 160
- Change in weight for height z-score from baseline to up to week 160

Safety Endpoints (Part A, B, and C):

- Incidence of treatment-emergent adverse events (TEAEs) during the 16-week double-blind treatment period
- Incidence of TEAEs during the 36-week extended treatment period
- Incidence of TEAEs during the 108-week open-label extension period
- Incidence of treatment-emergent serious adverse events (SAEs) during the 16-week double-blind treatment period
- Incidence of treatment-emergent SAEs during the 36-week extended treatment period
- Incidence of treatment-emergent SAEs during the 108-week open-label extension period
- Incidence of treatment-emergent adverse events of special interest (AESIs) during the 16-week double-blind treatment period
- Incidence of treatment-emergent AESIs during the 36-week extended treatment period
- Incidence of treatment-emergent AESIs during the 108-week open-label extension period
- Incidence of TEAEs leading to permanent discontinuation of study treatment during the 16-week double-blind treatment period
- Incidence of TEAEs leading to permanent discontinuation of study treatment during the 36-week extended treatment period
- Incidence of TEAEs leading to permanent discontinuation of study treatment during the 108-week open-label extension period
- Incidence of treatment-emergent ADA responses and titer during the 16-week double-blind, 36-week extended treatment periods, and 108-week open-label extension period

Clinical Pharmacology Endpoint:

Concentrations of functional dupilumab in serum by treatment regimen at each assessment time point from baseline to end of study

4.1.3. Exploratory Endpoints

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 caregivers of patients aged ≥1 to <12 years)
- Percent change in total PEIS-P (patient version) score from baseline to week 16 (for patients aged ≥8 to <12 years)

- Change in GIC-patient, caregiver, and clinician version score at up to week 52
- Change in GIS-patient, caregiver, and clinician version score from baseline to up to week 160/EOT
- 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

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, sex, race, weight, height, etc.), EoE disease characteristics, medical history, and medication history for each patient.

5.2. Efficacy Variables

The efficacy variables include measurements or scores for individual patients of the following:

- From the endoscopy with EoE-EREFS and biopsies procedure: peak esophageal intraepithelial eosinophil counts, score of EoE-HSS (including EoE grade and stage scores), and score of EoE-EREFS
- Patient-, caregiver-, or clinician-reported outcomes:
  - score of the PESQ-P (for patients aged ≥8 to <12 years) and the PESQ-C (for patients aged ≥1 to <12 years)
  - score of the PEIS-P (for patients aged ≥8 to <12 years) and the PEIS-C (for caregivers of patients aged ≥1 to <12 years)
  - score of the GIC-P (for patients aged ≥8 to <12 years), GIC-C (for caregivers of patients aged ≥1 to <12 years), and GIC-Clin (for patients aged ≥1 to <12 years)
  - score of the GIS-P (for patients aged ≥8 to <12 years), GIS-C (for caregivers of patients aged ≥1 to <12 years), and GIS-Clin (for patients aged ≥1 to <12 years)
  - score of the PEESSv2.0- caregiver version (for patients aged ≥1 to <12 years)
- Measurement of body weight and height or length for patients <2 years of age; body mass index will be programmatically calculated based on weight and height/length data

5.3. Safety Variables

Safety variables include recording, measurements, or laboratory test results for individual patients of the following: adverse events (AEs); vital signs including heart rate, blood pressure, respiration rate, and body temperature; physical examination findings; results of laboratory tests including hematology, blood chemistry, urinalysis, and pregnancy test.

5.4. Pharmacokinetic Variables

The PK variable is the concentration of functional dupilumab in serum and time point for individual patients. These sampling timepoints are specified in Table 1, Table 2, Table 3, and Table 4.

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, neutralizing antibody (NAb) status, and time point/visit. Samples in this study will be collected at the clinic visits specified in Table 1, Table 2, Table 3, and Table 4.

5.6. Pharmacodynamic and Other Biomarker Variables

Pharmacodynamic and biomarker variables include laboratory test results for individual patients of the following: serum total IgE and eotaxin-3.

6. STUDY DESIGN

6.1. Study Description and Duration

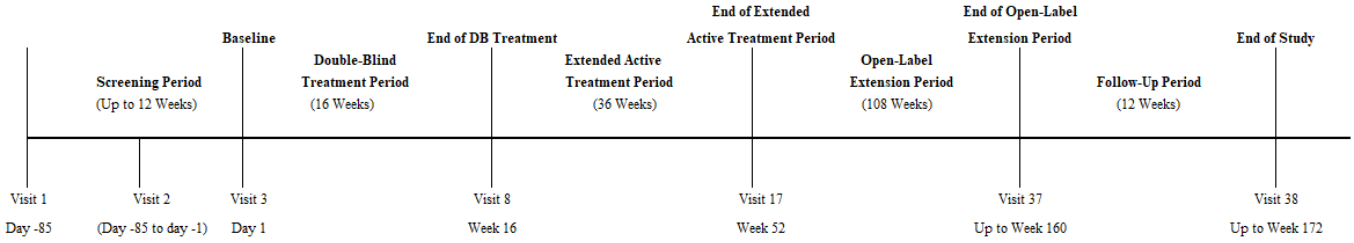
This is a phase 3, multicenter, randomized, 3-part, double-blind, placebo-controlled study investigating the efficacy, safety, tolerability, PK, and immunogenicity of dupilumab in pediatric patients (ages ≥1 to <12 years) with active EoE.

Approximately 90 patients will be randomized (1:1:1 ratio for higher exposure dupilumab group: lower exposure dupilumab group: placebo) at approximately 30 study sites globally. The dosing of the placebo group will be matched with higher exposure and lower exposure dupilumab regimens in the respective weight tiers and placebo with different dosing will be combined. The details on the randomization will be specified in an interactive voice/web response system (IVRS/IWRS) requirement document.

This study consists of 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), a 108-week open-label extension period (Part C) and a 12-week follow-up period. The open-label extension period (Part C) will add up to 108 weeks of open-label treatment or until dupilumab becomes commercially available in the country of the participating patients (whichever comes first).

The study flow diagram is provided in Figure 1.

Figure 1: Study Flow Diagram

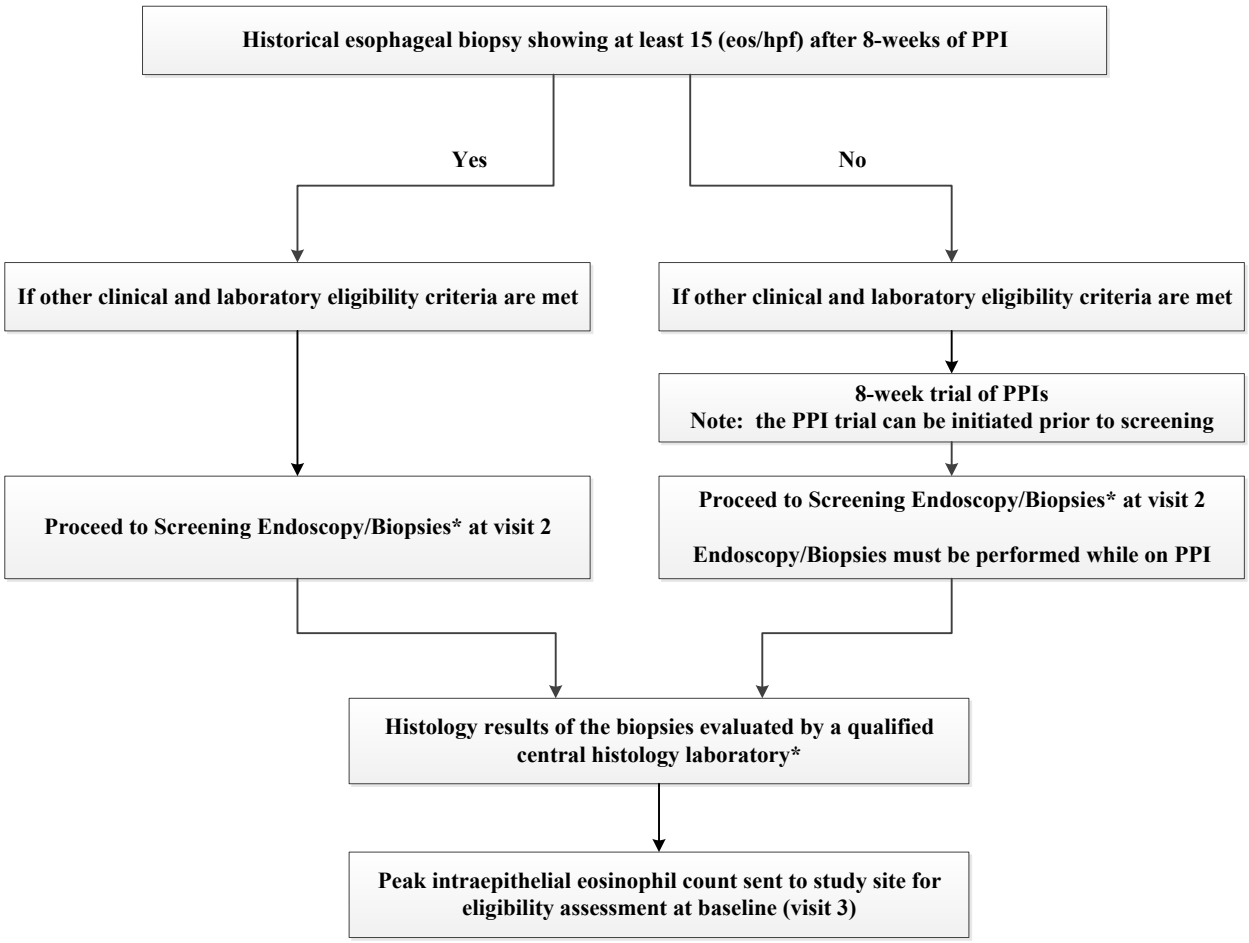


After patients and their legal parents/legal guardians provide informed assent (as appropriate) and informed consent, patients will be assessed for study eligibility.

Patients who have completed their end of study (EOS) visit prior to amendment 4 will be re-evaluated for eligibility at a Re-Entry visit for participation in the open-label extension period (Part C) and Safety Follow-up period (see Section 7.2.2.3). Patients who have entered the safety follow-up period after completing Part B at the time of amendment 4 approval may immediately enter the open-label extension (Part C) without being required to complete an EOS visit prior to entering Part C.

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. See Figure 2 for endoscopy/biopsy procedure flow chart.

Figure 2: Endoscopy/Biopsy Procedure Flow Diagram



* Biopsy specimens from the antrum and duodenum will be obtained in all patients to rule out alternate etiologies. All randomized patients found to have stomach and/or duodenal abnormalities at baseline will have follow-up stomach and/or duodenal biopsies at week 16, week 52, week 100, and week 160.

Patients who are on PPIs during the screening period to rule out EoE disease management with this treatment, 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; they then must remain off of PPIs during the entire study.

Biopsies will be obtained by endoscopy at the screening visit 2, week 16 visit, week 52, week 100 and week 160 visits, or immediately prior to start of rescue medication or procedures (only applies to rescue medication and/or procedures that occur before the week 52 visit). 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 Part A baseline 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 may receive concomitant medications (except for prohibited medications specified in Section 8.10.1) as needed, at the discretion of the investigator, while continuing study treatment. Frequency of use and type of product will be documented.

Efficacy, safety, laboratory assessments, and samples for assay of concentration of functional dupilumab in serum and potential ADA response to dupilumab, as well as research samples, will be performed or collected at specified time points throughout the study according to the Schedule of Events in Table 1, Table 2, Table 3, and Table 4.

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), the first visit of Part B and the first visit of Part C occur in the clinic. Endoscopies with biopsies are required at the visit 2 screening biopsy and at approximately week 16, week 52, week 100, and week 160. 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 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 are to 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.

6.1.1. End of Study Definition

The end of study is defined as the date the last patient completes the last study visit, withdraws from the study, or is lost to follow-up (ie, the study patient can no longer be contacted by the investigator).

6.2. Planned Interim Analysis

No interim analysis is planned for this study.

The primary analysis may be performed once all patients in the study have completed the 16-week double-blind treatment period in Part A as specified in the protocol (week 16 visit or earlier for those patients who are withdrawn prematurely from the study). If performed, this primary analysis will be considered the final analysis for the primary and week 16 secondary efficacy endpoints. A description of the statistical methods to be employed and blinding implications are in Section 11.

6.3. Study Committees

6.3.1. Independent Data Monitoring Committee

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

The DMC will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in the study.

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

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

Approximately 90 pediatric patients are planned to be enrolled.

7.2. Study Population

Eligible patients for this study consist of patients with active EoE, ages ≥1 to <12 years.

7.2.1. Inclusion Criteria

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

1. Male or female, ages ≥1 year to <12 years
2. A documented diagnosis of EoE by endoscopic biopsy prior to screening, as demonstrated by intraepithelial eosinophilic infiltration (peak eosinophil count ≥15 eos/hpf) (400×) from at least 1 esophageal region and performed after at least 8 weeks of treatment with a PPI regimen. If the patient discontinued PPI therapy, the biopsy must have been performed within 2 weeks of the date of discontinuation.

   If a prior (documented) endoscopic biopsy meeting these criteria is not available (or no prior biopsy is available), patients who meet other clinical and laboratory eligibility criteria will undergo treatment with a PPI regimen for at least 8 weeks during the screening period before their baseline endoscopy/biopsies.
3. Baseline endoscopic biopsies with a demonstration on central reading of intraepithelial eosinophilic infiltration (peak eosinophil count ≥15 eos/hpf) in at least 2 of the 3 biopsied esophageal regions (proximal, mid, or distal)
4. History (by patient or caregiver report) of symptom(s) determined by the investigator to be the result of EoE (eg, abdominal pain, chest pain, acid reflux, food regurgitation, dysphagia, vomiting, or refusal to eat) in the month prior to screening
5. Patients ≥8 to <12 years of age and caregiver or legal guardians of all patients must be able to understand and complete the study requirements and study-related questionnaires. At least 8 out of 14 days of eDiary for the PESQ-C should be completed prior to baseline/visit 3.
6. Parents or legal guardians must provide signed informed consent. Assent should be collected from patient, if applicable, as per local regulatory (competent authority/ethics) guidelines, based upon the age and level of maturity of the patient.

7.2.2. Exclusion Criteria

7.2.2.1. Exclusion Criteria for Part A - Double-Blind Treatment

A patient who meets any of the following criteria will be excluded from the study:

1. Body weight <5 kg or ≥60 kg at screening
2. Prior participation in a dupilumab clinical trial or past or current treatment with dupilumab
3. Initiation or change of a food-elimination diet regimen or re-introduction of a previously eliminated food group in the 6 weeks prior to screening. Patients on a food-elimination diet must remain on the same diet throughout the study.
4. Other causes of esophageal eosinophilia or the following conditions: eosinophilic gastroenteritis, hypereosinophilic syndrome, and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
5. Active Helicobacter pylori
6. Helminthic infection
7. History of Crohn's disease, ulcerative colitis, celiac disease, or prior esophageal surgery
8. Any esophageal stricture unable to be passed with a standard, diagnostic, upper endoscope or any critical esophageal stricture that requires dilation at screening
9. Treatment with swallowed topical corticosteroids within 8 weeks prior to baseline standard of care endoscopy
10. Treatment with subcutaneous immunotherapy (SCIT) unless on a stable maintenance dose for at least 1 year
11. Prior treatment with sublingual immunotherapy (SLIT), epicutaneous immunotherapy (EPIT), or oral immunotherapy (OIT)
12. Initiation, discontinuation, or change in the dosage regimen of the following medications within 8 weeks prior to the baseline endoscopy: PPIs, leukotriene inhibitors, and nasal and/or inhaled corticosteroids
13. Treatment with systemic immunosuppressant/immunomodulating drugs, including but not limited to systemic corticosteroids, mepolizumab, omalizumab, cyclosporine, mycophenolate-mofetil, interferon-gamma (IFN-γ), Janus kinase inhibitors, azathioprine, and methotrexate within 3 months prior to screening
    a. NOTE: One-time use of a corticosteroid as a part of the anesthetic preparation used during each endoscopy procedure is allowed.
14. Treatment with an investigational drug within 2 months or within 5 half-lives (if known), whichever is longer, prior to baseline visit

15. History of bleeding disorders or esophageal varices that, in the opinion of the investigator, would put the patient at undue risk for significant complications from an endoscopy procedure
16. Planned or anticipated use of any prohibited medications and procedures during the study
17. Planned or anticipated major surgical procedure during the study
18. Treatment with a live (attenuated) vaccine within 4 weeks before the baseline visit

    NOTE: For patients who have vaccination with live, attenuated vaccines planned during the course of the study (based on national vaccination schedule/local guidelines), it will be determined, after consultation with a pediatrician, whether the administration of vaccine can be postponed until after the end of study, or preponed to before the start of the study, without compromising the health of the patient:

    – Patients for whom administration of live (attenuated) vaccine can be safely postponed would be eligible to enroll into the study
    – Patients who have their vaccination preponed can enroll in the study only after at least 4 weeks following administration of the vaccine
19. Active parasitic infection or suspected parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization
20. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, or antifungals within 2 weeks before baseline visit

    NOTE: Patients may be re-screened after the infection resolves
21. Known or suspected immunodeficiency disorder, including history of invasive opportunistic infections (eg, tuberculosis [TB], non-tuberculous mycobacterial infections, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency, or prolonged infections suggesting an immune-compromised status, as judged by the investigator

    NOTE: Tuberculosis testing will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics committees (ECs).
22. Known history of human immunodeficiency virus (HIV) infection or positivity for Hepatitis B or Hepatitis C antigens
23. On current treatment for hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis, or hepatic failure, or has evidence of liver disease as indicated by persistent (confirmed by repeated tests ≥2 weeks apart) elevated transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) more than 3 times the upper limit of normal [ULN] during the screening period)
24. Any of the following abnormal laboratory values at screening:
    – Platelets $<100 \times 10^3/\mu L$

- Neutrophils $\leq 1.5 \times 10^3/\mu L$
- Estimated glomerular filtration rate (eGFR) (Totri, 2017) <30 mL/min/1.73 m^2

NOTE: If an abnormal value is detected at screening, a repeat test should be performed to confirm the abnormality. Only if the repeat test confirms the abnormality would the patient be categorized as a screen failure. Estimated glomerular filtration rate will be calculated using the Bedside Schwartz formula.

25. Severe concomitant illness(es) that, in the investigator's judgment, would adversely affect the patient's participation in the study. Examples include but are not limited to active malignancy, short life expectancy, uncontrolled diabetes, cardiovascular conditions (eg, New York Heart Association Class III or IV cardiac failure), severe renal conditions (eg, patients on dialysis), hepatobiliary conditions (eg, Child-Pugh class B or C), neurological conditions (eg, demyelinating diseases), active major autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc.), and other severe endocrinologic, gastrointestinal, metabolic, pulmonary, or lymphatic diseases. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, case report forms [CRF], etc.).
26. History of malignancy within 5 years prior to screening
27. History of alcohol or drug dependence within 6 months prior to screening, in the opinion of the investigator
28. Any other medical or psychological condition including relevant laboratory abnormalities at screening that, in the opinion of the investigator, suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments. The specific justification for patients excluded under this criterion will be noted in study documents.
29. Patient's immediate family is a member of the investigational team.
30. Patient is female who is pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study.
31. Patient is of childbearing potential* who is unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 12 weeks after the last dose. Highly effective contraceptive measures include:
    a. stable use of combined (estrogen and progestogen-containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
    b. intrauterine device; intrauterine hormone-releasing system (IUS)
    c. and/or sexual abstinence†, ‡.

    *Women of childbearing potential (WOCBP) are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile.

Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

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

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

32. Female patients who experience menarche and who are unwilling to follow the precautions for WOCBP
33. Known systemic hypersensitivity to dupilumab or the excipients of the drug product

7.2.2.2. Exclusion Criteria for Part B – Extended Active Treatment (and also for Entry into Part C for Patients with Uninterrupted Participation in the Study)

1. Patients who, during the double-blind treatment period (for entry into the extended active period) or during the extended active treatment period (for entry into the open-label extension period), developed an SAE and/or AE deemed related to study drug and which led to discontinuation of investigational product (patients who are prematurely discontinued from study drug due to lack of efficacy are eligible to enter Part B and/or Part C)
2. Patients who, during the double-blind treatment period (for entry into the extended active period), or extended active treatment period (for entry into the open-label extension period) were prematurely withdrawn because of a protocol violation, poor compliance, or inability to complete required study assessments
3. Patients who did not undergo endoscopy with biopsies at week 16 and/or week 52 or prior to receiving rescue treatment

   Note: If the endoscopy with biopsies could not occur due to COVID-19 restrictions and rescue treatment was needed to be initiated without delay, these patients will be eligible to participate in Part C.
4. Female patients who experience menarche and who are unwilling to follow the precautions for WOCBP

7.2.2.3. Exclusion Criteria for Patients Re-Entering the Study (for Entry into Part C for Patients Who Have Completed Their EOS Visit Prior to Amendment 4)

A patient who meets any of the following criteria will not be permitted to re-enter the study:

1. Patients who are ≥12 years old, weigh ≥40 kg (or minimum weight for which dupilumab is approved for EoE), and dupilumab is commercially available for the treatment of EoE in their country.

2. Patients who, during their previous participation in this clinical trial, developed an SAE and/or AE deemed related to dupilumab, which in the opinion of the investigator or of the medical monitor could indicate that continued treatment with dupilumab may present an unreasonable risk for the patient.
3. Patients who did not undergo endoscopy with biopsies at week 16 and/or week 52 or prior to receiving rescue treatment.

   Note: If the endoscopy with biopsies could not occur due to COVID-19 restrictions and rescue treatment was needed to be initiated without delay, these patients will be eligible to participate in Part C.
4. Patients who became pregnant during their previous participation in this dupilumab clinical trial.
5. Patients who, during their previous participation in this trial, were prematurely withdrawn because of a protocol violation, poor compliance, or inability to complete required study assessments.
6. Known history of HIV infection or HIV seropositivity.
7. Known history of positive HBsAg, HBcAb, or hepatitis C antibody.

   NOTE: Patients who are HBsAg negative and HBsAb positive are considered immune after a natural infection has cleared or they have been vaccinated against hepatitis B. Therefore, they are acceptable for the study.
8. Treatment with an investigational drug (other than dupilumab) within 2 months or within 5 half-lives (if known), whichever is longer, prior to the re-entry visit
9. Treatment with systemic immunosuppressant/immunomodulating drugs, including but not limited to mepolizumab, omalizumab, cyclosporine, mycophenolate-mofetil, interferon-gamma (IFN-γ), Janus kinase inhibitors, azathioprine, and methotrexate within 3 months prior to re-entry visit
10. Treatment with a live (attenuated) vaccine within 4 weeks before the re-entry visit.
11. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, or antifungals within 2 weeks before re-entry visit
12. Pregnant or breastfeeding females
13. Females unwilling to use adequate birth control, if of reproductive potential and sexually active (see Exclusion Criterion 31 above for applicable definitions).
14. Any other medical or psychological condition that, in the opinion of the investigator, may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the patient as a result of his/her participation in the trial, may make the patient's participation unreliable, or may interfere with study assessments. The specific justification for patients excluded under this criterion will be noted in the source documents.

7.3. Premature Withdrawal from the Study

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

The investigator and/or sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients who are withdrawn prematurely from the study will be asked to complete the early termination visit, as described in Section 9.1.2.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 8.4.2.

7.4. Replacement of Patients

Patients prematurely discontinued from study or study drug will not be replaced.

8. STUDY TREATMENTS

The following drug product will be provided. Instructions on dose preparation are provided in the pharmacy manual.

Patients will receive dupilumab injections at the frequency of QW, Q2W, or Q4W with matching placebo alternating with dupilumab doses so the injection frequency will be identical within weight tiers for regimen-blinding purposes (Parts A and B). Patients will remain within the originally assigned higher or lower dosing exposure arm throughout the study (Part A and Part B). For Part C, all patients will receive the higher exposure dupilumab weight tiered dosing regimen (QW, Q2W, or Q3W). No matching placebo will be administered in Part C.

Study drug administration at the study sites will be performed only by injection personnel who will not perform any clinical assessment/procedures (this restriction is not required during Part C) (Table 1, Table 2, Table 3, and Table 4).

Dupilumab:

- Dupilumab [redacted] mg/mL: Each 2.25 mL single-use, prefilled syringe with cap delivers [redacted] mg of study drug (2.0 mL of a [redacted] mg/mL solution)
- Dupilumab [redacted] mg/mL: Each 1.14 mL single-use, prefilled syringe with cap delivers [redacted] mg of study drug (1.14 mL of a [redacted] mg/mL solution)
- Dupilumab [redacted] mg/mL: Each 0.67 mL single-use, prefilled syringe with cap delivers [redacted] mg study drug (0.67 mL of a [redacted] mg/mL solution).

Placebo-matching dupilumab (for Parts A and B):

- 2 mL placebo matching [redacted] mg dupilumab formulation
- 1.14 mL placebo matching [redacted] mg dupilumab formulation
- 0.67 mL placebo matching [redacted] mg dupilumab formulation

8.1. Investigational and Reference Treatments

The weight-tiered dosing regimens of the study drug are described below.

- **Part A: 16-Week Double-Blind Treatment Period:** Part A is the double-blind, placebo-controlled portion of the study. Subcutaneous (SC) administration at tiered dosing regimens based on body weight at baseline.

Higher exposure dupilumab regimens (Part A):

- [redacted] mg Q2W in patients who weigh ≥5 kg to <15 kg
- [redacted] mg Q2W in patients who weigh ≥15 kg to <30 kg
- [redacted] mg Q2W in patients who weigh ≥30 kg to <60 kg

Lower exposure dupilumab regimens (Part A):

- [redacted] mg Q4W in patients who weigh ≥5 kg to <15 kg
- [redacted] mg Q4W in patients who weigh ≥15 kg to <30 kg

- [redacted] mg Q2W in patients who weigh ≥30 kg to <60 kg

NOTE: In Part A, patients will receive dupilumab injections at the frequency of Q2W or Q4W with matching placebo alternating with dupilumab doses so the injection frequency will be Q2W for both groups for regimen-blinding purposes per treatment assignment in Part A.

– Placebo for Part A: Dose matching placebo Q2W or alternating with dupilumab Q4W so the frequency will be Q2W for both groups for regimen-blinding purposes in Part A.

– See Figure 3: Weight-Tiered Dosing Regimens of Study Drug – Part A.

- **Part B: 36-Week Extended Active Treatment Period:** Part B is the extended active treatment portion of the study. All patients (Part A active and placebo) will receive dupilumab based on body weight at visit 8 (week 16, end of double-blinded treatment period or start of extended treatment period) per the higher and lower exposure group to which they were assigned at randomization. If weight tier has increased at visit 12 / week 32, patients will be re-assigned to an extended active treatment regimen based on weight tiered dosing regimens below.

Higher exposure dupilumab regimens (Part B):

- [redacted] mg Q2W in patients who weigh ≥5 kg to <15 kg
- [redacted] mg Q2W in patients who weigh ≥15 kg to <30 kg
- [redacted] mg Q2W in patients who weigh ≥30 kg to <60 kg
- [redacted] mg QW in patients who weigh ≥60 kg

Lower exposure dupilumab regimens (Part B):

- [redacted] mg Q4W in patients who weigh ≥5 kg to <15 kg
- [redacted] mg Q4W in patients who weigh ≥15 kg to <30 kg
- [redacted] mg Q2W in patients who weigh ≥30 kg to <60 kg
- [redacted] mg Q2W in patients who weigh ≥60 kg

NOTE: In Part B, study drug or matching placebo will be administered Q2W for all patients in <60 kg weight-groups and QW for all patients in ≥60 kg weight-groups. Patients will receive alternating doses of dupilumab or placebo Q2W for patients <60 kg assigned to Q4W regimens or QW for patients ≥60 kg assigned to Q2W regimens for regimen-blinding purposes

– Placebo for Part B: Dose matching placebo alternating with dupilumab Q2W or Q4W so the frequency will be Q2W for the weight-based groups <60kg and QW for the weight-based group of ≥60 kg for regimen-blinding purposes in Part B.

See Figure 4: Part B Weight-Tiered Dosing Regimens of Study Drug.

- **Part C: Up to 108-Week Open-Label Extension Period:** Part C is the open-label extension period of the study. All patients (Part C) will receive higher exposure dupilumab regimens based on body weight at visit 17 (week 52, end of extended active treatment period) or start of open-label period (for re-entry patients). All patients who received lower exposure dupilumab during Part B will be re-assigned to higher exposure dupilumab regimens at the start of the open-label (Part C) period. If weight increases place a patient into a higher weight tier at visit 17 / week 52 (or start of open-label period for re-entry patients) or at specified in-clinic visits in Part C, the patient will be re-assigned to an open-label treatment regimen based on the weight tiered dosing regimen specified below.

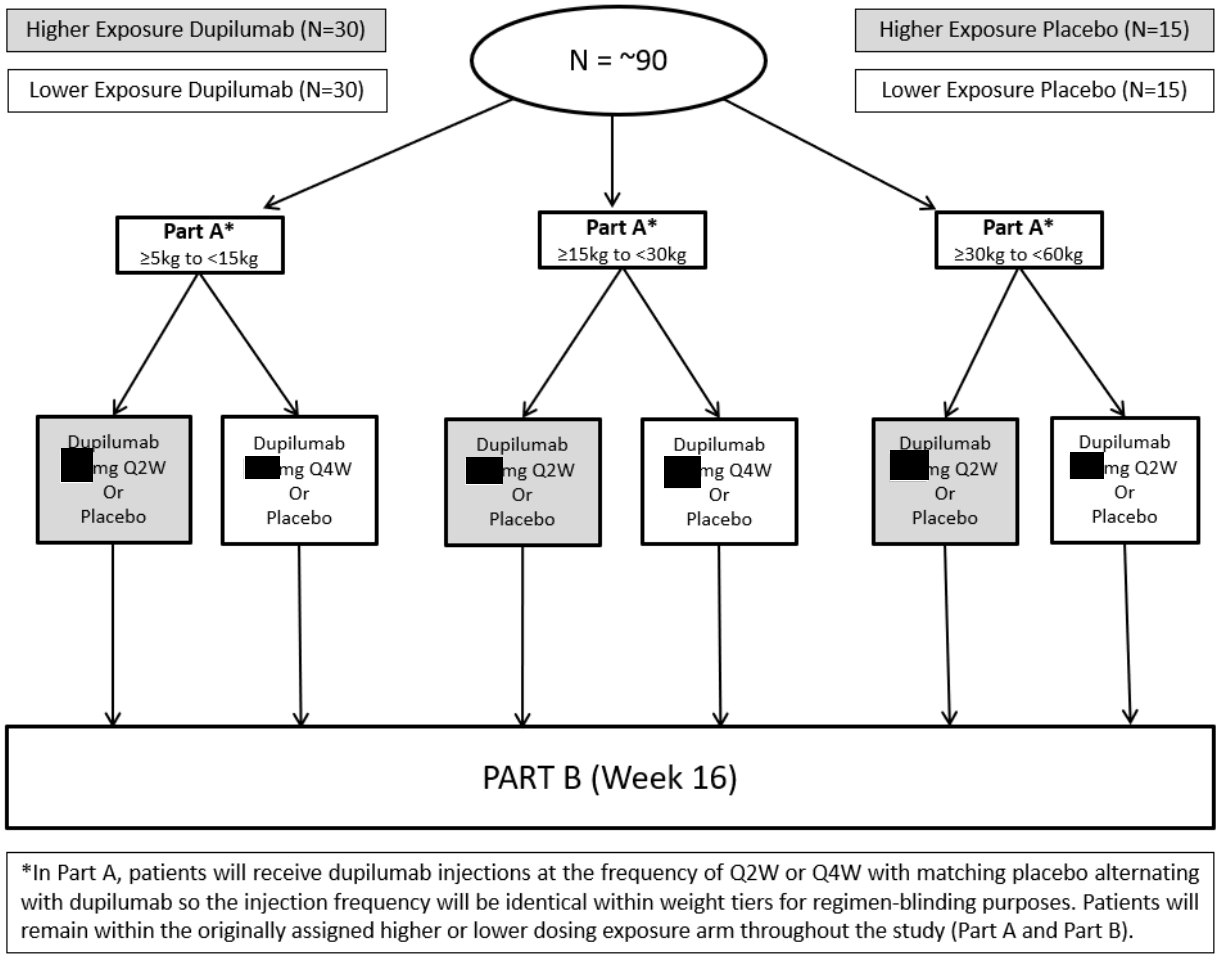
Higher exposure dupilumab regimens (Part C):

- [redacted] mg Q3W in patients who weigh ≥5 kg to <15 kg
- [redacted] mg Q2W in patients who weigh ≥15 kg to <30 kg
- [redacted] mg Q2W in patients who weigh ≥30 kg to <40 kg
- [redacted] mg QW in patients who weigh ≥40 kg

NOTE: In Part C, only active study drug (dupilumab) will be administered. No matching placebo will be administered in Part C. The weight-based dosing regimens will be as listed above (see Figure 5).

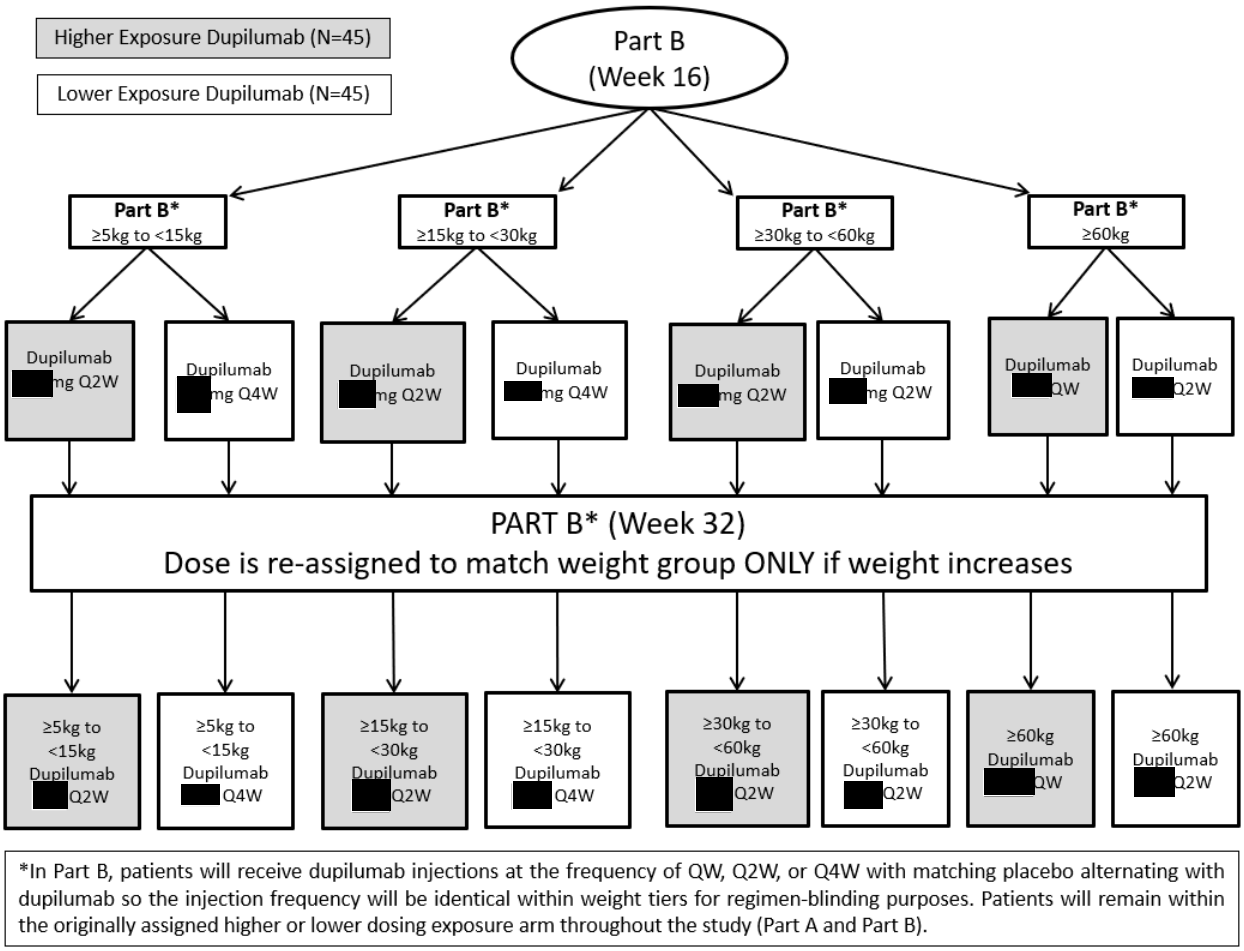
For Part C only: Patients located in a country where dupilumab is commercially available for treatment of EoE in patients ≥12 years old will be provided treatment with study drug until they are both (1) at least 12 years of age and (2) weigh at least 40 kg or the lowest weight for which the indication is approved for EoE. These patients will have an end of treatment visit at the next scheduled study visit upon meeting both criteria, followed by an end of study follow-up visit after 12 weeks.

Figure 3: Part A Weight-Tiered Dosing Regimens of Study Drug



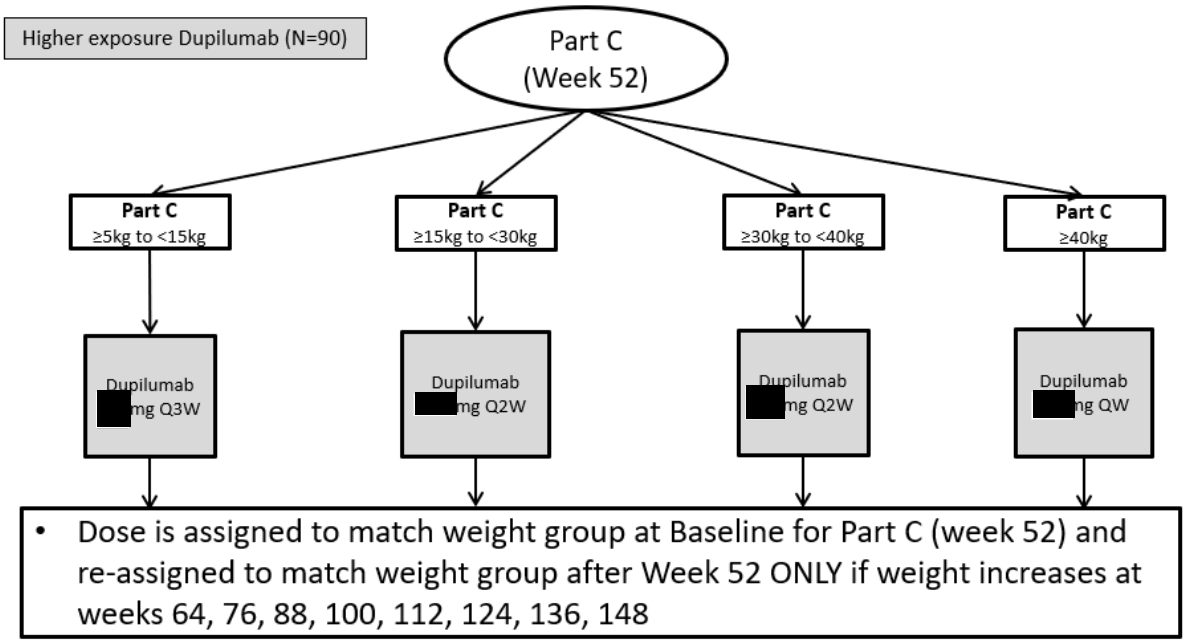
*In Part A, patients will receive dupilumab injections at the frequency of Q2W or Q4W with matching placebo alternating with dupilumab so the injection frequency will be identical within weight tiers for regimen-blinding purposes. Patients will remain within the originally assigned higher or lower dosing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

Figure 4: 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).

Figure 5: Part C (OLE) Weight-Tiered Dosing Regimens of Study Drug



8.2. Background Treatments

Patients who undergo a trial of PPI therapy prior to screening or during the screening period of Part A have the choice either to remain on the PPI regimen during Parts A and B or stop the PPI regimen prior to baseline; they then must remain off of PPIs during Parts A and B. Patients may adjust their PPI therapy use during Part C. Refer to the study binder for specific PPI dosing recommendations.

8.3. Rescue Treatments and Procedures

If medically necessary (eg, for treatment of intolerable EoE symptoms), rescue medications (systemic and/or swallowed topical corticosteroids) or emergency esophageal dilation are allowed for study patients. For Parts A and B, an endoscopy with biopsy will be performed prior to the initiation of rescue therapy. Patients who undergo an endoscopy with biopsy due to the initiation of rescue therapy during Parts A or B will not undergo the subsequent scheduled endoscopy/biopsy at week 16 and/or week 52, respectively. 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. For Part C (OLE), rescue treatment is also allowed. If rescue therapy is initiated during Part C (OLE), an endoscopy/biopsy before initiating rescue treatment is at discretion of the investigator discretion; future endoscopies/biopsies (week 100 and week 160) would still be required. If the endoscopy with biopsies cannot occur due to COVID-19 restrictions, rescue treatment should be initiated without delay and these patients will be eligible to participate in Part C.

Patients receiving rescue therapy may continue to receive study drug. They will remain blinded and will be asked to return to the clinic for all remaining study visits for the double-blind treatment period and the follow-up period, and participate in all assessments for these visits according to the Schedule of Events specified in Table 1, Table 2, Table 3, and Table 4 except for endoscopy/biopsy, as noted above. For the purpose of efficacy analyses for Part A, patients who receive rescue treatment during the study will be considered treatment failures.

8.4. Dose Modification and Study Treatment Discontinuation Rules

8.4.1. Dose Modification

Dose Modification, beyond what is specified by the protocol on dose regimen changes based on weight changes (see below), is not allowed.

Since dose is weight-tiered, weight at baseline will be used to determine dose for the 16-week double-blinded treatment period, weight at visit 8 (week 16) will be used to determine dose for start of the 36-week extended active treatment period and weight at Visit 17 / week 52 (or start of open-label period) will be used to determine the dose for the open-label extension period. All patients (Part C) will receive higher exposure dupilumab regimens based on body weight at visit 17 (week 52, end of extended active treatment period) or start of open-label period (for re-entry patients). Dose adjustments (based on increased weight) will be made during Part C at specified in-clinic visits as indicated in Table 4.

8.4.2. Study Drug Discontinuation

Patients who permanently discontinue from study drug should 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.

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 9.1.2 .

8.4.2.1. Reasons for Permanent Discontinuation of Study Drug

Study drug dosing will be permanently stopped in the event of:

- Evidence of pregnancy
- Serious or severe allergic reactions considered related to study drug
- Specific types of liver dysfunction [eg, Hy's law is met (Malmberg, 2009)]
- Patient or legal parent/legal guardian withdraws assent or consent
- Anaphylactic reaction or other severe systemic reaction deemed related to study drug
- Diagnosis of a malignancy during study
- Any infection that is opportunistic, such as TB and other infections whose nature or course may suggest an immunocompromised status

- Severe laboratory abnormalities:
  - Neutrophil count $\leq 0.5 \times 10^3/\mu L$
  - Platelet count $\leq 50 \times 10^3/\mu L$
  - ALT and/or AST values >3 × ULN with total bilirubin >2 × ULN, excluding confirmed Gilbert's Syndrome
  - Confirmed AST and/or ALT >5 × ULN (for more than 2 weeks)

8.4.2.2. Reasons for Temporary Discontinuation of Study Drug

Study drug dosing will be temporarily discontinued in the event of:

- An infection that requires parenteral treatment with antibiotic, antifungal, antiviral, antiparasitic, or antiprotozoal agents, or requires oral treatment with such agents for longer than 2 weeks
- Other intercurrent illnesses that may or may not require treatment with some prohibited medications (eg, systemic immunosuppressive/immunomodulating drugs) or major surgery, which could, in the opinion of the investigator, present an unreasonable risk to the patient as a result of his/her continued participation in the study and receiving study drug

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

After the condition leading to temporary discontinuation of study drug resolves, study drug dosing may resume. A decision to temporarily discontinue study drug and/or resume study drug dosing should be discussed with the Regeneron Pharmaceuticals, Inc. medical monitor.

If a patient requires a prohibited medication at any time during the study, the principal investigator should contact the Regeneron medical monitor (except for illness requiring prompt treatment). Based on the discussions, study drug may be continued or temporarily or permanently discontinued.

8.5. Management of Acute Reactions

8.5.1. Acute Injection Reactions

8.5.1.1. Systemic Injection Reactions

Emergency equipment and medication for the treatment of systemic reactions must be available for immediate use. All injection reactions must be reported as AEs (as defined in Section 10.2.1) and graded using the grading scales as instructed in Section 10.2.4.

Acute systemic reactions following injection of study drug (SC) should be treated using clinical judgment to determine the appropriate response according to typical clinical practice.

8.5.1.2. Local Injection Site Reactions

Local injection site reactions must be reported as AEs and graded according to Section 10.2.4.

8.6. Method of Treatment Assignment

In Part A, approximately 90 patients will be randomized in a 1:1:1 ratio to receive higher or lower exposure dose arms of dupilumab (dose regimen according to the weight tier described in Section 8.1) or placebo according to a central randomization scheme provided by an IVRS/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).

8.7. Blinding

Study patients, the principal investigators, and study site personnel will remain blinded to all randomization assignments. For Parts A and B, study drug administration at the study sites will be performed only by injection personnel who will not perform any clinical assessment/procedures. During the conduct of Parts A and B, the blinded Regeneron medical/study director, study monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all patient randomization assignments.

If the primary analysis is performed on Part A data (see Section 6.2), Part A will be unblinded for selected sponsor study personnel while Part B is ongoing. The team performing the primary analysis will be separate from the ongoing study team. No study personnel involved in the day-to-day conduct of the study will have access to any unblinded data before the database is locked for Part B of this study. All participants will receive open-label dupilumab during Part C.

Blinded study drug kits coded with a medication numbering system will be used for the double-blind (Part A) and extended active (Part B) treatment periods. In order to maintain the blind (until the database is locked for Part B), lists linking these codes with product lot numbers will not be accessible to individuals involved in study conduct. Part C study drug will be labeled with dupilumab.

During the double-blind (Part A) and extended active (Part B) treatment periods, anti-drug antibody, drug concentration results, any post-treatment tissue eosinophil counts and histologic results, and biomarker results (eotaxin-3 and total IgE) will not be communicated to the sites, and the sponsor's blinded study team will not have access to results associated with patient identification until after the database is locked for the respective study part.

8.8. Emergency Unblinding (Applies to Part A and Part B only)

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy) and when a treatment decision is contingent on knowing the patient's treatment assignment. Study drug will be discontinued for patients whose treatment has been unblinded (Section 8.4.2):

- If unblinding is required:
  - Only the investigator will make the decision to unblind the treatment assignment.
  - Only the affected patients will be unblinded.
  - The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind the patient. Unblinding is performed using the IVRS/IWRS which will notify Regeneron.
  - The investigator will notify Regeneron and/or designee as soon as possible after unblinding the patient.

Treatment assignment is not to be provided to site personnel, other than the unblinded study pharmacist (when applicable), at any time during the conduct of the study, except in the case of a true emergency and when a treatment decision is contingent on knowing the patient's treatment assignment. In the event that there is no study pharmacist, the individual at the site fulfilling that role will be the only unblinded member of the site personnel.

8.9. Treatment Logistics and Accountability

8.9.1. Packaging, Labeling, and Storage

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

Study drug will be stored at the site at a temperature of 2ºC to 8ºC; storage instructions will be provided in the pharmacy manual.

8.9.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed on site after sponsor approval or returned to the sponsor or designee.

8.9.3. Treatment Accountability

All drug accountability records must be kept current.

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

- dispensed to each patient
- returned from each patient (if applicable), and
- disposed of at the site or returned to the sponsor or designee.

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

8.9.4. Treatment Compliance

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

8.10. Concomitant Medications and Procedures

Any treatment administered from the time of informed consent/assent to final study visit will be recorded. Any treatment administered from the time of first dose of study drug to the final study visit will be considered concomitant treatment. This includes medications that were started before the study and are ongoing during the study.

8.10.1. Prohibited Medications and Procedures

Treatment with the following concomitant medications is prohibited through week 52 and may result in temporary or permanent discontinuation of study drug (see Section 8.4.2). While the investigator may suspend study treatment at any time, any change to study drug administration should be discussed with the medical monitor.

- Swallowed topical corticosteroids (may be used as rescue treatment for EoE) (Parts A and B only)
- Systemic corticosteroids (may be used as rescue treatment for EoE) (Parts A and B only)
  - NOTE: One-time use of a corticosteroid as a part of the anesthetic preparation used during each endoscopy procedure is also 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)
- For Parts A and B: 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
- For Parts A and B: 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 (For Parts A and B only)
- SLIT, OIT, or EPIT (For Parts A and B only)

- Treatment with a live (attenuated) vaccine, eg:
  - 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 (for Parts A and B):

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

8.10.2. Permitted Medications and Procedures

Other than the prohibited medications listed in Section 8.10.1, treatment with concomitant medications is permitted during the study. If there is any question regarding whether a concomitant medication may be used during the study, the study site should contact the medical monitor.

8.10.3. Restricted Medications and Procedures during the Follow-Up Period

Patients may receive the prohibited medications/procedures listed in Section 8.10.1 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.

8.11. Poststudy Treatments and Procedures

No poststudy treatments are required or planned.

9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

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

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Table 1: 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
Pediatric Eosinophilic Esophagitis Symptom Score: [15] Caregiver version (PEESSv2.0)			X					X

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**
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 2: Schedule of Events - Extended Active Treatment Period and Re-Entry Visit

	Part B: 36-Week Extended Active Treatment Period										Re-Entry Visit (for patients who re-enter the study for Part C)[13]
Study Procedure	**V8[1]**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17[12]**	
Week (W)	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**	
Day (D)	**D113**	**D141**	**D169**	**D197**	**D225**	**D253**	**D281**	**D309**	**D337**	**D365**	
Visit Window (Days [d])	**+7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**+7 d**	
Screening for Part B/C:											
Inclusion/Exclusion	X										X
Informed Consent											X
Medical History											X
Treatment:											
Administer Study Drug[4a, 4b]	X	X	X	X	X	X	X	X	X	X	
Con Meds/Procedures	X	X	X	X	X	X	X	X	X	X	
Efficacy:											
Age in months	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	
Pediatric EoE Sign/Symptom Questionnaire:[5] Patient version (PESQ-P) Caregiver version (PESQ-C)	← (Daily Diary) →										
Pediatric EoE Impact Scale:[5] Patient version (PEIS-P) Caregiver version (PEIS-C)	X				X					X	

Study Procedure	Part B: 36-Week Extended Active Treatment Period										Re-Entry Visit (for patients who re-enter the study for Part C)[13]
	V8[1]	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17[12]**	
Week (W)	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48**	**W52**	
Day (D)	**D113**	**D141**	**D169**	**D197**	**D225**	**D253**	**D281**	**D309**	**D337**	**D365**	
Visit Window (Days [d])	**+7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**+7 d**	
Global Impression of Change:[6] Patient version (GIC-P) Caregiver version (GIC-C) Clinician version (GIC-Clin)	X				X					X	
Global Impression of Severity:[6] Patient version (GIS-P) Caregiver version (GIS-C) Clinician version (GIS-Clin)	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]	

Study Procedure	Part B: 36-Week Extended Active Treatment Period										Re-Entry Visit (for patients who re-enter the study for Part C)[13]
	V8[1]	V9	V10	V11	V12	V13	V14	V15	V16	V17[12]	
Week (W)	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	
Day (D)	D113	D141	D169	D197	D225	D253	D281	D309	D337	D365	
Visit Window (Days [d])	+7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	+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	X
Adverse Events	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	
Anti-dupilumab antibody sample[2]	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)

Table 3: Schedule of Events - Early Termination Visits and Unscheduled Visits

Study Procedure	ET[1] (Before Part C)	ET[1] (During Follow-up)	ET[1] (During Part C)	Unscheduled Visit (before Rescue Treatment)	Unscheduled Visit (For Other Reasons)
Treatment:					
Con Meds/Procedures	X	X	X	X	X
Efficacy:					
Age in months	X	X	X	X	X
Weight, Height (or length for patients <2 years of age)	X	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	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	X	
Pediatric Eosinophilic Esophagitis Symptom Score:[6] Caregiver version (PEESSv2.0)	X		X	X	
Endoscopy with Biopsies with EoE-EREFS[4]	X[4, 4a]		X[4, 4a]	X[4b]	
Safety:					
Vital Signs	X	X	X	X	
Physical Examination	X		X	X	
Adverse Events	X	X	X	X	X

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

Table 4: Schedule of Events Open-Label Extension Part C (OLE) and EOS Schedule of Events

	Open-Label Extension Period																			**12-Week Follow-Up**
Study Procedure	**V 17[1,7]**	**PV 19[11]**	**PV 20[11]**	**V 21**	**PV 22[11]**	**V 23**	**PV 24[11]**	**V 25**	**PV 26[11]**	**V 27**	**PV 28[11]**	**V 29**	**PV 30[11]**	**V 31**	**PV 32[11]**	**V 33**	**PV 34[11]**	**V 35**	**PV 36[11]**	**EOT V37**	**EOS[13] V38**
Week (W)	**W 52**	**W 56**	**W 60**	**W 64**	**W 72**	**W 76**	**W 84**	**W 88**	**W 96**	**W 100**	**W 108**	**W 112**	**W 120**	**W 124**	**W 132**	**W 136**	**W 144**	**W 148**	**W 152**	**W 160**	**Last Visit +12 Wk**
Day (D)	**D 365**	**D 393**	**D 420**	**D 449**	**D 505**	**D 533**	**D 589**	**D 617**	**D 673**	**D 701**	**D 757**	**D 785**	**D 841**	**D 869**	**D 925**	**D 953**	**D 1009**	**D 1037**	**D 1065**	**D 1121**	**Last Dose +84D**
Visit Window (Days [d])	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**+7d**
Inclusion/ Exclusion	X																				
Treatment:																					
Administer study drug [redacted]	←																			→	
Study drug dispensation for [redacted]	[redacted]																				
Study drug dispensation for [redacted]	[redacted]																				
Study drug accountability	X			X		X		X		X		X		X		X		X		X	
Concomitant medications/ procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:																					

	Open-Label Extension Period																			12-Week Follow-Up
Study Procedure	**V 17[1,7]**	**PV 19[11]**	**PV 20[11]**	**V 21**	**PV 22[11]**	**V 23**	**PV 24[11]**	**V 25**	**PV 26[11]**	**V 27**	**PV 28[11]**	**V 29**	**PV 30[11]**	**V 31**	**PV 32[11]**	**V 33**	**PV 34[11]**	**V 35**	**PV 36[11]**	**EOT V37**	**EOS[13] V38**
Week (W)	**W 52**	**W 56**	**W 60**	**W 64**	**W 72**	**W 76**	**W 84**	**W 88**	**W 96**	**W 100**	**W 108**	**W 112**	**W 120**	**W 124**	**W 132**	**W 136**	**W 144**	**W 148**	**W 152**	**W 160**	**Last Visit +12 Wk**
Day (D)	**D 365**	**D 393**	**D 420**	**D 449**	**D 505**	**D 533**	**D 589**	**D 617**	**D 673**	**D 701**	**D 757**	**D 785**	**D 841**	**D 869**	**D 925**	**D 953**	**D 1009**	**D 1037**	**D 1065**	**D 1121**	**Last Dose +84D**
Visit Window (Days [d])	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**+7d**
Age in Months	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight, Height (or length for patients <2 years of age)[14]	X[9]			X		X		X		X		X		X		X		X		X	X
EoE-EREFS[10]										X										X	
Endoscopy with biopsies										X										X	
Pediatric Eosinophilic Esophagitis Symptom Score: Caregiver version (PEESSv2.0)[8]	X					X				X						X				X	
Pediatric EoE Impact Scale:[3]	X[9]					X				X						X				X	

	Open-Label Extension Period																			**12-Week Follow-Up**
Study Procedure	**V 17[1,7]**	**PV 19[11]**	**PV 20[11]**	**V 21**	**PV 22[11]**	**V 23**	**PV 24[11]**	**V 25**	**PV 26[11]**	**V 27**	**PV 28[11]**	**V 29**	**PV 30[11]**	**V 31**	**PV 32[11]**	**V 33**	**PV 34[11]**	**V 35**	**PV 36[11]**	**EOT V37**	**EOS[13] V38**
Week (W)	**W 52**	**W 56**	**W 60**	**W 64**	**W 72**	**W 76**	**W 84**	**W 88**	**W 96**	**W 100**	**W 108**	**W 112**	**W 120**	**W 124**	**W 132**	**W 136**	**W 144**	**W 148**	**W 152**	**W 160**	**Last Visit +12 Wk**
Day (D)	**D 365**	**D 393**	**D 420**	**D 449**	**D 505**	**D 533**	**D 589**	**D 617**	**D 673**	**D 701**	**D 757**	**D 785**	**D 841**	**D 869**	**D 925**	**D 953**	**D 1009**	**D 1037**	**D 1065**	**D 1121**	**Last Dose +84D**
Visit Window (Days [d])	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**+7d**
Patient version (PEIS-P) Caregiver version (PEIS-C)																					
Global Impression of Severity:[4] Patient version (GIS-P) Caregiver version (GIS-C) Clinician version (GIS-Clin)	X[9]					X				X						X				X	
Safety:																					
Vital signs	X			X		X		X		X		X		X		X		X		X	X
Physical examination										X										X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Open-Label Extension Period																			12-Week Follow-Up
Study Procedure	**V 17[1,7]**	**PV 19[11]**	**PV 20[11]**	**V 21**	**PV 22[11]**	**V 23**	**PV 24[11]**	**V 25**	**PV 26[11]**	**V 27**	**PV 28[11]**	**V 29**	**PV 30[11]**	**V 31**	**PV 32[11]**	**V 33**	**PV 34[11]**	**V 35**	**PV 36[11]**	**EOT V37**	**EOS[13] V38**
Week (W)	**W 52**	**W 56**	**W 60**	**W 64**	**W 72**	**W 76**	**W 84**	**W 88**	**W 96**	**W 100**	**W 108**	**W 112**	**W 120**	**W 124**	**W 132**	**W 136**	**W 144**	**W 148**	**W 152**	**W 160**	**Last Visit +12 Wk**
Day (D)	**D 365**	**D 393**	**D 420**	**D 449**	**D 505**	**D 533**	**D 589**	**D 617**	**D 673**	**D 701**	**D 757**	**D 785**	**D 841**	**D 869**	**D 925**	**D 953**	**D 1009**	**D 1037**	**D 1065**	**D 1121**	**Last Dose +84D**
Visit Window (Days [d])	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**+7d**
Laboratory Testing																					
Hematology, Chemistry										X										X	X
Pregnancy test[5]	Urine	Urine	Urine	Urine	Urine	Urine	Urine	Urine	Urine	Urine	Urine	Urine	Urine	Urine	Urine	Urine	Urine	Urine	Urine	Urine	Urine
Urinalysis[6]										X										X	X
PK and ADA Samples:																					
PK Sample[12]										X										X	X
Anti-dupilumab antibody sample										X										X	
Biomarkers:																					
Collection of plasma and serum sample for exploratory research	X[9]									X										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; PEIS-P = Pediatric EoE Impact Scale (patient version); PEIS-C = Pediatric EoE Impact Scale (caregiver 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); PV = Phone Visit; V = Clinic Visit

9.1.1. Footnotes for the Schedule of Events Tables

9.1.1.1. Footnotes for Table 1

1. For patients without a satisfactory prior endoscopy/biopsy (eg, histological criteria were not met, or the biopsy was not performed while patient was on at least 8 weeks of 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 2.
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 Tables 1 and 2. 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.

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 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 by 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.

9.1.1.2. Footnotes for Table 2

1. This visit is the same as the week 16 visit for the double-blind study portion (Table 1), and all other assessments indicated for week 16 (Table 1) 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.
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 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).
12. Assessments indicated for this week 52 (end of extended active treatment) visit should be performed for all patients. For patients who will enter the open-label extension period, there are additional events listed for the week 52 visit in Table 4.
13. For a complete list of procedures to be performed for Re-Entry patients, please see Table 4.

9.1.1.3. Footnotes for Table 3

1. Patients who are withdrawn from study drug will be asked to complete the 12-week follow-up period and the end of study visit.
2. 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.
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 any future scheduled endoscopy/biopsy (weeks 16, 52, 100 and/or 160).

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 years
6. 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) at an early termination and/or unscheduled visit before rescue visit(s).

9.1.1.4. Footnotes for Table 4

1. This visit is the same as the week 52 visit for the extended active treatment period for those patients entering Part C immediately after Part B (Table 2) or during the Safety follow-up period, and all other assessments indicated for week 52 (Table 2) should be performed prior to this portion of the visit.
2. Endoscopy with biopsies at visit 17/week 52 must be completed prior to administration of study drug for Part C - Open-Label Extension Period. Study drug administration is based on weight-tier (Section 8.1 Investigational and Reference Treatments) Weight must be collected at all in-clinic visits. Dose is assigned to match weight group for baseline for Part C (Week 52) and re-assigned after week 52 only if weight increases.
3. 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.
4. The GIS-P, GIS-C, and GIS-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.
5. All females post-menarche must have monthly pregnancy testing during Part C (Table 4). 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.
6. Urinalysis is only required for patients aged ≥6 years.
7. Patients who have completed their end of study visit (Visit 18 in previous protocol versions) prior to entering the open-label extension period must complete the procedures indicated for the Re-Entry Visit (Table 2) and are eligible for re-entry to the study for the open-label extension period and safety follow-up periods only. The Re-Entry Visit for eligible re-entry patients may be combined with the week 52 Visit procedures for Part C (Table 4).
8. 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).

9. These procedures are required for re-entry patients only.
10. EoE-EREFS imaging will be analyzed and scored by a central reading center. Minor esophageal features will be assessed by the investigator.
11. For the phone visits, patients are not required to come to the clinic. Patients may have study drug shipped to them and administered at home by their parents and/or caregivers; however, patients and their parents/caregiver have the option to come to the clinic and have study drug administered by site personnel if they prefer to do so. Phone contacts at any time during Part C are encouraged to ensure compliance and safety of study drug dosing.
12. Blood samples for dupilumab concentration measurement will be collected before the administration of study drug. The PK sample collected may be used for dupilumab ADA analysis based on the overall clinical presentation at that time. In the event of suspected SAEs, such as anaphylaxis or hypersensitivity, additional blood samples may be collected at or near the event for PK and ADA assessments.
13. The End of Study (EOS) visit may occur twice for Re-Entry patients.
14. Weight-based dosing should be adjusted based on the patient's weight at specified in-clinic visits.

9.1.2. Early Termination Visit

Patients who are withdrawn from the study will be asked to return to the clinic for an early termination visit consisting of the assessments described in Table 3.

9.1.3. Unscheduled Visits

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

9.1.4. Re-Entry Visit

Patients who have completed their end of study visit prior to entering the open-label extension period are eligible for re-entry to the study for the open-label extension period. The following study procedures are required at a Re-Entry Visit:

- Part C re-entry criteria (Section 7.2.2.2)
- Informed consent
- Updates for all relevant medical history and prior and concomitant medications/procedures
- Physical Examination
- Age, weight, height (length for patients <2 years of age)

9.2. Study Procedures

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population: demographics and medical history. Tuberculosis testing will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ECs.

9.2.2. Efficacy Procedures

9.2.2.1. Patient-, Caregiver-, or Clinician-Reported Outcome Measures

NOTE: The patient-, caregiver-, or clinician-reported outcome measures will be completed per appropriate age range (at screening visit 1) for the respective outcome measures specified in the subsections below. For outcome measures to be completed on visit days with assessments and study drug administration at the clinic, these outcome measures should be completed prior to receiving study drug. Patients ≥8 to <12 years of age and caregiver or legal guardians of all patients must be able to understand and complete the study requirements and study-related questionnaires. At least 8 out of 14 days of eDiary for the PESQ-C should be completed prior to baseline / visit 3.

9.2.2.1.1. Pediatric EoE Sign/Symptom Questionnaire (PESQ)

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

- The 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 will measure occurrence and severity of EoE symptoms and will be completed once daily via an electronic diary. [redacted]
- The 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 will measure occurrence of signs of EoE and will be completed once daily via an electronic diary. [redacted]

9.2.2.1.2. Pediatric EoE Impact Scale (PEIS)

The Pediatric EoE Impact Scale (PEIS) has a patient version (PEIS-P) and a caregiver version (PEIS-C). The PEIS-P and PEIS-C will be completed per the Schedule of Events in Table 1, Table 2, Table 3, and Table 4.

- The 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 patients' health-related during the past 1 week.
- The 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.

9.2.2.1.3. 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, GIC-C, and GIC-Clin will be completed per the Schedule of Events in Table 1, Table 2, and Table 3 .

- 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.

9.2.2.1.4. 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, GIS-C, and GIS-Clin will be completed per the Schedule of Events in Table 1, Table 2, Table 3, and Table 4.

- 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 outcomes 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 outcomes 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.

9.2.2.1.5. 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. The total PEESSv2.0 score ranges from 0 to 100; higher scores indicate greater symptom burden of among pediatric EoE patients. This questionnaire will be collected on paper per the Schedule of Events (Table 1, Table 2, Table 3 and Table 4).

9.2.2.1.6. Exit Interview

- Exit interviews will be conducted by a trained interviewer by 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. This exit interview will support interpretation of clinically meaningful change in signs/symptoms during the study. Detailed instructions related to these interviews will be available at the clinical site. Patient caregiver contact details will be provided by the clinical site to a trained interviewer to schedule and complete the exit interview.

9.2.2.2. Body Weight and Height

Body weight in kg and height in cm (or length for patients <2 years of age) will be measured at time points according to Table 1, Table 2, Table 3 and Table 4. Body mass index will be programmatically calculated based on the weight and height data.

9.2.2.3. Endoscopy with EoE-EREFS, Biopsies, and Imaging

Imaging for EoE-EREFS and biopsies will be assessed. Video is the preferred method of imaging, but photographs may be used in special circumstances (eg, technical difficulty). Training will be provided to study sites on performing these procedures and will be conducted prior to biopsies. All biopsies performed during this study will be evaluated by a qualified central histology laboratory.

The endoscopy/EoE-EREFS/biopsy procedure will be performed per the Schedule of Events in Table 1, Table 2, Table 3 and Table 4.

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). Imaging should be collected for EoE-EREFS analysis and scoring by a centralized reading center. Video is the preferred method of imaging, but photographs may be used in special circumstances (eg, technical difficulty).

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, present)
- Rings (absent, mild, moderate, severe)
- Exudates (absent, mild, severe)
- Furrows (absent, mild, severe)
- Stricture (absent, present)

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).

Biopsies

Biopsies will be obtained by endoscopy at the second screening visit (visit 2), week 16, week 52, week 100, and week 160 visits, and immediately prior to start of rescue medication or procedures (only applies to rescue medication/or procedures that occur before Week 52 visit). The screening endoscopy should be performed at a time during the screening period that will allow results to be available prior to day -1 for assessment of eligibility. 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. Residual biopsy samples processed for histopathological analyses may also be used for exploratory research; samples may be used for immunohistochemical or RNAscope analyses (Section 9.2.7).

In addition, 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, week 52, week 100 and week 160.

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. These samples will be assessed for peak eosinophil count per hpf, and EoE grade scores and stage scores will be assigned. 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, and then it will not be included in the overall EoE grade and stage scores. Severity (grade) and extent (stage) of abnormalities will be scored using a 4-point scale (0 normal; 3 maximum change). The endoscopy with biopsies procedure will be performed the same way at all scheduled visits.

Histology results will be interpreted by a pathologist at a central pathology reading center who will be blinded to the treatment assignment. Detailed instructions for biopsy sample collection and handling will be provided in the study regulatory binders.

Video and/or Photographs

Video and/or photographs should be taken by the site as part of the endoscopic procedure and biopsy collection. A copy of these video and/or photographs will be requested from the study sites. Details for collecting and sending these video and/or photographs will be provided in the study regulatory binders. Video is the preferred method of imaging, but photographs may be used in special circumstances (eg, technical difficulty).

9.2.3. Safety Procedures

9.2.3.1. Vital Signs

Vital signs, including heart rate, blood pressure, respiratory rate, and body temperature will be collected predose and 30 minutes post-dose at time points listed in Table 1, Table 2, Table 3, and Table 4. 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.

9.2.3.2. Physical Examination

A thorough and complete physical examination will be performed at time points according to Table 1, Table 2, Table 3, and Table 4. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

9.2.3.3. Laboratory Testing

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by a central laboratory. Samples will be collected predose at time points listed in Table 1, Table 2, Table 3, Table 4. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites. 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 Table 1, Table 2, and Table 3, and Table 4.
- Tuberculosis testing will be performed on a country-by-country basis according to local guidelines if required by regulatory authorities or ethics boards.

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the medical/study director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 10.1.1.

9.2.4. Drug Concentration and Measurements

Samples for drug concentration measurement will be collected at visits listed in Table 1, Table 2, and Table 3, and Table 4 .

9.2.5. Immunogenicity Measurements and Samples

Samples for ADA and NAb assessment will be collected at time points listed in Table 1, Table 2, and Table 3, and Table 4. Samples positive in the ADA assay will be analyzed for the presence of neutralizing antibody in the NAb assay.

9.2.6. Pharmacodynamic and Exploratory Biomarker Procedures

In this study, research assessments will be performed to explore EoE, how dupilumab may modify the underlying disease process in EoE, type 2 inflammation, and predictors of dupilumab safety and efficacy. Samples may also be used to evaluate markers related to toxicity, if needed.

Samples for total IgE, serum, and eotaxin-3 (heparinized plasma) will be collected at time points according to Table 1, Table 2, and Table 3,. The biomarkers studied are relevant to the pathophysiology of EoE, response to treatment (ie, assessment of type 2 inflammation), and dupilumab mechanism of action, and will be assessed for predictive utility.

Any residual samples left over from the main study may be used for exploratory research.

9.2.6.1. Type 2 Inflammatory and Disease-Related Biomarkers

Eotaxin-3 and total IgE are measures of type 2 inflammation, and are known pharmacodynamic markers for dupilumab in AD, asthma, and nasal polyposis.

9.2.6.1.1. Total IgE

IL-4 and IL-13 regulate B cell class switching to IgE. Dupilumab has been shown to suppress IgE (total and allergen-specific) in AD, asthma, and CRSwNP patients. Serum concentrations of total IgE will be measured at time points indicated in Table 1, Table 2, and Table 3 . Modulation of IgE is a pharmacodynamic measure. Data analysis will be described in the statistical analysis plan (SAP) and the results will be provided in the clinical study report (CSR).

9.2.6.1.2. Eotaxin-3

Eotaxin-3 (also known as CCL26), an eosinophil chemokine, is up-regulated in esophageal mucosa of EoE patients relative to controls (Blanchard, 2006), and variants in the gene have been associated with disease risk. Eotaxin-3 mRNA expression in skin is down-regulated by dupilumab in AD (Hamilton, 2014). Circulating concentrations have been shown to decrease in asthma and nasal polyposis patients treated with dupilumab. Eotaxin-3 will be measured in heparinized plasma from samples collected at time points indicated in Table 1, Table 2, and Table 3. Modulation of eotaxin-3 is a pharmacodynamic measure. Data analysis will be described in the SAP and the results will be provided in the CSR.

9.2.6.2. EoE Diagnostic Panel and Type 2 Inflammation Transcriptomics

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 the SAP. In a phase 2 study of EoE (R668-EE-1324), dupilumab significantly decreased the disease, EDP and type 2 transcriptome signatures (Regeneron unpublished data).

Normalized Enrichment Score (NES) reflects the degree to which the activity level of a set of transcripts is overrepresented at the extremes (top or bottom) of the entire ranked list of transcripts within a sample and is normalized by accounting for the number of transcripts in the set (Barbie, 2009) (Subramanian, 2005). NES scores will be calculated for each transcriptome signature for each sample for statistical analyses in Table 1, Table 2, Table 3 and Table 4 .

9.2.7. Biopsy Analyses

Biopsy samples will be used for exploratory research related to EoE, dupilumab efficacy and safety, and inflammation.

Residual biopsy samples processed for histopathological analyses may also be used for exploratory research described above. Samples may be used for immunohistochemical or RNAscope analyses.

Biopsies processed for RNA extraction will be used for RNA expression profiling. RNA sequencing, qRT-PCR, and other methods may be used to evaluate expression profiles before and after treatment.

9.2.8. Future Biomedical Research (Optional)

Patients/legal parents or legal guardians who agree for their child to participate in the future biomedical research sub-study will be required to assent/consent to this optional sub-study before samples are banked in long-term storage. The unused biomarker samples for study-related research, as well as unused PK and ADA samples, will be stored for up to 15 years after the final date of the database lock. The unused samples may be utilized for future biomedical research that may or may not be directly related to the study, including being used as reference samples and assay development or validation. After 15 years, any residual samples will be destroyed. The results of these future biomedical research analyses will not be presented in the CSR.

9.2.8.1. Pharmacogenomic Analysis (Optional)

Patients/legal parents or legal guardians who agree for their child to participate in the genomics sub-study will be required to assent/consent to this optional sub-study before collection of the samples. Cheek swab samples for DNA extraction should be collected on day 1/baseline (predose), but can be collected at a later study visit. DNA samples will be collected for pharmacogenomics analyses to understand the genetic determinants of efficacy and safety associated with the treatments in this study, and the molecular basis of EoE and related diseases. The samples will be single-coded as defined by the International Council for Harmonisation (ICH) guideline E15. Samples will be stored for up to 15 years after the final date of the database lock. If there are specific site or country requirements involving the pharmacogenomic analyses which the sponsor is unable to comply with, samples will not be collected at those sites.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical or biomarker response to dupilumab, other EoE clinical outcome measures, and possible AEs. In addition, associations between genomic variants and prognosis or progression of EoE, as well as related allergic/atopic diseases, may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug, target pathway, or EoE and related diseases.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, and DNA copy number variation may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period. Results from the genomic analyses will not be reported in the CSR.

Research findings from the optional genomic sub-study will not be disclosed to the patient or principal investigator, even if they have implications for a patient's health and management. Genetic results from this sub-study are for research purposes only and not for medical diagnosis or for reproductive decision-making

10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study data collection period, from the time of signing the informed consent form (ICF) to the end of study. Medical conditions that existed or were diagnosed prior to the signing of the ICF will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of informed consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the patient. Adverse events may be directly observed, reported spontaneously by the patient or by questioning the patient at each study visit. Patients should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 10.2. The investigator's assessment must be clearly documented in the site's source documentation with the investigator's signature. The investigator should follow up on SAEs (and AESIs) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation or dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the Informed Consent Form) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any SAE that may occur subsequent to the reporting period (end of the follow-up period) that the investigator assesses as related to study drug should also be reported.

All AEs, SAEs, AESIs, and pregnancy reports are to be reported according to the procedures in Section 10.1.3.

10.1.2. Reporting Procedure

All events (serious and non-serious) must be reported with the investigator's assessment of the event's seriousness, severity, and causality to the (when applicable: blinded) study drug. For SAEs and AESIs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE CRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc.) will be summarized in the narrative on the AE CRF, and retained at the study center and available upon request.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.1.3. Events that Require Expedited Reporting to Sponsor

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

- **SAEs**.
- **Adverse Events of Special Interest** (AESI; serious and nonserious)**:** Adverse events of special interest for this study include the following:
  - Anaphylactic reactions
  - Systemic hypersensitivity reactions
  - Helminthic infections
  - Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)
  - Any severe type of conjunctivitis or blepharitis
  - Keratitis
  - Severe injection site reactions
  - Herpes simplex infection
  - Arthralgia
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female study patient during the study or within 12 weeks of the last dose of study drug. Any complication of pregnancy affecting a female study patient, and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

10.2. Definitions

10.2.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

10.2.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

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

Criteria for reporting SAEs must be followed for these events.

10.2.3. Adverse Events of Special Interest

An AESI, serious or non-serious, is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

10.2.4. Severity

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

Mild: Does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.

Moderate: Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptoms may be needed.

Severe: Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

Injection Site Reactions

The severity of injection site reactions will be graded according to the following scale (semi-colon indicates "or" within description of grade:

Mild: Pain that does not interfere with activity; mild discomfort to touch; <5 cm of erythema or induration that does not interfere with activity

Moderate: Pain that requires repeated use of non-narcotic pain reliever >24 hours or interferes with activity; discomfort with movement; 5.1 cm to 10 cm erythema or induration or induration that interferes with activity

Severe: Pain that requires any use of narcotic pain reliever or that prevents daily activity; significant discomfort at rest; >10 cm erythema or induration; prevents daily activity; requires emergency room visit or hospitalization; necrosis or exfoliative dermatitis

10.2.5. Causality

The investigator must provide causality assessment as to whether or not there is a reasonable possibility that the drug caused the AE, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

For double-blinded studies using an active comparator, the investigator should consider all study drugs in determining event causality.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset versus time drug was administered
- Nature of the reactions: immediate versus long term
- Clinical and pathological features of the events
- Existing information about the drug and same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Response to dechallenge (drug discontinuation) or dose reduction
- Response to rechallenge (re-introduction of the drug) or dose increase, when applicable
- Patient's medical and social history

Causality to the study drug (including study drug administration):

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its class of drugs, or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

Causality to the study conduct (protocol-specified procedure):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol-specified procedure, and cannot be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol-specified procedure, or can be reasonably explained by the nature of the reaction, patient's clinical state

(eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

10.3. Safety Monitoring

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

10.4. Notifying Health Authorities, Institutional Review Board/Ethics Committee, and Investigators

During the study, the sponsor and/or the CRO will inform health authorities, ECs/institutional review boards (IRBs), and the participating investigators of any SUSARs (suspected unexpected serious adverse reactions) occurring in other study centers or other studies of the active study drug dupilumab, as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements. All notifications to investigators will contain only blinded information.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the IRB/EC unless delegated to the sponsor.

Event expectedness for study drug (dupilumab) is assessed against the Reference Safety Information section of the Investigator's Brochure that is effective for expedited safety reporting.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the CSR to health authorities and ECs/IRB as appropriate.

11. STATISTICAL PLAN

This section provides the basis for the SAP for the study.

Endpoints are listed in Section 4. Analysis variables are listed in Section 5.

Data collected through the implementation of new CRFs regarding the impact of the COVID-19 pandemic on patients will be summarized (eg, discontinuation due to COVID-19). Any additional analyses and methods required to investigate the impact of COVID-19 on the efficacy (eg, missing data due to COVID-19) and safety evaluation will be specified in the SAP.

11.1. 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 and adjustment for multiplicity will be undertaken for Parts B and C.

11.2. Justification of Sample Size

The planned sample size is a total of approximately 90 patients (1:1:1 ratio, 30 patients in the higher dupilumab exposure group, 30 patients in the lower dupilumab exposure group, and 30 patients in the placebo group). See Section 3.2.2 for dose selection rationale.

The assumptions used in sample size calculation were based on Part A of the R668-EE-1774 study (a phase 3 study for adults and adolescents with EoE) and R668-EE-1324 (a phase 2 study for adults with EoE). In Part A of the 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 the 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%. In the R668-EE-1324 study, the proportions of patients achieving histologic response at week 12 were 65% and 0% for dupilumab and placebo, respectively. The efficacy of dupilumab can be established as early as week 12. Based upon the similarity of pathophysiology and expected similarity of 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 is 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. 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 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 (ie, 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 made using nQuery Advisor 7.0.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Sets for Part A

For Part A, the full analysis set (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.

11.3.2. Safety Analysis Set for Part A

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

11.3.3. Analysis Set for Parts B and C

For efficacy and safety analyses of Parts B and C, only a subset of SAF for Part A will be included, which is defined as those patients who received at least 1 dose of Part B or/and Part C study drug.

11.3.4. Pharmacokinetic Analysis Sets for All Parts

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.

11.3.5. Immunogenicity Analysis Sets for All Parts

The ADA analysis set includes all patients who received any study drug and had at least 1 non-missing ADA result following the first study dose.

The NAb analysis set includes all patients who received any study drug and who are negative in the ADA assay or with at least 1 non-missing result in the NAb assay (patients who are ADA-negative are set to negative in the NAb analysis set).

11.4. Statistical Methods

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

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

11.4.1. Patient Disposition

The following will be provided:

- The total number of screened patients who have signed the ICF
- The total number of randomized patients: received a randomization number
- The total number of patients who discontinued the study, and the reasons for discontinuation
- The total number of patients who discontinued from study treatment, and the reasons for discontinuation

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group, and by all patients combined.

11.4.3. Efficacy Analyses

11.4.3.1. Primary Efficacy Analysis

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). The randomization stratification of baseline weight group may be pooled to ensure the sufficient sample size of each stratum.

For the primary estimands of interest for the primary endpoint, the intercurrent events, strategies, and the corresponding missing data handling approaches are provided as below:

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: 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 to be non-responders	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.

Sensitivity analyses will assess alternative methods to impute missing data. The sensitivity analyses will include tipping point analysis approach and worst observation carried forward – multiple imputation (WOCF-MI) approach.

Subgroup analyses (eg, by weight) may be performed. Details will be specified in the SAP.

11.4.3.2. Secondary Efficacy Analysis

Efficacy Endpoints at Week 16 (Part A)

Secondary efficacy endpoints that measure binary responses (eg, peak esophageal intraepithelial eosinophil count <15 eos/hpf) will be analyzed in the same fashion as the primary endpoint.

Continuous secondary efficacy endpoints will be analyzed using an analysis of covariance (ANCOVA) model for the FAS with treatment group, randomization stratification factor, and relevant baseline measurement as a covariate included in the model.

To account for 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 (eg, change in the proportion of days with 1 or more EoE signs from baseline to week 16 as measured by PESQ-C), missing data will be imputed by the pattern-mixture approach. Specifically, the WOCF-Multiple Imputation (WOCF-MI) approach, where the WOCF approach will be used for the missing data due to rescue treatment/AE/lack of efficacy and the MI approach will be used for the missing due to other reasons.

For continuous efficacy data that are scheduled to be measured only once post-baseline up to week 16, missing values at week 16 will be imputed with patient's baseline value or the available post-baseline value, whichever is worse, ie, a WOCF approach.

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. P-values will be reported.

Efficacy Endpoints at Week 52 (Part B)

Efficacy 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. These descriptive analyses may include statistical tests depending on the type of data in the same way as described above.

Efficacy Endpoints (Part C)

Efficacy data in Part C will be summarized with descriptive statistics for treatment received in Part C as well as by treatment group as in Part A (double-blind treatment period) and Part B (extended active treatment period). No missing values will be imputed.

11.4.4. Control of Multiplicity

For multiplicity adjustment, a hierarchical procedure will be used to control the overall Type-1 error rate at 0.05 for the primary endpoint and the selected secondary efficacy endpoints for each dupilumab dose regimen 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 primary endpoint will be tested for the higher exposure dupilumab group first and then for the lower exposure dupilumab group. The hierarchical order of the secondary endpoints will be specified in the SAP.

As Part B and C data will be summarized using descriptive statistics, there is no multiplicity issue.

11.4.5. Safety Analysis

Safety analysis will be based on the SAF in the respective study part. This includes reported TEAEs and other safety data (ie, clinical laboratory evaluations and vital signs). A descriptive summary of safety results will be presented for each study part by treatment that patients receive in respective part as below:

- Part A: placebo, lower dupilumab exposure group, higher dupilumab exposure group and combine dupilumab group

- Part B: lower dupilumab exposure group, higher dupilumab exposure group and total

Pooled Part A and Part B may be presented and details will be specified in SAP.

- Part C: higher dupilumab exposure group

11.4.5.1. Adverse Events

Definitions

For safety variables, 2 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment-emergent period is defined as the day from first dose of study drug to end of study. The treatment-emergent period includes the double-blind treatment period, extended active treatment period, and open-label extension period (up to 160 weeks in total) and the 12-week follow-up period.
  - Treatment period: date of the first dose of study drug to week 160 visit date for those patients who completed the week 160 visit with available visit date; or date of the first dose of study drug to study day 1121 (study day 1 being the first dose date) or the date of patient last contact, whichever is earlier, for those patients who did not complete week 160 visit or had missing week 160 visit date
  - Follow-up period: date after the end of treatment period to end of study

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

Analysis

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®).

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 10.2.4), presented by SOC and PT
- Treatment-related TEAEs, presented by HLT, SOC and PT
- TEAEs leading to permanent treatment discontinuation, presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)

Serious adverse events leading to death and other SAEs will be summarized by treatment group.

11.4.5.2. Other Safety

Vital Signs

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

The number and percentage of patients with a treatment-emergent potentially clinically significant value (PCSV) will be summarized for each vital sign variable. The criteria for treatment-emergent PCSV will be defined in the SAP.

Laboratory Tests

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

Number and percentage of patients with a treatment-emergent PCSV will be summarized for each clinical laboratory test. The criteria for treatment-emergent PCSVs will be defined in the SAP.

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

11.4.5.3. Treatment Exposure

The duration of exposure during part A, part B and part C of the study will be presented by treatment group and calculated as:

(Date of last study drug injection in the specific study part – date of first study drug injection in the specific study part) + 14 days

Number (%) of patients exposed to study drug during each study part and cumulatively across study parts will be presented by specific time periods for each treatment group. The time periods of interest will be specified in the SAP.

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

A summary of the number of doses by treatment group will be provided.

11.4.5.4. Treatment Compliance

The compliance with study treatment will be calculated for each study part as follows:

> Treatment Compliance = (Number of study drug injections during exposure period)/(Number of planned study drug injections during exposure period) × 100%

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

11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

The concentrations of functional dupilumab in serum will be summarized by descriptive statistics at each time point. No formal statistical hypothesis testing will be performed.

11.4.7. Analysis of Immunogenicity Data

Immunogenicity will be characterized by the ADA and NAb response observed:

- Pre-existing immunoreactivity, defined as a positive ADA assay response at baseline, with all post-dose ADA results negative, or a positive assay response at baseline, with all post-dose ADA assay responses less than 4-fold over baseline titer levels
- Treatment-emergent ADA response, defined as any post-dose positive ADA assay response when the baseline results are negative or missing
- Treatment-boosted ADA response, defined as any post-dose positive ADA assay response that is 4-fold over baseline titer levels when baseline is positive in the ADA assay
- Maximum ADA titer values
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)
- NAb status for samples that are positive in the ADA assay

Incidence of treatment-emergent ADA and NAb will be assessed as absolute occurrence (N) and percent of patients (%), grouped by dose group and ADA titer level.

Plots of drug concentrations will be examined and the influence of ADAs and NAbs on individual PK profiles evaluated. Assessment of impact of ADA and NAbs on safety and efficacy may be provided.

11.4.8. Analysis of Pharmacodynamic and Exploratory Biomarker Data

Biomarker results will be summarized by baseline, measured values, change from baseline, and percent change from baseline to each scheduled assessment time point with descriptive statistics. Exploratory analyses performed on biopsies will not be reported in the CSR. Other exploratory analyses may be performed but will not be described in the SAP or CSR.

11.4.9. Timing of Statistical Analysis

The primary analysis may be performed when the last patient completes 16 weeks of treatment duration in Part A. No changes in the conduct of the study will be made based on this primary analysis. The assessment of primary and secondary endpoints specified in Section 4.1.1 and Section 4.1.2 will be analyzed descriptively in Part B as the final analysis. Part C will be described descriptively. Hence, there will be no need for alpha adjustment due to the primary analysis.

In order to maintain study integrity (with respect to the extended active treatment and post-treatment follow-up safety visits) in the event a decision is made to perform the primary analysis, a dissemination plan will be written. This plan will clearly identify the team (including the statistician) that will perform the primary analysis and all related activities, restrict other clinical team members and other sponsor personnel from access to individual patient treatment allocation and site level analysis results, and ensure that the dedicated team will not participate in the data review or data decisions for the following extended active treatment safety analyses.

11.5. Statistical Considerations Surrounding the Premature Termination of a Study

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

12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Data Management

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

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

The CRF data for this study will be collected with an electronic data capture (EDC)/paper CRF.

12.1.2. Electronic Systems

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

- IVRS/IWRS system – randomization, study drug supply
- EDC system – data capture – Medidata Rave
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database
- nQuery Advisor – sample size calculations
- Digital archive system for endoscopic photographic and video images

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

The study monitor and/or designee (eg, CRO monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. This study will use the principles of risk-based monitoring (ICH). This means that the number of visits for any given site may vary based on site risk indicators. The investigator must allow study-related monitoring.

The study monitors will perform ongoing source data review to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and CRF data are timely, accurate, and complete.

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

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic case report forms (eCRFs) within the EDC system by trained site personnel. All required CRFs must be completed for each and every patient enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

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

12.3. Audits and Inspections

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

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

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

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

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRF/eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final CRF/eCRF that will be provided to the sponsor.

12.4.2. Retention of Records

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

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

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

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

13.2. Informed Consent

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

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

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient and his/her parent(s) or legal guardian(s) prior to the patient's participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the fullest possible extent in language that the patient and the parent(s) or legal guardian(s) can understand. The ICF should be signed and dated by the patient's parent(s) or legal guardian(s) and the same investigator or designee who explained the ICF.

Local law must be observed in deciding whether 1 or both parents'/guardians' consent is required. If only 1 parent or guardian signs the consent form, the investigator must document the reason the other parent or guardian did not sign. The patient may also be required to sign and date the ICF, as determined by the IRB/EC and in accordance with the local regulations and requirements.

- Patients who can write but cannot read will have the assent form read to them before writing their name on the form.
- Patients who can understand but who can neither write nor read will have the ICF/assent read to them in the presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

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

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

13.3. Patients Confidentiality and Data Protection

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

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

13.4. Institutional Review Board/Ethics Committee

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

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

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

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

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

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

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

15.1. Premature Termination of the Study

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

15.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

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

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

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

19. REFERENCES

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20. INVESTIGATOR'S AGREEMENT

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

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

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

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

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

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

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

Protocol Number: R668-EE-1877

Protocol Version: R668-EE-1877 Amendment 4

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

Signature Page for VV-RIM-00153963 v2.0

Approval/eSignature	[redacted] 02-Aug-2022 17:34:49 GMT+0000
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