Ther Adv Gastroenterol

2025, Vol. 18: 1–13

DOI: 10.1177/17562848251383782

Study design of the phase IV, randomized, placebo-controlled REMOdeling with Dupilumab in Eosinophilic esophagitis Long-term (REMODEL) trial

Evan S. Dellon, Edoardo V. Savarino, Sherif Zaghloul, James T. Angello, Mei Zhang, Bram P. Raphael, Amr Radwan and Albert J. Bredenoord

Abstract

Background: Esophageal distensibility, measured by endoluminal functional lumen imaging probe (EndoFLIP), identifies esophageal fibrostenotic changes and is impaired in patients with eosinophilic esophagitis (EoE). Early-phase clinical trials suggested dupilumab could increase esophageal distensibility. However, there are limited data on the long-term impact of dupilumab treatment on fibrostenosis.

Objectives: To evaluate the long-term efficacy of dupilumab, including its impact on esophageal fibrostenotic progression, in adult patients with EoE.

Design: The phase IV study is comprised of a randomized, double-blind, placebo-controlled trial period for 24 weeks, followed by an open-label extension for 104 weeks.

Methods and analysis: In total, 69 adult patients with endoscopically and histologically active EoE have been recruited from 30 global sites and randomized 2:1 to receive dupilumab 300 mg once weekly (qw) or placebo during the double-blind treatment period. Eligible patients continuing into the open-label extension period will receive dupilumab 300 mg qw. The primary endpoint is absolute change from baseline in esophageal distensibility plateau at week (W)24 measured by EndoFLIP. Secondary endpoints include change in esophageal distensibility plateau at W76 and W128; histologic, endoscopic, and molecular features of EoE at W24, W76, and W128; and long-term safety. After the double-blind treatment period, endpoints will be summarized with descriptive statistics.

Ethics: REMODEL will be conducted in accordance with the Declaration of Helsinki, the Council for International Organizations of Medical Sciences international ethical guidelines, and the International Council for Harmonisation Good Clinical Practice guidelines. The protocol was approved by an institutional review board before study initiation.

Discussion: REMODEL will address whether long-term dupilumab treatment can mitigate fibrostenotic progression in patients with EoE and may provide new insights into the roles of interleukin-4 and -13 in the pathophysiology and progression of EoE.

Trial registration: All patients will provide informed consent. REMODEL was registered on ClinicalTrials.gov (NCT06101095) on October 19, 2023.

Correspondence to:
Evan S. Dellon
Center for Esophageal Diseases and Swallowing, Division of Gastroenterology and Hepatology, University of North Carolina School of Medicine, 130 Mason Farm Road, Chapel Hill, NC 27599-7080, USA
evan_dellon@med.unc.edu

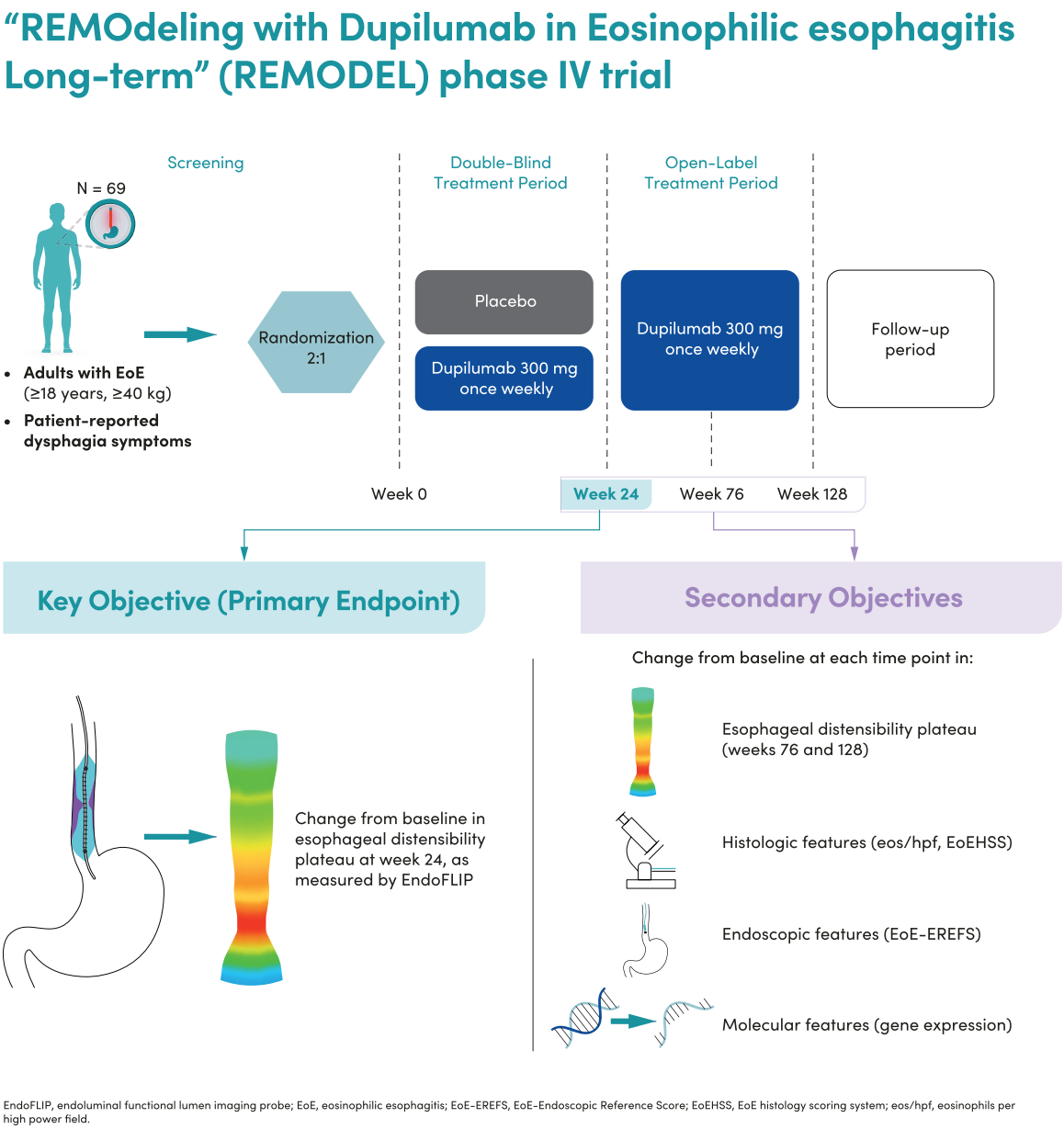
Edoardo V. Savarino
Department of Surgical Oncology and Gastroenterological Services, University Hospital of Padova, Padua, Italy

Sherif Zaghloul
James T. Angello
Mei Zhang
Sanofi, Morristown, NJ, USA

Bram P. Raphael
Amr Radwan
Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

Albert J. Bredenoord
Amsterdam University Medical Center, Amsterdam, The Netherlands

Graphical abstract



EndoFLIP, endoluminal functional lumen imaging probe; EoE, eosinophilic esophagitis; EoE-EREFS, EoE-Endoscopic Reference Score; EoEHSS, EoE histology scoring system; eos/hpf, eosinophils per high power field.

Plain language summary

Why is the study being done? Eosinophilic esophagitis (EoE) is a long-term disease of the esophagus caused by an overactive part of the immune system called type 2 inflammation. If EoE is untreated, the accumulation of eosinophils (a type of white blood cell) and other immune cells in the esophagus lining can progress to a more severe disease involving physical changes and narrowing of the esophagus. Dupilumab, a medication that targets key and central drivers of type 2 inflammation, is approved in the USA and EU for people

with EoE aged 1 year or older, weighing at least 15 kg. In previous studies, dupilumab improved EoE features, including evidence of improving physical changes of the esophagus. The REMODEL study will use a medical device called an endoluminal functional lumen imaging probe (EndoFLIP) to assess dupilumab's effect on esophageal physical changes in adults with EoE, and other outcomes of treatment.

What will the researchers do? REMODEL has recruited 69 adults with EoE across 30 clinics in the USA, Brazil, Israel, Canada, and Switzerland. Patients were randomly selected to receive either dupilumab or a dummy treatment for 24 weeks, and EndoFLIP will be used to compare physical changes in the esophagus between groups. Features of the esophagus seen using an endoscope camera, microscopic features of EoE in esophagus tissue, and changes in gene expression (if genes related to EoE are turned up or down) will also be compared between groups. Symptoms of EoE, anxiety, and depression will be measured using questionnaires. After 24 weeks, all patients will receive dupilumab for 104 weeks, and researchers will continue to monitor results and possible side effects from treatment.

What will the findings mean? REMODEL will provide new data on how long-term treatment with dupilumab affects physical changes in the esophagus in EoE. The study will also expand understanding of dupilumab's long-term safety and its impact on features and symptoms of the disease.

Keywords: dupilumab, EndoFLIP, eosinophilic esophagitis, phase IV, remodeling

Received: 18 July 2025; revised manuscript accepted: 15 September 2025.

Introduction

Eosinophilic esophagitis (EoE) is a chronic, progressive disease characterized by esophageal eosinophilia and symptoms associated with esophageal dysfunction, and is rising in incidence and prevalence.[1,2] EoE is driven by type 2 inflammation, a specific immune response involving pro-fibrotic and homeostatic signaling via the key type 2 cytokines interleukin (IL)-4, IL-5, IL-13, and IL-33, and the actions of activated mast cells, basophils, eosinophils, and pro-fibrotic macrophages.[3,4] If left untreated, persistent uncontrolled type 2 inflammation contributes to pathologic fibrosis and epithelial remodeling,[4–6] leading to the development of a fibrostenotic EoE phenotype.[7–9] Fibrostenosis causes the clinical manifestations and complications of EoE, including dysphagia, strictures, and food impactions,[10] that can significantly impact patients' quality of life (QoL).[11]

Clinical guidelines for EoE recommend intervention with an empirical food elimination diet and/or pharmacologic therapies such as swallowed topical corticosteroids (STCs), proton-pump inhibitors (PPIs), and biologics.[12] While capable of inducing histologic remission in a proportion of patients with EoE, loss of response and relapse are common with PPIs and STC drugs.[13,14] Dupilumab, a fully human monoclonal antibody that blocks the shared receptor component for IL-4 and IL-13, is approved in the USA and EU for the treatment of patients with EoE aged $\geqslant$1 year, weighing $\geqslant$15 kg.[15] Guidance on the use of dupilumab for EoE, particularly in patients with PPI-refractory disease,[12] is based on results from the pivotal phase III LIBERTY EoE TREET and EoE KIDS studies, which show improvements in histologic, symptomatic, and endoscopic features.[16,17] Once EoE treatment has achieved control of underlying inflammation, maintenance therapy should be continued to prevent relapse.[18] Throughout treatment, in addition to determining patient symptom response, ongoing endoscopic and biopsy-based histologic monitoring is required to ensure effective management of eosinophilic mucosal inflammation. However, detection of esophageal strictures in EoE can be difficult via endoscopy. Although esophageal narrowing is obvious when the esophageal lumen is constricted and passage of a standard

endoscope is more difficult, endoscopy is less sensitive than other tools for accurate assessment of esophageal diameter.[19] Endoluminal functional lumen imaging probe (EndoFLIP) is a sensitive method that can be used to assess fibrostenotic changes in EoE[12] and to quantify the esophageal distensibility plateau. Defined as the narrowest diameter along the esophagus that demonstrates resistance to distention, the esophageal distensibility plateau provides a quantitative assessment of esophageal remodeling[20] and has been shown to be significantly impaired in patients with EoE.[21,22]

There are limited data on how effective therapies may be at preventing fibrotic remodeling of the esophagus in EoE.[14] In a phase II study, compared with placebo, dupilumab was associated with increased esophageal distensibility at 12 weeks, measured by EndoFLIP in an exploratory endpoint.[23] However, there is a need for more data to determine the efficacy of dupilumab in reducing inflammation and preventing and/or reducing fibrostenosis over longer treatment periods. The REMOdeling with Dupilumab in Eosinophilic esophagitis Long-term (REMODEL) trial aims to assess the long-term efficacy of dupilumab, including its impact on esophageal function and remodeling, in adult patients with EoE (ClinicalTrials.gov identifier: NCT06101095). The primary objective of REMODEL is to assess the efficacy of dupilumab in improving the esophageal distensibility plateau. The secondary objectives of the study include determining the long-term effect of dupilumab on esophageal function and histologic, endoscopic, and molecular features of EoE.

Methods

Study design

REMODEL is a multicenter, multinational, randomized, placebo-controlled, phase IV trial with a long-term open-label extension (Figure 1) that has recruited across 30 sites in Brazil, Canada, Israel, Switzerland, and the USA. Adult patients were eligible for enrollment if they had endoscopically and histologically active EoE with evidence of dysphagia symptoms at screening. Key eligibility criteria are detailed in Table 1.

The study was preceded by an up to 12-week screening period during which baseline characteristics were recorded, such as patient demographics, medical history including current and/or history of treatment and existing comorbidities, and molecular biomarkers. For further information regarding prohibited concomitant and historic therapies, see the Supplemental Appendix. Following screening, eligible patients were randomized 2:1 to receive dupilumab or a matching placebo for 24 weeks. Concealed treatment randomization was stratified by dilation history and performed centrally using an interactive response technology. The interactive response technology telephone number and/or log-in information were provided along with directions for use to each site prior to activation.

During the 24-week double-blind treatment period, all patients, care providers, and investigators will be blinded to the study intervention. To achieve blinding, study patients, care providers, and investigators will not have access to the randomization list, and study drugs will be visually indistinguishable. If rescue treatment is medically necessary, and at the discretion of the investigator, patients can switch to open-label treatment or receive emergency dilation, and the patient's intervention will be unblinded before rescue. The investigator will have sole responsibility for determining if unblinding of a patient's intervention assignment is warranted, with patient safety being the first consideration in making the decision. Sponsor staff may unblind the intervention assignments for any patient with a serious adverse event. The study will be unblinded at the first early analyses, when all patients complete the 24-week treatment period, or upon early discontinuation from the study (see Supplemental Methods for further information). The 24-week, randomized, double-blind, placebo-controlled period will be followed by an open-label period of 104 weeks in which all patients will receive dupilumab. Recruitment for REMODEL ended in May 2025, and the primary data readout of the double-blind, placebo-controlled treatment period is anticipated in December 2025.

Study interventions

For the first 24 weeks, patients will be randomized to receive either dupilumab 300 mg once weekly (qw), corresponding with the US Food and Drug Administration-approved dupilumab dosing in adults with EoE, or placebo.[16] During the open-label period, all patients will receive dupilumab 300 mg qw. Dupilumab 300 mg and placebo will be provided in identically matched, 2 mL prefilled

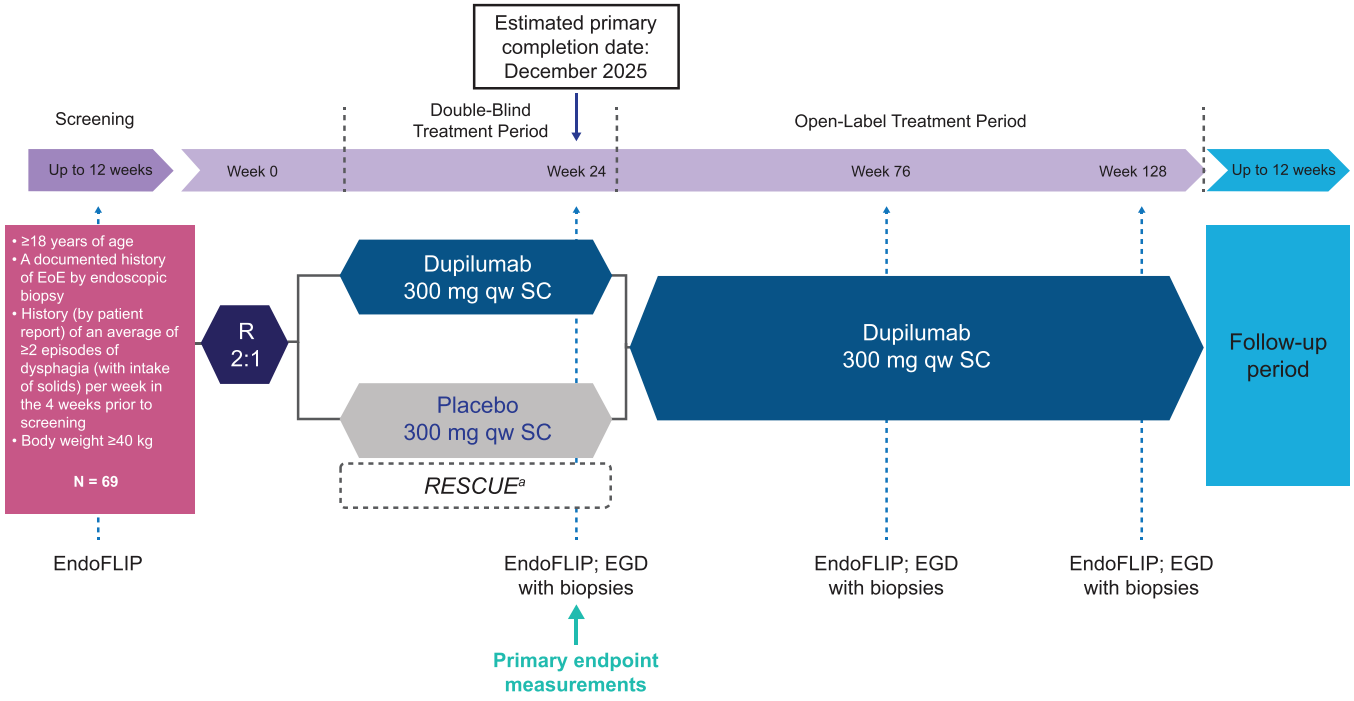


Figure 1. REMODEL study design.
[a]If medically necessary, patients can switch to open-label treatment, or have emergency dilation and switch to open-label treatment, at any time during the study and at the discretion of the investigator. All assessments, including endoscopy with biopsy, EndoFLIP, mucosal impedance, and patient-reported outcomes, must be performed before dilation and/or switch to open-label treatment and at all specified time points.
EGD, esophagogastroduodenoscopy; EndoFLIP, endoluminal functional lumen imaging probe; EoE, eosinophilic esophagitis; qw, once weekly; R, randomization; SC, subcutaneous.

syringes and will be administered by subcutaneous injection, which, after appropriate training, can be administered by the patient at home. Patients' adherence to treatment will be monitored during the study by site investigators (see Supplemental Methods).

Assessments

Baseline assessments are taken on day 1 of the study or, in the case of measures obtained via endoscopy, taken during screening and up to 21 days before study initiation. All primary, secondary, and exploratory endpoints assessed throughout the study are listed in Table 2. The primary objective and endpoint of the study will be to assess absolute change from baseline in esophageal distensibility plateau as measured by EndoFLIP at week 24. The secondary objective will be to assess long-term effects of dupilumab on esophageal function by measuring the percent change from baseline in esophageal distensibility plateau as measured by EndoFLIP at week 24 (the key secondary endpoint) and absolute and relative change from baseline in esophageal distensibility plateau at weeks 76 and 128. Additional secondary objectives will be to assess the long-term effects of dupilumab on histologic, endoscopic, and molecular features of EoE, measuring endpoints at weeks 24, 76, and 128. The long-term safety of dupilumab for the treatment of EoE will also be assessed as a secondary objective. Incidents of adverse events of special interest, serious adverse events, and treatment-emergent adverse events will be monitored throughout the study. Exploratory objectives will be to assess the long-term effect of dupilumab on disease modification, the need for rescue treatments, peak eosinophil count, gene and protein expression, and symptoms and QoL at weeks 24, 76, and 128.

Endpoint measures

During endoscopy, esophageal distensibility will be assessed using EndoFLIP 3.0 (Medtronic, Minneapolis, MN, USA) by both local and central reading; the central read will be used for the

Table 1. REMODEL key inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• Aged ⩾18 years at the time of study entry • A documented diagnosis of EoE by endoscopic biopsy before screening, as demonstrated by intraepithelial eosinophilic infiltration (peak cell count ⩾15 eos/hpf) from at least one esophageal region • Baseline endoscopic biopsies with a demonstration on central reading of intraepithelial eosinophilic infiltration in at least two of the three biopsied esophageal regions (proximal, mid, or distal) • History by patient report of an average of ⩾2 episodes per week of dysphagia with intake of solids in the 4 weeks before screening • At least four episodes of dysphagia in the 2 weeks before baseline, two of which required liquids, coughing or gagging, vomiting, or medical attention to obtain relief • Completed at least 11 of 14 days of DSQ eDiary data entries in the 2-week period before baseline • Baseline DSQ ⩾10 • Body weight ⩾40 kg • Willing and able to comply with site visits and study-related procedures • Able to understand and complete study-related questionnaires • Capable of giving signed and informed consent	• Other causes of esophageal eosinophilia or the following conditions: hypereosinophilic syndrome or eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) • Active *Helicobacter pylori* infection • History of achalasia, Crohn's disease, ulcerative colitis, celiac disease, and/or prior esophageal surgery • Any esophageal stricture unable to be passed with a standard, diagnostic, 9–10 mm upper endoscope, or any critical esophageal stricture that requires dilation at screening • History of bleeding disorders or esophageal varices • Treatment with STCs ⩽8 weeks before baseline • Initiation, discontinuation, or change in the dosage regimen ⩽8 weeks before baseline endoscopy of PPIs (except for patients who require PPI treatment before baseline endoscopy), leukotriene inhibitors, and/or nasal and/or inhaled corticosteroids • Initiation of or change to a food elimination diet regimen or reintroduction of a previously eliminated food group ⩽6 weeks before screening • Participation in prior dupilumab clinical study or patients currently treated or have been treated with commercially available dupilumab, or contraindicated to dupilumab per local labeling

DSQ, Dysphagia Symptom Questionnaire; EoE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field; PPI, proton-pump inhibitor; REMODEL, REMOdeling with Dupilumab in Eosinophilic esophagitis Long-term; STC, swallowed topical corticosteroid.

endpoint data. The EndoFLIP device is a catheter-based procedure that measures the cross-sectional area at multiple sites along the esophagus with simultaneous intraluminal pressure recordings during volumetric distension of the esophagus. The analyses of cross-sectional area versus pressure relationships of the esophagus allow for the determination of esophageal compliance as well as the distensibility plateau, defined here as the narrowest esophageal lumen diameter that fails to expand despite increasing intra-balloon measures. The device consists of a 240 mm-long, 3 mm outer diameter catheter, with a 16 cm balloon mounted on the distal end (EF-322N; Medtronic). The catheter within the balloon contains 16 paired impedance planimetry electrodes spaced at intervals of 1 cm. The balloon is filled with a conductive fluid via an 80 mL syringe, and serial measurements are taken, starting from 30 mL, with 10 mL step-ups to 40 mL, 50 mL, 60 mL, and finally to a max fill of 70 mL. Esophageal distensibility is calculated based on simultaneous measurement of pressure within the balloon by the solid-state transducer.[24,25] EndoFLIP measurements for the calculation of the esophageal distensibility plateau will be taken at the distal region of the esophagus only.

Additional endoscopic features of EoE will be assessed using the EoE-Endoscopic Reference Score (EoE-EREFS), a validated scoring system that assesses the inflammatory and remodeling features of EoE using an overall score and scores for each individual characteristic (edema, rings, exudates, furrows, and strictures).[26] The EoE-EREFS will be performed by both the investigators performing the endoscopies and a centralized reading center using endoscopy imaging. Proximal and distal esophageal regions will be scored separately (range 0–9) using EoE-EREFS, and the overall score calculated from the sum of both regions (range 0–18). During endoscopy, esophageal epithelial impedance will be measured using mucosal impedance analysis (MiVu; Diversatek Healthcare, Milwaukee, WI, USA), which provides real-time, quantitative assessment of epithelial integrity and esophageal barrier function.[27] A total of 12 mucosal pinch biopsies will be collected during endoscopy, from three esophageal regions: four proximal, four mid, and four distal.

Table 2. Primary and secondary endpoints assessed throughout REMODEL.

Study objective	Endpoints
Primary • To assess the effect of dupilumab on esophageal distensibility at week 24	• Absolute change from baseline in esophageal distensibility plateau as measured by EndoFLIP at week 24
Secondary • Key secondary: To determine the long-term effect of dupilumab on esophageal function • To assess the long-term effect of dupilumab on histologic (eos/hpf, EoE-HSS), endoscopic (EoE-EREFS), and molecular (gene expression) endpoint measures • To determine long-term safety with dupilumab	• Percent change from baseline in esophageal distensibility plateau as measured by EndoFLIP at week 24 (key secondary endpoint) • Absolute and percent change from baseline in esophageal distensibility plateau as measured by EndoFLIP at 76 and 128 weeks • Change from baseline in EoE-EREFS at weeks 24, 76, and 128 • Change from baseline in EoE-HSS grade at weeks 24, 76, and 128 • Change from baseline in EoE-HSS stage at weeks 24, 76, and 128 • Proportion of patients who achieved peak esophageal intraepithelial eosinophil count of ⩽6 eos/hpf at weeks 24, 76, and 128 • Proportion of patients who achieved peak esophageal intraepithelial eosinophil count of ⩽15 eos/hpf at weeks 24, 76, and 128 • NES for the relative change from baseline to weeks 24, 76, and 128 in the EDP transcriptome signature • NES for the relative change from baseline to weeks 24, 76, and 128 in the type 2 inflammation transcriptome signature • Incidence of TEAEs and SAEs • Incidence of AESIs
Exploratory • To assess the effect of dupilumab on disease modification with long-term data on restoring barrier function and reduction in rescue treatment • To assess the long-term effect of dupilumab on peak eos/hpf, gene and protein expression, symptoms, and QoL • To assess the long-term effect of dupilumab on HCRU	• Change from baseline in mucosal impedance at weeks 24, 76, and 128 • Proportion of patients who receive rescue treatments at weeks 24, 76, and 128 • Percent change in peak eos/hpf from baseline to weeks 24, 76, and 128 • Assessing changes from baseline in esophageal spatial gene/protein expression at weeks 24, 76, and 128 • Absolute and percent change from baseline for blood eotaxin-3 at weeks 24, 76, and 128 • Absolute and percent change from baseline in health-related QoL as measured by EoE-QoL-A at weeks 24, 76, and 128 • Absolute and percent change from baseline in anxiety as measured by HADS at weeks 24, 76, and 128 • Absolute and percent change from baseline in depression as measured by HADS at weeks 24, 76, and 128 • Cumulative number of HCRU events

AESI, adverse event of special interest; EDP, EoE Diagnostic Panel; EndoFLIP, endoluminal functional lumen imaging probe; EoE, eosinophilic esophagitis; EoE-EREFS, EoE-Endoscopic Reference Score; EoE-HSS, EoE histology scoring system; EoE-QoL-A, adult EoE QoL questionnaire; eos/hpf, eosinophils per high-power field; HADS, Hospital Anxiety and Depression Scale; HCRU, healthcare resource utilization; NES, normalized enrichment score; QoL, quality of life; REMODEL, REMOdeling with Dupilumab in Eosinophilic esophagitis Long-term; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Three samples from each region will be used for histology and other tissue analyses, including but not limited to immunohistochemistry, RNA in situ hybridization, RNA sequencing, and spatial transcriptomic/proteomic analysis. Any remaining tissue samples will be banked. Biopsy samples will be processed locally and sent to a central laboratory (Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA) to be assessed for peak eosinophil counts per high-power field, spatial biomarker analyses (transcriptomic and proteomic) bulk RNA sequencing analysis, and histologic severity using the EoE histology scoring system, a validated scoring system used to measure the severity (grade) and extent (stage) of histopathologic features in EoE.[28]

The impact of disease on patient health-related QoL will be assessed using the adult EoE QoL questionnaire, a validated and EoE-specific patient-reported outcome (PRO) tool[11,29] that evaluates the impact of disease on several domains, including social and emotional functioning and daily life experiences.[30] Changes in

anxiety and depression experienced by patients will be assessed using the Hospital Anxiety and Depression Scale, a validated PRO tool used extensively across multiple diseases to screen for symptoms specific to anxiety and depression regardless of disease state.[31]

Ethical considerations and data collection

REMODEL will be conducted in accordance with (i) consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and the applicable amendments[32] and Council for International Organizations of Medical Sciences international ethical guidelines,[33] and (ii) applicable regulatory requirements in accordance with the International Council for Harmonisation Good Clinical Practice E6 (R2) guidelines.[34] The protocol and other relevant documents were submitted for institutional review board (IRB) review and were approved before the study was initiated. Any substantial amendments to the protocol will require health authority and IRB/independent ethics committee (IEC) approval before implementation, except for changes necessary to eliminate an immediate hazard to study patients. The reporting of this study conforms to the SPIRIT statement (Supplemental Appendix).[35]

During enrollment, patients were informed that their participation was voluntary and were required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations 50, local regulations, International Council for Harmonisation guidelines, privacy and data protection regulations, and the requirements of the IRB/IEC and/or study center. The informed consent form contains two separate sections, each subject to independent consent, that address the use of patients' data and/or samples for future research. Written consent was obtained by the investigator or an authorized representative. Data will be collected and stored in accordance with the General Data Protection Regulation and any other applicable data protection laws (details related to data access and dissemination are found in the Supplemental Methods).

A placebo arm consisting of patients who may be exposed to background therapies, including PPIs and/or dietary therapy, was deemed necessary to assess natural disease progression and robustly measure dupilumab treatment effects while controlling for other factors, for example, background treatment adherence. A randomization ratio of 2:1 for the active treatment versus placebo was used to limit the number of patients exposed to placebo and avoid excessive and unjustified burden on patients. All patients were appropriately informed and provided written consent for the potential eventuality of receiving a placebo and may withdraw from the study intervention or from the study at any time. Furthermore, if medically necessary and at the discretion of their physician, patients may receive other treatments, switch to open-label treatment, and/or have emergency dilation at any time.

Statistical analysis

The study has recruited 69 adult male and female patients with active EoE. Assuming a 10% dropout rate by week 24, this sample size will provide 90% power with a 0.05 two-sided significance level to detect a treatment difference (standard deviation) of 2.3 (2.42) mm in esophageal distensibility between dupilumab and placebo groups. This design is based on a conservative prediction of potential treatment effect, powered to detect a value that is less than that seen in the phase II trial.[23] Baseline values are defined as the last available value before the first dose of the double-blind study drug. The primary endpoint will be compared between the dupilumab and placebo groups using an analysis of covariance model, with dilation treatment history and baseline EndoFLIP measurements as covariates. For patients who undergo rescue treatment for EoE, data collected after rescue treatment will be set to missing and imputed by multiple imputation. For patients who discontinue the study drug without having rescue treatment, the data collected after treatment discontinuation will be included in the analysis. If a patient still has missing data after all efforts, the missing data will be imputed by multiple imputation. Statistical inference obtained from all imputed data will be combined using Rubin's rule. Binary secondary endpoints at week 24 will be analyzed using the Cochran–Mantel–Haenszel test to assess the difference in the proportion of responders, adjusting for dilation history as the randomization stratification factor. Continuous secondary endpoints at week 24 will be analyzed using the analysis of covariance model in the same fashion as for the primary endpoint. After the double-blind treatment period of the study, all efficacy endpoints will be summarized with descriptive statistics. Early analysis is planned at week 24.

Discussion

REMODEL is a parallel-group, phase IV study that consists of a 24-week, randomized, double-blind, placebo-controlled treatment period followed by an open-label period during which all patients receive dupilumab for 104 weeks. Previous phase III dupilumab clinical studies established the link between treating type 2 inflammation and achieving durable (up to 52 weeks) improvements in histologic, symptomatic, endoscopic, and molecular (transcriptomic) features of EoE.[16] REMODEL aims to address an important data gap—that is, to explore whether long-term treatment of type 2 inflammation potentially modifies fibrostenotic progression of EoE. Addressing this data gap could have implications for whether treatment could prevent or modify overall EoE disease progression.

Esophageal eosinophilia often does not correlate with symptoms or endoscopic features of EoE, including esophageal distensibility,[36] nor is it a predictor for the development of clinical complications.[37] A more comprehensive evaluation of EoE beyond eosinophil counts to determine disease extent and response to treatment is therefore required.[38] In addition to its application in research, EndoFLIP has the potential to provide valuable clinical information in EoE.[25] Decreased esophageal distensibility, as measured by EndoFLIP, has been shown to be associated with an increased risk of clinical complications, including food impaction and the requirement for dilation in patients with EoE.[25] As a measure of fibrostenotic disease, EndoFLIP may provide information relevant to risks for clinical complications that have been shown to directly impact patient QoL.[11] Demonstrating prevention of fibrostenotic progression and reversal of existing fibrosis in EoE is therefore a key target for long-term management of the disease. Dupilumab has previously been shown to have the potential to reverse fibrosis in EoE, increasing esophageal distensibility in a phase II study.[23] In REMODEL, EndoFLIP will be used to provide a quantitative assessment of esophageal fibrosis and rigidity in response to dupilumab treatment compared with placebo, and may therefore provide novel evidence of an EoE therapy that can reverse and modify disease progression.

In addition to the primary aims of the study, REMODEL will assess several secondary endpoints to build upon findings from previous studies, including the effect of dupilumab on epithelial and transcriptomic endpoints associated with EoE disease activity. Growing evidence suggests that type 2 inflammation may contribute to impaired barrier function of the esophageal epithelium, ultimately contributing to esophageal remodeling.[10,39] Several genes in the epidermal differentiation complex, of which down-regulation by type 2 cytokines results in barrier dysfunction of the skin, are also down-regulated in primary esophageal epithelial cells in vitro.[39] Furthermore, a reduced expression of the epidermal differentiation complex gene *FLG* and the esophagus-specific esophagin (small proline-rich protein 3) was observed in esophageal biopsies from patients with EoE compared with controls.[39] Expression of these genes was normalized in the phases II and III trials of dupilumab for the treatment of EoE.[40] This suggests that, in addition to driving an inflammatory response, type 2 cytokines may directly contribute to epithelial barrier dysfunction in the esophagus, indicating that treatment targeting type 2 inflammation has the potential to address esophageal epithelial remodeling and improve barrier function and consequently esophageal fibrosis. Data from REMODEL may help to further elucidate the molecular mechanisms linking type 2 inflammation with esophageal remodeling and fibrostenotic development in EoE.[41,42] Furthermore, REMODEL will provide novel data through its application of MiVu to measure mucosal impedance, which could be used to assess the correlation of mucosal integrity with endoscopy, EndoFLIP, and spatial biomarkers—analyses that have not previously been explored in EoE.

Additional secondary endpoints of REMODEL will provide data for the long-term efficacy of dupilumab in improving histologic, symptomatic, endoscopic, and molecular (transcriptomic) features of EoE by assessing its efficacy over 128 weeks (~2.5 years). This study will also provide long-term safety data in EoE, adding to the years of follow-up data for dupilumab in other type 2 inflammatory diseases.[43,44] In addition, REMODEL will assess disease-related anxiety and depression, endpoints that are not often assessed in EoE clinical trials, despite patients being at an increased risk of decreased mental health.[45]

Limitations

EndoFLIP is not often used in clinical practice,[12] and therefore, standardization of the procedure in

patients with EoE is not well established. REMODEL may provide evidence to help standardize this process and support the use of EndoFLIP for patient monitoring, particularly in patients with fibrostenotic disease. Fibrotic remodeling in EoE likely progresses over substantial periods of time,[7,8,10] with observational data indicating that increased EoE duration is directly correlated with a fibrostenotic phenotype.[9] Clinically significant fibrostenosis may therefore take longer to develop than the study duration, limiting potential conclusions regarding disease modification. In addition, stipulating evidence of dysphagia as an eligibility criterion limits the study population to patients who likely have established fibrostenotic disease. Although this population is likely to derive treatment benefit, this may preclude assessment of dupilumab in preventing the initial stages of fibrostenotic progression. Data collected during the extended treatment period may be influenced by open-label bias, particularly in PROs. However, evidence suggests that the potential for bias should not prevent the interpretation of potentially meaningful treatment effects.[46]

Conclusion

REMODEL aims to build upon findings from previous dupilumab EoE studies, providing long-term data for the efficacy and safety of dupilumab to improve histologic, endoscopic, and molecular features of EoE. In addition, the primary endpoint of REMODEL is novel and will assess the impact of dupilumab on fibrostenotic progression and esophageal remodeling in patients with EoE, exploring the potential for long-term EoE disease modification with dupilumab. The study may also increase our understanding of the roles of IL-4 and IL-13 in fibrostenotic progression of EoE and provide valuable insight into anxiety and depression experienced by patients with EoE. Recruitment for REMODEL ended in May 2025, and the estimated primary completion date is December 2025.

Declarations

Ethics approval and consent to participate

The study will be conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. The protocol was approved by the IECs/IRBs of each participating center according to local requirements (including: WCG IRB, approved August 10, 2023, IRB#20233509; Advarra IRB, approved September 26, 2023, IRB#00000971; Cantonal Ethics Committee, approved March 15, 2023, 2023-02021; Pontifical Catholic University of Rio Grande do Sul, approved October 8, 2023, 6.413.911). The local IECs/IRBs at each study center will oversee trial conduct and documentation. Patients were informed that their participation is voluntary and were required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations 50, local regulations, International Council for Harmonisation guidelines, privacy and data protection regulations, and the requirements of the IEC/IRB and/or study center.

Consent for publication

Not applicable.

Author contributions

Evan S. Dellon: Writing – original draft; Writing – review & editing.

Edoardo V. Savarino: Writing – original draft; Writing – review & editing.

Sherif Zaghloul: Conceptualization; Methodology; Writing – original draft; Writing – review & editing.

James T. Angello: Conceptualization; Methodology; Writing – original draft; Writing – review & editing.

Mei Zhang: Conceptualization; Methodology; Writing – original draft; Writing – review & editing.

Bram P. Raphael: Conceptualization; Methodology; Writing – original draft; Writing – review & editing.

Amr Radwan: Conceptualization; Methodology; Writing – original draft; Writing – review & editing.

Albert J. Bredenoord: Writing – original draft; Writing – review & editing.

Acknowledgments

We would like to acknowledge the sad passing of Dr. Ikuo Hirano, who contributed significantly to the gastroenterology community and to the

concept of this study and manuscript. Medical writing/editorial support was provided by Emily Prior, MSc, of Adelphi Group, Macclesfield, UK, funded by Sanofi and Regeneron Pharmaceuticals, Inc., according to the Good Publication Practice guidelines.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Research funded by Sanofi (Morristown, NJ, USA) and Regeneron Pharmaceuticals, Inc. (Tarrytown, NY, USA). The sponsors contributed to the study design and will support the collection, management, analysis, and interpretation of study data. ClinicalTrials.gov identifier: NCT06101095.

Competing interests

E.S.D.: AbbVie, Adare/Ellodi, Akesobio, Alfasigma, ALK, Allakos, Amgen, Apollo, Aqilion, Arena/Pfizer, Aslan, AstraZeneca, Avir, Biocryst, Bryn, Calypso, Celgene/Receptos/BMS, Celldex, Dr. Falk Pharma, EsoCap, Eupraxia, Ferring, GI Reviewers, GSK, Holoclara, Invea, Knightpoint, LucidDx, Morphic, Nexstone Immunology/Uniquity, Nutricia, Parexel/Calyx, Phathom, Regeneron Pharmaceuticals, Inc., Revolo, Robarts/Alimentiv, Sanofi, Shire/Takeda, Target RWE, Upstream Bio—consultant fees. Adare/Ellodi, Allakos, Arena/Pfizer, AstraZeneca, Celgene/Receptos/BMS, Celldex, Eupraxia, Ferring, GSK, Meritage, Miraca, Nutricia, Regeneron Pharmaceuticals, Inc., Revolo, Sanofi, Shire/Takeda—research funding. Allakos, Aqilion, Holoclara, Invea—educational grants. E.V.S.: AbbVie, Agave, Alfasigma, Biogen, Bristol Myers Squibb, Celltrion, Dr. Falk Pharma, Eli Lilly, Fenix Pharma, JB Pharmaceuticals, Johnson & Johnson, Merck & Co, Nestlé, Pfizer, Reckitt Benckiser, Regeneron Pharmaceuticals, Inc., Sanofi, SILA, Sofar, Takeda, Unifarco—consultant fees. Bonollo, Difass, Pfizer, Reckitt Benckiser, SILA, Sofar, Unifarco, Zeta Farmaceutici—research funding. AbbVie, Agave, AGPharma, Alfasigma, CaDiGroup, Celltrion, Dr. Falk Pharma, EG Stada Group, Eli Lilly, Fenix Pharma, Galapagos, Innovamedica/Adacyte, JB Pharmaceuticals, Johnson & Johnson, Malesci, Mayoly Biohealth, Omega Pharma, Pfizer, Reckitt Benckiser, Sandoz, SILA, Sofar, Takeda, Tillotts, Unifarco—speaker fees. S.Z., J.T.A., M.Z.: Sanofi—employees, may hold stock and/or stock options in the company. B.P.R., A.R.: Regeneron Pharmaceuticals, Inc.—employees and shareholders. A.J.B.: Alimentiv, Aqilion, AstraZeneca, Dr. Falk Pharma, Eupraxia, Laborie, Medtronic, Reckitt, Regeneron Pharmaceuticals, Inc., Sanofi—consultant fees. Dr. Falk Pharma, Norgine, Nutricia, Regeneron Pharmaceuticals, Inc., Sanofi, SST, Thelial—research funding. Alimentiv, Aqilion, AstraZeneca, Dr. Falk Pharma, Eupraxia, Laborie, Medtronic, Reckitt, Regeneron Pharmaceuticals, Inc., Sanofi—speaker fees.

Availability of data and materials

Not applicable.

ORCID iDs

Evan S. Dellon https://orcid.org/0000-0003-1167-1101

Edoardo V. Savarino https://orcid.org/0000-0002-3187-2894

Trial status

Protocol version number 1 (electronic 2.0). Recruitment began on November 29, 2023 and ended in May 2025. The estimated primary completion date is December 2025.

Supplemental material

Supplemental material for this article is available online.

References

1. Navarro P, Arias A, Arias-Gonzalez L, et al. Systematic review with meta-analysis: the growing incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies. *Aliment Pharmacol Ther* 2019; 49(9): 1116–1125.
2. Straumann A and Katzka DA. Diagnosis and treatment of eosinophilic esophagitis. *Gastroenterology* 2018; 154(2): 346–359.
3. Minutti CM, Knipper JA, Allen JE, et al. Tissue-specific contribution of macrophages to wound healing. *Semin Cell Dev Biol* 2017; 61: 3–11.
4. Van Dyken SJ and Locksley RM. Interleukin-4- and interleukin-13-mediated alternatively activated macrophages: roles in homeostasis and disease. *Annu Rev Immunol* 2013; 31: 317–343.

5. Gieseck RL 3rd, Wilson MS and Wynn TA. Type 2 immunity in tissue repair and fibrosis. *Nat Rev Immunol* 2018; 18(1): 62–76.

6. Wynn TA and Vannella KM. Macrophages in tissue repair, regeneration, and fibrosis. *Immunity* 2016; 44(3): 450–462.

7. Schoepfer AM, Safroneeva E, Bussmann C, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. *Gastroenterology* 2013; 145(6): 1230–1236.e1231–2.

8. Warners MJ, Oude Nijhuis RAB, de Wijkerslooth LRH, et al. The natural course of eosinophilic esophagitis and long-term consequences of undiagnosed disease in a large cohort. *Am J Gastroenterol* 2018; 113(6): 836–844.

9. Dellon ES, Kim HP, Sperry SLW, et al. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. *Gastrointest Endosc* 2014; 79(4): 577–585.e4.

10. Hirano I and Aceves SS. Clinical implications and pathogenesis of esophageal remodeling in eosinophilic esophagitis. *Gastroenterol Clin North Am* 2014; 43(2): 297–316.

11. Stern E, Taft T, Zalewski A, et al. Prospective assessment of disease-specific quality of life in adults with eosinophilic esophagitis. *Dis Esophagus* 2018; 31(4): 1–7.

12. Dellon ES, Muir AB, Katzka DA, et al. ACG clinical guideline: diagnosis and management of eosinophilic esophagitis. *Am J Gastroenterol* 2025; 120(1): 31–59.

13. Laserna-Mendieta EJ, Casabona S, Savarino E, et al. Efficacy of therapy for eosinophilic esophagitis in real-world practice. *Clin Gastroenterol Hepatol* 2020; 18(13): 2903–2911.e4.

14. Greuter T, Godat A, Ringel A, et al. Effectiveness and safety of high- vs low-dose swallowed topical steroids for maintenance treatment of eosinophilic esophagitis: a multicenter observational study. *Clin Gastroenterol Hepatol* 2021; 19(12): 2514–2523.e2.

15. DUPIXENT® (dupilumab). Highlights of prescribing information. *US Food and Drug Administration*, https://www.regeneron.com/sites/default/files/Dupixent_FPI.pdf (2024, accessed March 2025).

16. Dellon ES, Rothenberg ME, Collins MH, et al. Dupilumab in adults and adolescents with eosinophilic esophagitis. *N Engl J Med* 2022; 387: 2317–2330.

17. Chehade M, Dellon ES, Spergel JM, et al. Dupilumab for eosinophilic esophagitis in patients 1 to 11 years of age. *N Engl J Med* 2024; 390(24): 2239–2251.

18. Greuter T, Bussmann C, Safroneeva E, et al. Long-term treatment of eosinophilic esophagitis with swallowed topical corticosteroids: development and evaluation of a therapeutic concept. *Am J Gastroenterol* 2017; 112(10): 1527–1535.

19. Gentile N, Katzka D, Ravi K, et al. Oesophageal narrowing is common and frequently under-appreciated at endoscopy in patients with oesophageal eosinophilia. *Aliment Pharmacol Ther* 2014; 40(11–12): 1333–1340.

20. Chen JW, Pandolfino JE, Lin Z, et al. Severity of endoscopically identified esophageal rings correlates with reduced esophageal distensibility in eosinophilic esophagitis. *Endoscopy* 2016; 48(9): 794–801.

21. Kwiatek MA, Hirano I, Kahrilas PJ, et al. Mechanical properties of the esophagus in eosinophilic esophagitis. *Gastroenterology* 2011; 140(1): 82–90.

22. Lin Z, Kahrilas PJ, Xiao Y, et al. Functional luminal imaging probe topography: an improved method for characterizing esophageal distensibility in eosinophilic esophagitis. *Therap Adv Gastroenterol* 2013; 6(2): 97–107.

23. Hirano I, Dellon ES, Hamilton JD, et al. Efficacy of dupilumab in a phase 2 randomized trial of adults with active eosinophilic esophagitis. *Gastroenterology* 2020; 158(1): 111–122.e10.

24. Pannala R, Krishnan K, Watson RR, et al. Devices for esophageal function testing. *Gastrointest Endosc* 2022; 95(1): 27–29.

25. Hirano I, Pandolfino JE and Boeckxstaens GE. Functional lumen imaging probe for the management of esophageal disorders: expert review from the clinical practice updates committee of the AGA Institute. *Clin Gastroenterol Hepatol* 2017; 15(3): 325–334.

26. Hirano I, Moy N, Heckman MG, et al. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. *Gut* 2013; 62(4): 489–495.

27. Patel DA, Higginbotham T, Slaughter JC, et al. Development and validation of a mucosal impedance contour analysis system to distinguish esophageal disorders. *Gastroenterology* 2019; 156(6): 1617–1626.e1.

28. Collins MH, Martin LJ, Alexander ES, et al. Newly developed and validated eosinophilic esophagitis histology scoring system and evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring. *Dis Esophagus* 2017; 30(3): 1–8.

29. de Rooij WE, Bennebroek Evertsz F, Lei A, et al. Mental distress among adult patients with eosinophilic esophagitis. *Neurogastroenterol Motil* 2021; 33(7): e14069.

30. Taft TH, Kern E, Kwiatek MA, et al. The adult eosinophilic oesophagitis quality of life questionnaire: a new measure of health-related quality of life. *Aliment Pharmacol Ther* 2011; 34(7): 790–798.

31. Zigmond AS and Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983; 67(6): 361–370.

32. The Helsinki Declaration of the World Medical Association (WMA). Ethical principles of medical research involving human subjects. *Pol Merkur Lekarski* 2014; 36(215): 298–301.

33. van Delden JJ and van der Graaf R. Revised CIOMS international ethical guidelines for health-related research involving humans. *JAMA* 2017; 317(2): 135–136.

34. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH harmonised guideline: integrated addendum to ICG E6 (R1): guideline for good clinical practice E6 (R2). Current Step 5 version 2016. Geneva, Switzerland, 2016.

35. Chan AW, Boutron I, Hopewell S, et al. SPIRIT 2025 statement: updated guideline for protocols of randomized trials. *Nat Med* 2025; 31(6): 1784–1792.

36. Kochar B and Dellon ES. Endoscopic findings in eosinophilic esophagitis and esophageal distensibility: a proxy for transmural modeling? *Gastroenterology* 2017; 152(1): 298–299.

37. Nicodème F, Hirano I, Chen J, et al. Esophageal distensibility as a measure of disease severity in patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2013; 11(9): 1101–1107.e1.

38. Hirano I, Dellon ES, Falk GW, et al. Ascending to new heights for novel therapeutics for eosinophilic esophagitis. *Gastroenterology* 2024; 166(1): 1–10.

39. Blanchard C, Stucke EM, Burwinkel K, et al. Coordinate interaction between IL-13 and epithelial differentiation cluster genes in eosinophilic esophagitis. *J Immunol* 2010; 184(7): 4033–4041.

40. Collins MH. Dupilumab improves histological outcomes and normalizes disease and type 2 inflammation transcriptome signatures in adult and adolescent patients with eosinophilic oesophagitis: results from the 3-part phase 3 LIBERTY EoE TREET study. *Allergy* 2023; 78: S111. EAACI Annual Congress 2022; Prague Abstract: 001140.

41. Cheng E, Souza RF and Spechler SJ. Tissue remodeling in eosinophilic esophagitis. *Am J Physiol Gastrointest Liver Physiol* 2012; 303(11): G1175–G1187.

42. Avlas S, Shani G, Rhone N, et al. Epithelial cell-expressed type II IL-4 receptor mediates eosinophilic esophagitis. *Allergy* 2023; 78(2): 464–476.

43. Wechsler ME, Ford LB, Maspero JF, et al. Long-term safety and efficacy of dupilumab in patients with moderate-to-severe asthma (TRAVERSE): an open-label extension study. *Lancet Respir Med* 2022; 10(1): 11–25.

44. Deleuran M, Thaçi D, Beck LA, et al. Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study. *J Am Acad Dermatol* 2020; 82(2): 377–388.

45. Taft TH, Guadagnoli L and Edlynn E. Anxiety and depression in eosinophilic esophagitis: a scoping review and recommendations for future research. *J Asthma Allergy* 2019; 12: 389–399.

46. Lord-Bessen J, Signorovitch J, Yang M, et al. Assessing the impact of open-label designs in patient-reported outcomes: investigation in oncology clinical trials. *JNCI Cancer Spectr* 2023; 7(2): pkad002.